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Tuberculosis Medicines Technology and Market Landscape

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UNITAID Secretariat
World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland
T +41 22 791 55 03
F +41 22 791 48 90
unitaid@who.int
www.unitaid.org

UNITAID is hosted and administered by the World Health Organization

Components of this report were prepared by Patrick Aylward, Janet Ginnard, Brian Kaiser, Barbara Laughon, Megan Paterson, Kelly Roney, Doris Rouse, Diana Severynse Stevens, Anita Woodring, and members of the Working Group on New TB Drugs of the STOP TB Partnership with support from UNITAID. Overall coordination of this report was undertaken by Janet Ginnard. All reasonable precautions have been taken by the authors to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the authors, UNITAID or the World Health Organization be liable for damages arising from its use.

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List of abbreviations

AIDS	Acquired immunodeficiency syndrome
API	Active pharmaceutical ingredient
BRICS	Brazil, Russia, India, China and South Africa
CHMP	Committee for Medicinal Products for Human Use (EMA)
DDI	Drug-drug interaction
DR TB	Drug-resistant tuberculosis
DS TB	Drug-susceptible tuberculosis
DST	Drug susceptibility testing
EMA	European Medicines Agency
ERP	Expert Review Panel
FDC	Fixed-dose combination
GDF	The Stop TB Partnership's Global Drug Facility
HIV	Human immunodeficiency virus
INR	Indian rupee
IPT	Isoniazid preventive therapy
IRD	*Institut de Recherche pour le Developpement*
IUATLD	International Union Against Tuberculosis and Lung Disease
LTBI	Latent TB infection
MCC	Medicines Control Council (South Africa)
MDR TB	Multidrug-resistant tuberculosis
MTB	Mycobacterium tuberculosis
NIAID	National Institute of Allergies and Infectious Diseases (United States)
NIH	National Institutes of Health (United States)
OFLOTUB	Gatifloxacin for TB (formerly OFLOxacin-containing TUBerculosis regimen)
PaMZ	PA-824, moxifloxacin, and pyrazinamide
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
R	Rifampicin
REMoxTB	Rapid Evaluation of Moxifloxacin
STREAM	Standardised Treatment REgimen of Anti-tuberculosis drugs for patients with Multi-drug resistant tuberculosis
TB Alliance	The Global Alliance for TB Drug Development
TB	Tuberculosis
TDR	United Nations Children's Fund (UNICEF)/United Nations Development Programme (UNDP)/World Bank/World Health Organization (WHO) – Special Programme for Research and Training in Tropical Diseases
US FDA	United States Food and Drug Administration
USAID	United States Agency for International Development
USD	United States Dollar
VAT	Value-added tax
WHO	World Health Organization
XDR TB	Extensively drug-resistant tuberculosis
ZAR	South African Rand

Foreword

Tuberculosis (TB) is a curable disease, but among the 8.7 million new cases in 2011, there were 1.4 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 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 consolidation of demand, negotiation of prices, and scale-up of appropriate, quality-assured TB medicines.

This report is part of a broad and ongoing effort by UNITAID to understand the landscape for TB medicines so as to complement other tools and initiatives. As data on TB medicines markets are incomplete, UNITAID intends this report to serve primarily as a platform for stimulating discussion. That is, this report should be considered a *preliminary* analysis to: 1) engage key stakeholders in discussion of critical market shortcomings related to TB medicines; and 2) to identify potential market-based approaches to remedy these and establish or restore functional market dynamics.

Executive summary

The public health problem of TB and access issues related to TB medicines

A serious threat to public health worldwide, TB caused 1.4 million deaths in 2011 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 medicines—critically lacking in so many resource-limited settings—is vital for the control of TB.

In 2011, 2.9 million people with active TB—one-third of all new cases—were not reported and likely not treated according to WHO recommendations. Access for TB patients infected with drug-resistant strains is even lower: in 2011, only 56,000 patients (of an estimated 310,000 total) were enrolled on second-line treatment. Access to TB care for children is poor: although up to 1 million children may need TB treatment each year, only 327,000 paediatric TB cases were reported to national programmes in 2011. 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 potential tools to improve TB treatment. The emphasis of this section is on recent developments, given the 2013 introduction of the first novel agents approved in 40 years based on phase II clinical trial data. One new molecular entity, bedaquiline, has received accelerated approval by the United States Food and Drug Administration (US FDA) for the treatment of multidrug-resistant TB (MDR TB). Another novel compound, delamanid, is under formal regulatory review by the European Medicines Agency (EMA). Two major phase III clinical trials investigating later-generation fluoroquinolones are in final stages, with results expected in late 2013. Phase II studies initiated in 2012-2013 offer early insights into the efficacy, pharmacokinetics, safety, and drug-drug interactions for promising candidates including: pyrazinamide, moxifloxacin, and PA-824; and high-dose rifapentine to shorten duration of treatment for drug-susceptible TB (DS TB).

New evidence may enable modifications to MDR TB treatment guidelines and contribute to shorter randomized, controlled clinical trials in the future. In November 2012, data on the 9-month 'Bangladesh regimen' of seven TB drugs for MDR TB indicated that the high cure rates reported in 2010 had been sustained, with durability of cure in many subjects for five years following treatment. The related 12-month 'Cameroon regimen' of seven TB drugs for MDR TB also continues to show high cure rates, with 85.5% of patients remaining bacteriologically negative 12 months after treatment cessation. These findings—along with evidence from a separate phase III, randomized, controlled study—could impact MDR TB treatment guidelines and/or practice.

TB medicines market landscape

The total value of the TB medicines market in 2011 (public and private sectors) is estimated to be approximately $700 million, including $430 million for first-line treatment of TB in adults and $300 million for treatment of MDR TB in adults. Estimates are uncertain, particularly for children—a segment probably worth less than $10 million globally in 2011.

There is no single dominant purchaser of TB medicines. 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 (1), but are very poorly understood in low-income countries. While the market for first-line TB medicines is relatively stable, analysis suggest high potential for growth in the MDR-TB medicines market.

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 ($4,000-6,000 vs. $22 per regimen), and treatment duration is longer (20-24 vs.

6 months), volumes are extremely low. 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 (20-24 months, including eight months of injections), and can have severe side effects. Quality-assured MDR-TB drugs are expensive, and make up only a fraction of the global market. TB medicines are especially prone to supply shortages and stock-outs—in part due to unstable supply of raw input materials—and inappropriate medicine selection and use can occur, particularly in the private sector. The lack of appropriately-dosed, quality-assured, paediatric TB fixed-dose combinations means that many children receive treatment inconsistent with WHO guidelines.

Table 1. Market shortcomings related to MDR-TB medicines.

Market shortcoming and description	Reasons
Availability: Lack of short, effective, streamlined MDR-TB regimens (current regimens are complex and expensive; last 20-24 months, including eight months of injections, and have severe side effects)	• Limited market incentives: small target population, diminished further by underdiagnosis • Inherent high risk in new drug development, as resistance evolves; one-at-a-time approach to drug development means development of novel regimens is long and challenging
Affordability: Quality-assured MDR-TB drugs are expensive (e.g., $4,000-$6,000+ per treatment course for a standard 24-month regimen including 8 months' injectable capreomycin.[1])	• Increased manufacturing costs driven by complex production, quality assurance requirements, low total volumes, and market fragmentation • Limited competition: few suppliers exist for finished products and active ingredients • Price increases due to manufacturer exit and product shortages
Quality: Quality-assured 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 National Treatment Programmes (NTPs) can be of variable or unknown quality, as some procurers prioritize price or other factors over quality assurance
Acceptability/Adaptability: Long 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 drug susceptibility testing (<4% of patients in 2011) 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 focus more on first-line than MDR TB
Delivery: Supply shortages, stock-outs, and long lead times	• Limited number of suppliers, especially of active pharmaceutical ingredients (APIs) • Lack of reliable forecasting of MDR-TB treatment numbers—in part due to difficulty in predicting speed of scale-up of drug susceptibility testing. This leads to low and variable demand, which 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 note: *1 GDF catalogue prices. Refer to Section 6.5.1 for additional detail.*

Table 2. Market shortcomings related to paediatric TB medicines.

Market shortcoming and description	Reasons
Affordability: Paediatric TB medicines are more expensive than those for adults, despite containing less active ingredient	• Few suppliers for quality-assured formulations • Increased risk for manufacturers: small market and fragmented demand, higher development costs and greater complexity in manufacturing
Quality: Many children receive unknown-quality drugs in non-standard doses (e.g., split adult fixed-dose combinations (FDCs)	• No appropriately-dosed FDCs (i.e., FDCs that correspond to the dosing recommended in the 2010 guideline update) exist • Private sector and non-donor public-sector procurement can have varying quality standards
Acceptability/Adaptability: No appropriately-dosed, quality-assured, paediatric FDC on the market consistent with 2010 WHO treatment guideline revision. Delays in needed paediatric trials for novel medicines. Of MDR-TB drugs, only amakacin and levofloxacin exist in paediatric formulations, but are not widely available	• Small, fragmented quality-assured paediatric market is unattractive 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, for both finished product and APIs • Lack of reliable forecasting and low and variable demand contributes to 'made-to-order' production
Delivery: TB diagnostics are not appropriate for children. 90% of children with TB are smear negative, and specimen collection in children is challenging	• Smear microscopy is not suited for children because: it requires sputum, which is hard 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 detail.*

Potential opportunities for TB medicines market interventions

TB medicines markets are a challenging area in which to intervene. The range and complexity of shortcomings related to MDR-TB medicines markets suggest that multiple interventions may be appropriate—i.e., a combination of broad and targeted approaches. As market segments are often closely linked (e.g., APIs and finished pharmaceutical products; diagnostics and medicines), potential interventions are often interdependent, with complementary approaches in multiple areas necessary to ensure success. Given the limited leverage of donors in funding procurement of TB medicines, potential market interventions also must be coordinated with other key stakeholders, such as country governments and private-sector providers.

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

- Consolidate demand for TB medicines by aligning different segments of the market, through mechanisms such as harmonizing quality standards and other requirements across different procurers or engaging with government or private-sector stakeholders in TB medicines markets in novel ways. Reducing the complexity of MDR-TB treatment could facilitate demand consolidation—e.g., by identifying and reducing non-essential variation in current TB treatment; and/or by establishing the necessary evidence base to identify priority TB medicines and regimens around which to focus the market;
- Improve demand forecasts for TB medicines, reducing the risk in production planning and enabling more efficient manufacture and supply management;
- Reduce supply vulnerability through robust procurement processes and supply chain improvements;
- Enhance the function and efficiency of specific product markets through mechanisms to assure demand or provide technical assistance, accounting for the economics of different markets (e.g., API vs. finished product);
- Facilitate improved manufacturing processes for MDR medicines to lower costs, improve quality, and support supply security through mechanisms such as process chemistry changes, production and scale efficiencies;

- Support manufacturers with an interest in producing quality-assured TB medicines but without the necessary technical expertise, through technical assistance to support technology transfer, quality manufacturing or increased production capacity; and
- Support appropriate access to new medicines to improve TB treatment and encourage further innovation, recognizing different trade-offs for new vs. 'repurposed' medicines or regimens.
- Potential opportunities in the paediatric TB medicines market may include interventions to:
- Consolidate demand, negotiate prices, and scale up appropriately-dosed, quality-assured medicines, when available;
- Incentivize development and facilitate uptake of novel TB diagnostics appropriate for children; and
- Develop mechanisms to accelerate paediatric trials of novel compounds/regimens.

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.

In addition to authors of particular sections (see Section 2, Methodology), UNITAID gratefully acknowledges the insights and suggestions of those who contributed to the development of this report, especially: Patrick Aylward, Miry Choi, Silas Holland, Andrew Jones, Joel Keravec, Barbara Laughon, Sana Mostaghim, Megan Paterson, Kelly Roney, Sheena Talwar, William Wells, and Prashant Yadav.

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, WHO policies and systematic reviews, corporate prospectuses, developer web sites, and 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 and others noted below (see Section 2.3).

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.

2.3. Methods to develop technology landscape

In 2012, UNITAID published a detailed TB medicines technology landscape, which reviewed current TB medicines and expected (pipeline) products currently in development. The 2012 edition of the report, prepared by Treatment Action Group with support from UNITAID, is available at: http://www.unitaid.org/resources/publications/technical-reports. Technology landscape material included in this report focuses specifically on recent changes (August 2012 to May 2013) to the TB drug pipeline, manufacturing or regulatory plans, and other new developments that may affect the TB medicines market.

Technology landscape material in Section 5.2 (including Box 2) was authored and compiled by Kelly Roney (RTI International, Research Triangle Park, NC, USA), members of the Working Group on New TB Drugs of the STOP TB Partnership www.newtbdrugs.org, and Elliot Pauli (RTI International, Research Triangle Park, NC, USA), and was supported by UNITAID. Additional assistance was provided by Doris Rouse, Anita Woodring, and Diana Severynse-Stevens (RTI International, Research Triangle Park, NC, USA). The general guidance and editorial assistance of Barbara Laughon (NIAID, NIH, Bethesda, Maryland, USA) is acknowledged. Unless otherwise noted, material in Section 5.2 of this report is current through May 2013.

Material was gathered by the authors from publicly available information, including published and unpublished reports and articles, peer-reviewed journals, regulatory websites, company websites, interviews with TB drug developers, and interviews or websites of key institutions focused on the accessibility and/or rational use of TB medicines. Information obtained from interviews that was not publicly available was confirmed by draft review with the source. Emphasis was placed on new material from 2012 to May 2013.

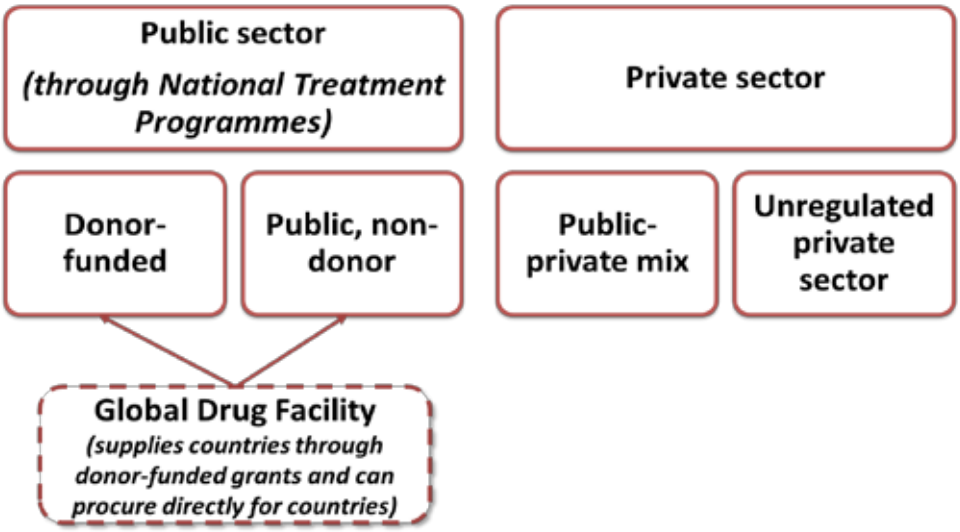
Databases searched include: clinicaltrials.gov, PubMed, European Medicines Agency (EMA), and the United States Food and Drug Administration (US FDA). The search terms for the databases included “tuberculosis,” “pediatric tuberculosis,” “tuberculosis regimen,” “new tuberculosis drug,” “delamanid,” “OPC-67683,” “gatifloxacin,” “moxifloxacin,” “rifapentine,” “bedaquiline,” “TMC207,” “AZD5874,” “linezolid,” “PA-824,” “SQ-109,” “sutezolid,” “PNU-100480,” “TBA-354,” “tuberculosis phase I,” “tuberculosis phase II,” and “tuberculosis phase III.” Additional information was obtained from references within reports or articles, peer-reviewed articles, or through interviews.

Section 5.1, Technology overview: current available medicines and treatment guidelines, was authored and compiled by Brian Kaiser and Megan Paterson for UNITAID.

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 called out in boxes (see below). Contextual material in this report was gathered from publicly available information, 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 with support from Patrick Aylward for UNITAID.

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.

Global Drug Facility (GDF): The GDF supports both donor-funded and public non-donor segments shown in Figure 1. That is, the GDF supplies quality-assured TB medicines for two channels: the donor-funded segment (i.e., for countries included in donor grants) and direct procurement for countries (i.e., for countries buying TB medicines with their own or other funds). (2) Significant excerpts of transaction-level data were provided by Thierry Cordier-Lassalle (GDF) during development 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 are from GDF annual reports 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 3 March 2013. Records for 232 transactions flagged in the PQR as "pending verification" and listed with a null quantity were excluded from the analytic dataset. The final dataset included 2720 procurements of TB medicines costing over US$ 200 million with purchase order dates from 2007–2012.

Public sector, non-donor: This analysis extrapolated data reported to WHO from 99 countries accounting for 85% of global drug-susceptible TB cases and 29% of multidrug-resistant (MDR) TB cases receiving treatment (3). For South Africa only, the analysis used actual tender data. Figures related to South Africa reflect analysis of bids *HP01-2011TB & HP01-2011TB/01, Supply and delivery of Anti-Tuberculosis Medicines to the Department of Health for Period 01 August 2011 to 31 July 2013*. (4) (5) Historical exchange rates were used, from date first contract signed: 6.8915 ZAR = 1 USD on 16 July 2011 (x-rates.com). Where relevant, it was assumed that the 2011 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 6) was derived from analysis of public data on Indian Government purchases of TB medicines in FY 2010-11. 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). (6) 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 = 1 USD (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 (7) and funded approximately three-quarters of the total value of GDF purchases of MDR-TB medicines ($63 million of $85 million). (7) 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. (6)

For analysis of transactional data, purchases in a given year were considered to reflect treatments in that same year—i.e., value estimates for 2011 reflect medicines purchased in 2011, even though an individual patient's treatment would be expected to extend beyond 2011. 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] programs or in the unregulated private sector; number of treatment regimens procured through PPM programs 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 WHO global market estimates ($300 million for all MDR-TB medicines (3)).

Box 4 is an excerpt of a summary authored by Sana Mostaghim of the Clinton Health Access Initiative.

Box 5 is an excerpt of a summary authored by Prashant Yadav of the William Davidson Institute. 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 modeling 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.

Details of analyses for specific charts and tables can be found in Appendix A.

3. Public health problem

TB is a communicable airborne disease caused by *Mycobacterium tuberculosis* (MTB) which typically affects the lungs. Transmission occurs by the inhalation of MTB from a person with an active TB infection via microscopic droplets released by coughing, speaking, or sneezing. (8) Transmission of MTB most often leads to a latent TB infection (LTBI) that is noninfectious and asymptomatic. However, approximately 5 to 10% of latently infected individuals who are human immunodeficiency virus (HIV)-negative will develop active TB during their lifetime. People living with HIV are more susceptible to TB, having an estimated 5 to 15% *annual* risk of developing active disease from latent infection. (9)

TB is a serious threat to public health worldwide, declared a global emergency by the World Health Organization (WHO) in 1993. (10) WHO estimates that about one-third of the world population has LTBI (i.e., inactive disease). (11) In 2011, 8.7 million incident cases of active TB occurred globally, and 1.4 million TB-related deaths occurred. (3) A leading cause of death among people co-infected with HIV, the burden of TB has been profoundly affected by the spread of HIV/AIDS: (11) approximately 13% of all TB cases and over 30% of all TB deaths occurred in people co-infected with HIV, and TB accounts for a quarter of all HIV-related deaths. (11) In addition, TB is among the three leading causes of death for women of reproductive age (12), killing more women than all other causes of maternal mortality combined. (13) (14)

If active TB is left untreated, or if a person has a drug-resistant strain, mortality is high and the infection can remain transmissible. (15) Treatment of drug-susceptible (DS) TB typically takes six months with first-line antibiotic TB medicines (ethambutol, isoniazid, pyrazinamide, and rifampicin). Multidrug-resistant (MDR) TB, on the other hand, is resistant to isoniazid and rifampicin and requires treatment with second-line medicines for 20 to 24 months. (8) Multidrug-resistant TB is a growing concern, with 630,000 prevalent cases estimated in 2011. (3) Approximately 9% of the MDR-TB cases also have resistance to two other classes of drugs, resulting in extensively drug-resistant (XDR) TB. XDR TB is resistant to isoniazid, rifampicin, fluoroquinolone, and at least one injectable second-line drug, leaving limited treatment options. The success rate in treating MDR TB was 48% in 2009, and far lower for XDR TB. (16)

The burden of TB is concentrated in 22 high-burden countries, which account for over 80% of cases worldwide. Most TB cases occur in middle-income countries, which accounted for almost three in four estimated cases of TB in 2011. However, TB incidence and mortality rates are highest in low-income countries: over half of all TB deaths in 2011 occurred in lower-middle-income countries, and the highest TB death rates are in low-income countries. Access to TB commodities is also unequal, with especially pronounced commodity access issues related to medicines for MDR and paediatric TB (refer to Sections 4.1 and 4.2).

4. Commodity access issues

Although treatment with a six-month course of first-line TB medicines cures almost 90% of TB cases, (3) lack of access to appropriate medicines persists. In 2011, 2.5 million people with active TB—30% of all new cases—were not treated according to WHO recommendations.[1] (3) Commodity access issues are even more pronounced in MDR and paediatric TB, as described below.

4.1. Commodity access issues related to MDR-TB medicines

Access to MDR-TB medicines is growing—but need still far outstrips demand, with the vast majority of MDR-TB cases never even being diagnosed. In 2011, fewer than one in five MDR-TB cases were appropriately diagnosed and treated. WHO reports that in 2011, only 59,549 patients (of an estimated 310,000 total) were diagnosed, and only 55,597 enrolled on second-line treatment. (3) In addition, while 19% case detection was achieved globally, variation by region is wide: from 5% in the Eastern Mediterranean region, 6% in the Western Pacific, and 7% in Southeast Asia, to 28% in Africa, 43% in Europe, and 50% in the Americas. Case detection also varies within regions, across countries. (3)

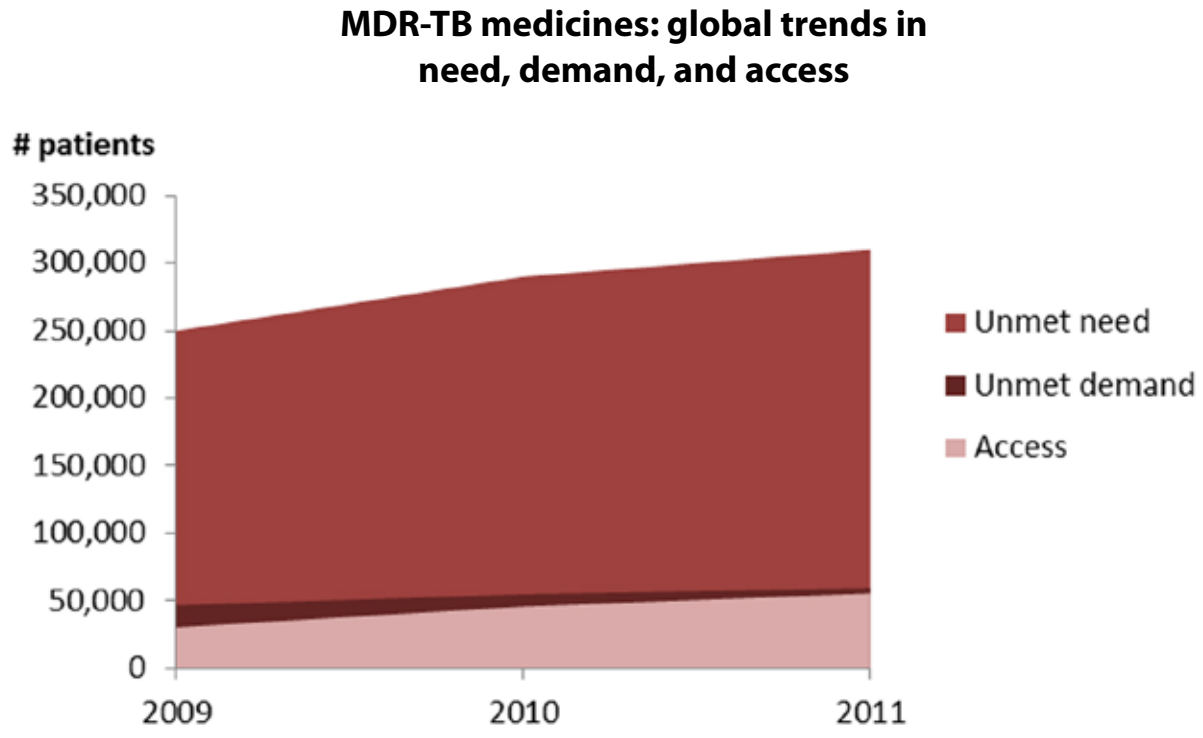
1 In 2011, WHO reported a global case detection rate of 66%; that is, approximately two-thirds of all estimated incident TB cases were diagnosed, reported to national treatment programmes, and started on treatment.

Figure 2 provides an overview of global trends in MDR-TB medicines need, demand and access—where 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.

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 were enrolled on treatment. By 2010, the market had grown to approximately 45,000 treatment courses (over 80% of notified MDR-TB cases). (3) In 2011, nearly 56,000 patients (over 90% of notified MDR-TB cases) received treatment. In contrast, forecasts for MDR-TB treatment coverage through 2015 suggest that the gap between need and access will remain significant: 63,000 patients are expected to be enrolled on treatment in 2013; 66,000 in 2014; and 70,000 in 2015—well short of targets and need. (17)

New developments could help narrow this access gap. An innovative diagnostic, the Xpert MTB/RIF assay, is the first of several in a pipeline of emerging new technologies that can diagnose TB quickly and accurately and give some indication of drug resistance. Endorsed by WHO in 2010, the Xpert MTB/RIF assay is now being rolled out on a wide scale and could increase demand for MDR-TB drugs. In parallel, 2013 sees the launch of the first novel medicines in 40 years aimed at MDR TB. (18) Future trends in MDR-TB medicines access are difficult to predict for reasons including: fragmentation of procurement, the small base of reliable data and lack of systematic demand forecasting, complexity of treatment, use of MDR-TB medicines for indications outside of TB, and 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 (Figure 7).

Figure 2. Global trends in MDR-TB medicines need, demand and access



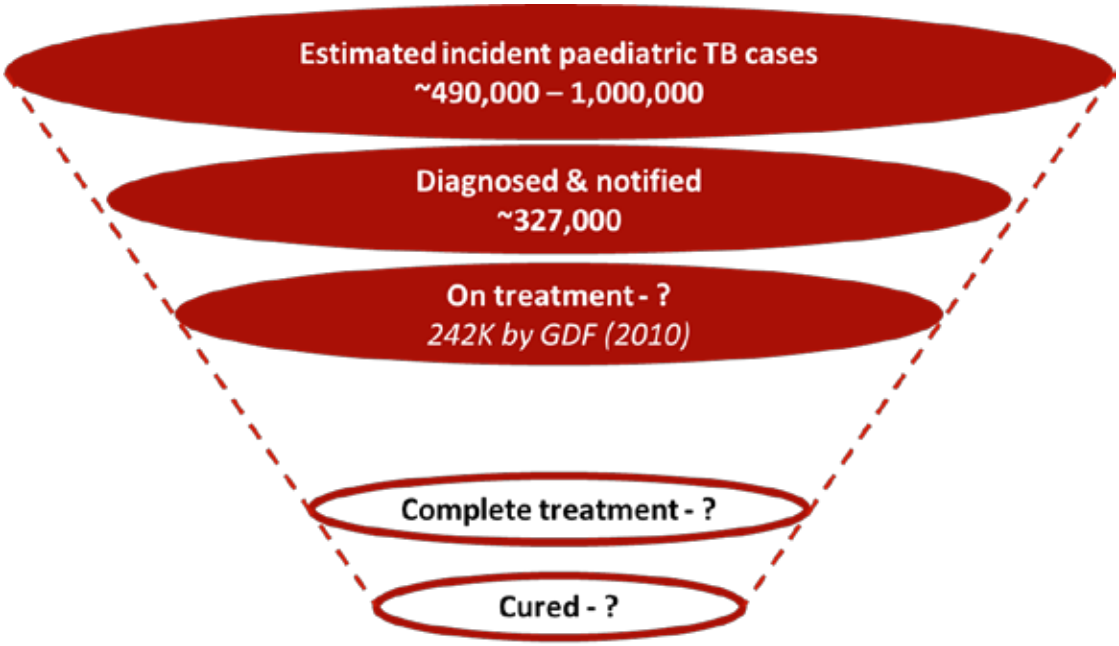
Source and notes: *Figures from the WHO Global Tuberculosis Report 2012 (3): need defined here as the number of estimated cases (among TB patients with pulmonary TB); demand, as the number of notified cases; and access, as the number of patients enrolled on treatment.*

4.2. Commodity access issues related to paediatric TB medicines

TB is one of the top 10 causes of death in children. The WHO estimates that 490,000 cases of TB occurred in children under 15 years in 2011. (3) Actual figures are likely much higher due to challenges in diagnosis; up to 1 million children may need treatment for TB each year. (3) Access to TB care is poor: only 327,000 paediatric TB cases were reported to national TB programs in 2011, (3) and surveys suggest that only half of cases are treated in some key high-burden countries. (19) Even when paediatric TB is diagnosed, there are no appropriate TB medicines with which to treat. Although WHO-prequalified fixed-dose combinations (FDCs) of the four commonly used first-line medicines exist, none is aligned with current WHO treatment guidelines for children. (20) This is due, in part, to the lack of a market incentive and barriers to market entry. Figure 3 illustrates the attrition from estimated burden of paediatric TB, through diagnosis and treatment.

For patients with MDR TB, including children, 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. However, for ethical reasons, paediatric trials generally are not started until efficacy 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). While 2013 sees the launch of the first novel TB medicines in 40 years, for MDR TB, (18) paediatric versions will be substantially later to market.

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



Sources and notes: *490,000 estimated incident TB cases in children in 2011; assumes ratio of notified to incident cases (66%) is the same for adults and children. (3) 327,000 total childhood notifications in 2011: new TB case notifications among children aged <15 years, based on countries that reported notifications disaggregated by age. GDF data from annual report. (7) There were 64,000 deaths from TB among HIV-negative children in 2011, but deaths from TB among HIV-positive children are classified as HIV-related deaths. (3)*

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 drug-sensitive 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. (21)

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] and PAS sodium); and
- Agents with unclear efficacy (e.g., clofazimine, linezolid).

The 2011 MDR-TB guidance from WHO recommends an intensive phase lasting at least eight months, and total duration of MDR-TB treatment lasting at least 20 months. (22) In addition, WHO recommends design of a second-line regimen according to the following principles:

- A fluoroquinolone should be used (strong recommendation, very low-quality evidence) (22)
- A later-generation floroquinolone is preferred to an earlier-generation floroquionolone (conditional recommendation, very low-quality evidence) (22)
- Ethionamide (or prothionamide) should be used (strong recommendation, very low-quality evidence) (22)
- 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) (22)
- 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) (22)

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 drug-susceptibility testing, previous use of TB medicines and the outcome of that treatment) and overall background resistance in the setting. (22)

Released in 2012, 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. (23) 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. (23)

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. (24) This guidance was revised in 2010 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); (20)
- Removal of streptomycin as a first-line TB medicine due to evidence of increasing resistance and unacceptable side effects; and (20)

- 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). (20) (25)

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. (26) However, the continued use of unmodified FDCs often results in sub-therapeutic doses. (20) Incorrect dosing can lead, in turn, to treatment failure in individual patients and contribute to drug resistance more generally.

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

Drug	Dose range (mg/kg)	Maximum dose (mg)
Isoniazid	10-15	300
Rifampicin	10-20	600
Pyrazinamide	30-40	2000
Ethambutol	15-25	1200

Source: *WHO Rapid Advice Treatment of TB in Children 2010, (20) Guidance on TB and HIV 2010 (25)*

5.1.4. Isoniazid preventative therapy for treatment of latent TB infection

Isoniazid preventative therapy (IPT) uses isoniazid to prevent progression of latent TB 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 six months and up to 36 months. (27) This includes pregnant women and people on antiretroviral therapy, without regard to the degree of immunosuppression. Children older than 12 months who are living with HIV, who are unlikely to have TB and who have no contact with a person with active TB disease should receive six months of IPT. (28) 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. (28) 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 has completed. (28)

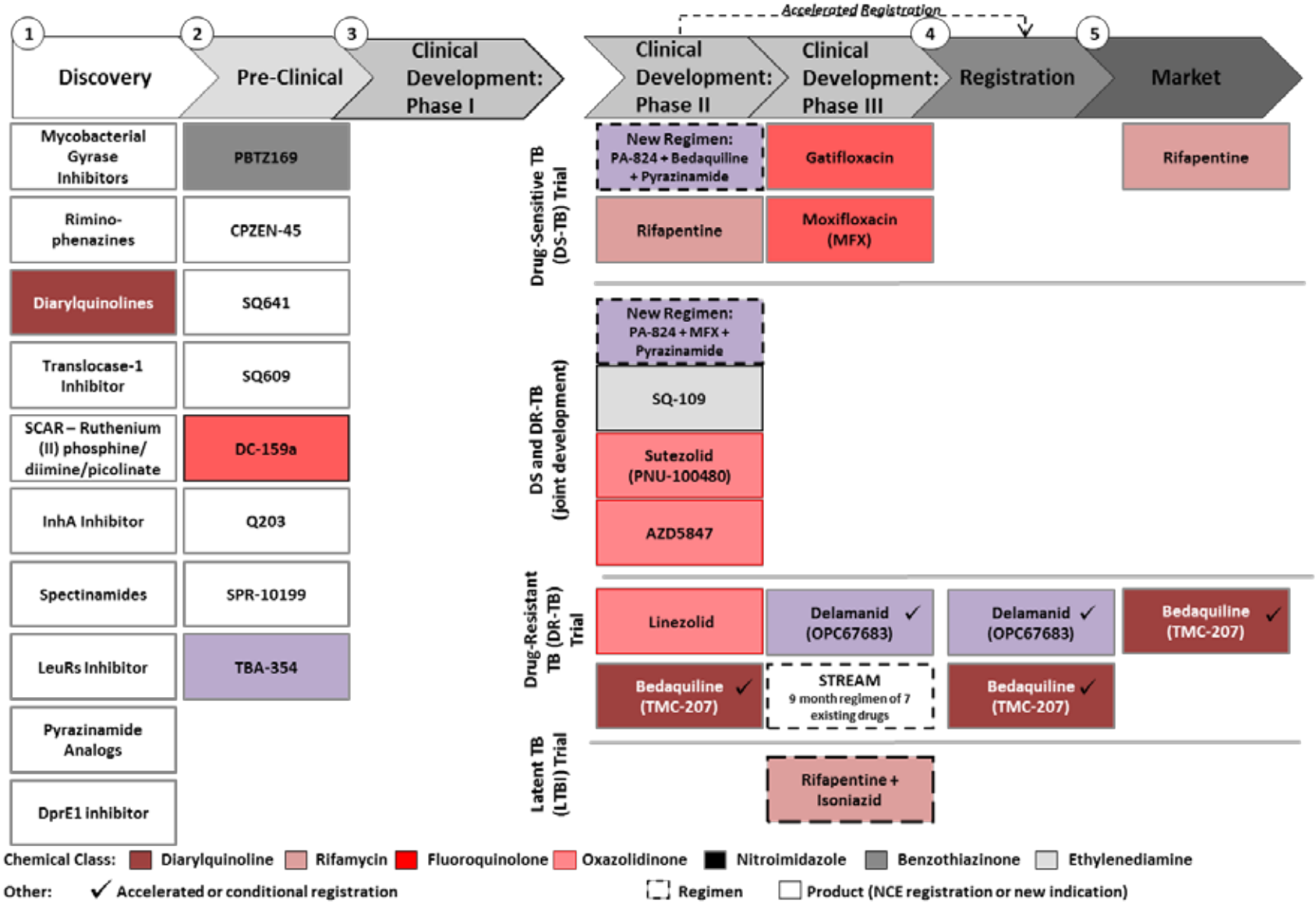
Treatment of LTBI in HIV-negative people is currently not recommended globally. A few countries have developed guidelines to treat LTBI to prevent progression to active TB, but these countries tend to have a low TB prevalence. For example, the United States Center for Disease Control and Prevention recommends nine months of isoniazid once-daily—or, in some patients, 12 weeks of isoniazid and rifapentine once-weekly via directly-observed therapy. (29)

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

The current TB medicines pipeline includes both novel drugs with a new mechanism of action and repurposed drugs that are being studied to treat latent, DS, DR, pre-XDR, and XDR TB. The current TB pipeline (Figure 4) includes five drugs for which phase III trials are currently ongoing or are planned to begin in 2013, including bedaquiline, delamanid, gatifloxacin, moxifloxacin, and rifapentine. Other studies of MDR-TB treatment-shortening regimens utilizing current drugs are ongoing. Drugs to treat TB in phase II of development (ongoing or planned) include PA-824, SQ-109, sutezolid, linezolid, and AZD5847. For a brief overview of the patent situation of a number of these compounds, see Appendix C. Additional compounds with potential to treat TB are in earlier stages of development, including TBA-354 and capreomycin in phase I, and other candidates in lead optimization or preclinical development (reviewed by Zumla *et al.*). (30)

The remainder of this section provides a brief description of the most advanced TB treatment options in development and recent key updates. Unless otherwise noted, the time period for these updates is August 2012 to May 2013.

Figure 4. Overview of TB medicines pipeline (May 2013)



Sources and notes: *Adapted from Global TB Drug Pipeline, Working Group on New TB Drugs, by Kelly Roney, RTI International, for UNITAID.*

Bedaquiline

Bedaquiline (TMC207, Sirturo™) is a novel bactericidal compound in the diarylquinoline class, developed by Janssen. Janssen has used a surrogate endpoint and phase II data to support bedaquiline regulatory submission. In December 2012, bedaquiline received accelerated US FDA approval for treatment of pulmonary MDR-TB as part of combination therapy in adults. (31) (32) (33) Janssen has filed for approval of bedaquiline for MDR-TB with regulatory authorities in Europe (file date August 2012, decision expected Q4 2013), China (file date October 2012), South Africa (file date December 2012), Thailand (file date March 2013), and India (file date May 2013). (34) (32) Janssen has licensed Pharmstandard JSC for development and commercialization of bedaquiline for MDR-TB in Russia and countries in the Commonwealth of Independent States. (35) In December 2012, South Africa's Medicines Control Council approved expanded access for bedaquiline in treatment of XDR-TB cases where other therapeutic options are not possible. (36) Janssen's risk management plan includes guidance on patient selection, use, and safety signals and centralized drug distribution via select institutions within the United States, the first launch market. (34) (37)

Janssen has granted the Global Alliance for TB Drug Development (TB Alliance) the right to develop bedaquiline for the treatment of DS-TB. The TB Alliance recently completed two phase II studies of bedaquiline in treatment-naive sputum smear-positive subjects. An additional phase II study of bedaquiline in DS-TB is ongoing.

Key updates:

- In December 2012, the US FDA approved bedaquiline for MDR-TB on the basis of phase II data, making it the first new TB medicine with a new mechanism of action in over 40 years. (38) Bedaquiline became commercially available under controlled distribution at qualified TB treatment centers in the US in April 2013. (39)
- Interim analysis of the phase II study C209, submitted as part of the US FDA regulatory package, indicated similar positive results against TB to those from completed study C208. (40)
- The US FDA-approved indication for bedaquiline includes a boxed warning, noting "An increased risk of death was seen in the SIRTURO treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%)". The note also stated that "Only use SIRTURO when an effective treatment regimen cannot otherwise be provided", and "QT prolongation can occur with SIRTURO. Use with drugs that prolong the QT interval may cause additive QT prolongation." (41) (33).
- A phase III study of bedaquiline for MDR-TB is expected to begin in Quarter 3 of 2013 as a confirmatory trial following regulatory approval. (34) The phase III trial will add bedaquiline to a standardized background regimen similar to the 9-month Bangladesh regimen. (37)
- A phase II study of early bactericidal activity of bedaquiline as part of a novel combination for the treatment of DS TB has completed enrolment, with data expected to be available in Quarter 4 of 2013 (42) (43).

Unless noted otherwise, the material in this section is current through May 2013. Box 1 has been included to describe June 2013 WHO interim guidance on the use of bedaquiline to treat MDR TB.

Box 1. June 2013 WHO interim guidance on the use of bedaquiline to treat MDR TB

In June 2013, WHO issued interim guidance on the use of bedaquiline to treat MDR TB, noting:

"There has … been considerable interest in the potential of this drug to treat MDR-TB. However, information about this new drug remains limited and it has only been tested for safety and efficacy in two phase IIb trials. WHO has therefore issued interim policy guidance.

This interim guidance provides advice on the inclusion of bedaquiline in combination therapies for MDR-TB in accordance with the existing WHO Guidelines for the Programmatic Management of Drug-resistant TB (2011 Update).

The interim guidance lists five conditions that must be in place if bedaquiline is used to treat adults with MDR-TB:

1. ***Effective treatment and monitoring:*** *Treatment must be closely monitored for effectiveness and safety, using sound treatment and management protocols approved by relevant national authorities.*

2. ***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.*

3. ***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.*

4. ***Adherence to WHO recommendations:*** *All principles on which WHO-recommended MDR-TB treatment regimens are based, must be followed, particularly the inclusion of 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.*

5. ***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.*

WHO strongly recommends the acceleration of phase III trials to generate a more comprehensive evidence base to inform future policy on bedaquiline."

Delamanid

Delamanid (OPC-67683), a member of the nitroimidazole class, is a novel TB medicine that has been filed for initial regulatory approval. Delamanid is being developed by Otsuka Pharmaceutical Development & Commercialization, Inc. (Otsuka). (44)

Otsuka has completed three phase II clinical trials for delamanid and is sponsoring one ongoing phase III clinical trial. (45) In addition, Otsuka is in discussion with the National Institute of Allergy and Infectious Diseases (NIAID) to assess a study of the drug-drug interaction of delamanid with the recently approved drug bedaquiline. (44) This trial could inform the possibility of using both delamanid and bedaquiline as part of a new regimen.

Otsuka filed a Marketing Authorization Application with EMA in December 2011 for regulatory approval of delamanid as a treatment for pulmonary MDR-TB in combination with an optimized background regimen. (44) Otsuka announced in March 2013 that they filed for regulatory approval of delamanid in Japan, and have received orphan designation by the Japanese Ministry of Health, Labour, and Welfare. (46)

On 25 July 2013, the EMA's Committee for Medicinal Products for Human Use (CHMP) issued a negative opinion, recommending that EMA refuse marketing authorization. Concerns cited by the CHMP included insufficient data to demonstrate benefit and determine appropriate dose at this time. (47) A phase III trial is now enrolling.

Key updates:

- Otsuka applied for regulatory approval of delamanid for pulmonary MDR-TB in March 2013 in Japan and received orphan status. (46) The EMA's CHMP issued a negative opinion on delamanid in July 2013, recommending that EMA refuse marketing authorization. (47) Otsuka plans to file for regulatory approval with the US FDA in 2014. (44)
- Results of a phase II trial extension demonstrate that patients who received delamanid for more than six months have a more favorable outcome that those receiving less than two months of delamanid. (48) As of May 2013, enrolment into the phase III study was nearly 50% complete (44).
- Drug-drug (DD) interaction studies with HIV drugs efavirenz, tenofovir, and lopinavir/ritonavir suggest no clinically relevant impact on antiretroviral drugs. (49) (50) Assessment of a study to investigate the DD interaction between delamanid and bedaquiline is in discussion with the company sponsors and NIAID for 2013.

Gatifloxacin

Gatifloxacin is a later-generation fluoroquinolone that demonstrated increased sterilizing activity over ethambutol in a phase II study of patients with newly diagnosed TB, suggesting potential to shorten treatment. (51)

Gatifloxacin is under study in the OFLoxacin-containing TUBerculosis regimen (OFLOTUB) study, a phase III, randomized, open-label, multicenter, controlled trial in DS-TB adult patients sponsored by WHO TDR, *Institut de Recherche pour le Developpement* (IRD) and collaborators: UNICEF, World Bank, and European Commission. (52) The OFLOTUB study will compare the efficacy and safety of a four-month regimen containing gatifloxacin and standard regimen (isoniazid, rifampicin, and pyrazinamide) to a standard six-month regimen (ethambutol, isoniazid, rifampicin, and pyrazinamide). (53) This study completed enrolment in 2008; however, because of difficulties with the clinical database and funding, results of trial analysis have been delayed. (54) (55)

During the course of the study, gatifloxacin received a boxed warning label from the US FDA due to reported disturbances of blood glucose (dysglycemia) in older adults. Bristol-Myers Squibb ceased manufacturing and sales of gatifloxacin in 2006, (56) and gatifloxacin for oral administration has been withdrawn from most commercial markets because of dysglycemia concerns. The TDR team modified the OFLOTUB protocol to include monitoring of dysglycemic events, and initial analysis shows few events of this type across the study arms. (54) Contributions from the TB Alliance and the University of Oxford have helped fund final analysis of the study, and results are now expected in late 2013. (54)

Key updates:

- OFLOTUB study data are in final analysis by the WHO TDR, which reports high patient retention over the 24-month follow-up period. Study results, potentially demonstrating that the substitution of gatifloxacin for ethambutol in the standard treatment for four months will achieve similar cure rates to the standard six-month treatment of DS-TB, are expected to be released publicly in October-November 2013. (54)
- Although gatifloxacin is no longer on the market for TB treatment, favourable results and the limited toxicities noted in OFLOTUB study may increase interest in further review of safety data. (54)
- Open-label studies of shortened (9- or 12-month) treatment regimens for DR-TB that include gatifloxacin have demonstrated efficacy and may provide data to support use of a shorter, standardized regimen for the treatment of MDR TB.

Moxifloxacin

Moxifloxacin is one of the fluoroquinolones recommended by WHO as part of second-line treatment, but does not have regulatory approval for treatment of TB. (55) Moxifloxacin is being evaluated in multiple phase I and phase II studies for TB treatment, including many evaluating the potential of moxifloxacin as part of a treatment-shortening regimen. The TB Alliance, in collaboration with Bayer, Medical Research Council, University College of London, and the European and Developing Countries Clinical Trials Partnership is currently conducting a phase III study, REMoxTB (Rapid Evaluation of Moxifloxacin), exploring two potential treatment-shortening regimens that contain moxifloxacin.

Key updates:

- The REMox phase III study has completed enrolment and final analysis is expected by the first quarter of 2014. (57) If positive results demonstrating that moxifloxacin is safe and effective are obtained from the study, regulatory filing for DS TB is planned for 2014. (57)
- The STREAM study evaluating moxifloxacin as part of a shortened regimen to treat MDR TB is ongoing, with a total of 70 patients out of 400 randomized and completion of the study and results expected by Q4 of 2016. (58)
- In addition, development of novel drug PA-824 by the TB Alliance includes studies in combination with moxifloxacin. For example, phase II study NC-002 will examine the combination PA-824, moxifloxacin, and pyrazinamide (PaMZ) in subjects with both DS-TB and MDR-TB. (59) Enrolment in the study is complete, with results expected in 2013. (57) If results from NC-002 are positive, the TB Alliance is planning for a large, multinational phase III study to begin in 2014, (57) and subsequent registration of PA-824 in combination with pyrazinamide and moxifloxacin for the treatment of TB. (43)

From drugs to regimens, and from regimens to treatment delivery packages

Although the sections above have discussed drugs individually, TB treatment requires multidrug regimens. Some of the trials described have, indeed, tested regimens, so the options for national programs to consider would be clear. However, without further trials, it will be difficult to know how to use the new MDR-TB medicines—e.g., whether a new product can replace an injectable agent, or reduce the time of treatment. Only further trials will yield these answers. Until then, uncertainty may reduce market volumes for new medicines.

Meanwhile, with several new potential first-line treatments in phase II or III trials (e.g., OFLOTUB, REMoxTB, and PaMZ), there has been increased interest in how new diagnostics and drugs can be best combined. Ideally, the most critical drug susceptibility testing (DST) methods would be available when a new regimen is launched (60)—i.e., a package of new technologies that address both the diagnostic and treatment needs of the patient population.

Shortened regimens for the treatment of MDR-TB

An observational, nonrandomized study conducted in Bangladesh, conducted by the Damien Foundation, demonstrated superior efficacy of a nine-month standardized regimen of high-dose gatifloxacin, clofazimine, ethambutol, and pyrazinamide plus prothionamide, kanamycin, and high-dose isoniazid for the first four months of treatment, compared to longer regimens with ofloxacin in patients with MDR TB. (61) Additional data reported at the IUATLD 2012 meeting in Kuala Lumpur confirmed that the nine-month regimen provided a long-term cure of at least 12 months in 88% of patients (n=410), and a long-term cure of five to six years in 77% of patients (n = 101). (62) This study has generated much interest in the field, as treatment shortening could reduce drug costs, requirements for health care visits, and adverse drug reactions.

A similar observational study, ongoing in Cameroon, demonstrated similar results in MDR-TB patients treated with gatifloxacin, prothionamide, clofazimine, ethambutol, and pyrazinamide for 12 months plus kanamycin and isoniazid for the first four months of treatment. As of late 2012, a total of 105 of 126 patients were considered cured at the end of treatment. (63)

The STREAM study, sponsored by The International Union against Tuberculosis and Lung Disease (IUATLD) with United States Agency for International Development (USAID) as the primary donor, is a randomized study that will further evaluate the potential of a standardized shortened regimen to treat MDR TB. (64) The STREAM study includes a modified regimen similar to that used in the study in Bangladesh: moxifloxacin, clofazimine, ethambutol, pyrazinamide, plus prothionamide, kanamycin and isoniazid for first four months, given as directly observed therapy. (64) Moxifloxacin was used instead of gatifloxacin due to difficulties obtaining gatifloxacin. (58) A total of 70 patients out of the targeted 400 have been enrolled and randomized into the study, with enrolment expected to complete in the third quarter of 2014 and completion of the 27-month follow-up of all subjects and results expected by Q4 of 2016. (58) Potential expansion of the STREAM trial to include an additional study regimen arm is being explored. Unlike the study that took place in Bangladesh, the STREAM study is randomized instead of observational, and multicenter, which should provide more robust data on the efficacy of a shortened regimen. Additionally, the greater HIV prevalence in the countries where STREAM is taking place could provide data on use of shortened regimens in conjunction with antiretroviral therapy.

Rifapentine

Rifapentine is a long-acting rifamycin, approved for use in the United States for treatment of pulmonary TB in combination with other TB drugs since 1998. (65) Rifampicin, a main component for standard therapy of TB, is also a rifamycin, as is rifabutin. Studies of rifapentine in mice have demonstrated an improved pharmacokinetic profile, increased anti-TB activity, and the potential to shorten treatment duration compared to rifampicin. (66) Rifapentine is currently being investigated as a potential treatment-shortening agent for LTBI and DS TB. (55)

Key Updates:

- The RIFAQUIN trial results show that a six-month regimen of once weekly rifapentine (1200 mg) and moxifloxacin in the continuation phase was noninferior to standard therapy (67). This study demonstrates that a high dose of rifapentine was safe and effective.
- Rifapentine (10 mg/kg) has similar efficacy to rifabutin when both are given at 10 mg/kg in the intensive phase in combination with a standard background regimen (68).
- The ongoing Tuberculosis Trials Consortium study 33 is comparing adherence to LTBI treatment of 12 weeks of once weekly rifapentine and isoniazid as directly observed therapy, self-administered therapy, or self-administered therapy combined with a text message reminder (69).

By the end of 2013, using data from the PREVENT TB trial, Sanofi plans to file a supplemental New Drug Application in the United States for approval of their existing formulation of rifapentine for the indication of latent TB. (70)

Summary of technologies in development

Despite promising developments in the TB medicines landscape, access to appropriate medicines remains poor—with many access issues traceable to market shortcomings. Supply of MDR-TB medicines in particular remains a problem for many countries, including low- and lower-middle-income countries. Since many of these drugs (except the fluoroquinolones) are manufactured specifically for TB, the market is limited. Box 2 reviews the relevance of some of the key updates described in this section to TB medicines market access. Section 6 characterizes the market for TB medicines and details specific challenges related to market dynamics.

Box 2. Applying lessons from recent development updates to market challenges for TB medicines

The *UNITAID 2012 Tuberculosis Medicines Technology Landscape* highlighted key market shortcomings included inadequate access to quality medicines and inadequate investment in new TB medications. (55) Contributing factors include poor market forecasting, unclear regulatory environments, and challenges in medicine procurement and distribution in both public and private sectors. These market shortcomings persist in 2013. However, recent development updates also reveal new potential approaches to accelerated market access and appropriate use of TB medicines.

For example, innovative phase II study design such as the MAMS-TB-01 trial in South Africa and Tanzania allows for comparison of four experimental regimens to standard therapy, and discontinuation of ineffective regimens at interim points in the study. This approach could accelerate the lengthy process of selecting combinations and dosages. Such adaptive study design is likely to improve regimen evaluations and inform design of large phase III efficacy trials. (71) Other recent approaches include: Janssen's use of a surrogate endpoint and phase II data to support bedaquiline regulatory submission; Janssen's risk management plan for bedaquiline including controlled distribution and guidance on patient selection, use, and safety; and Otsuka's expected launch of a diagnostic resistance test to guide appropriate use of delamanid. (44)

Source: *Kelly Roney, RTI International, report for UNITAID*

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 2011, of an estimated 8.7 million new cases of TB, only two-thirds were diagnosed, notified to national TB control programs and reported to WHO. (3) Access to appropriate diagnostics and TB medicines is significantly lower in people with multidrug resistant (MDR) TB: only 19% of MDR-TB cases were diagnosed and notified in 2011, and even fewer received appropriate treatment. (3) Similarly, TB in children is significantly underdiagnosed and undertreated. Although reporting is incomplete, WHO estimates that of 490,000 cases of paediatric TB in 2011, only 327,000 were notified. (3) Poorly adapted diagnostics mean that many cases of TB in children go undetected: up to 1 million children may need treatment for TB each year. (72) (73) In addition, no appropriately-dosed, quality-assured, paediatric formulations of TB medicines exist, so even those children who do receive treatment often take TB medicines intended for adults (e.g., split or crushed tablets). (19)

The total volume of the TB medicines market in 2011 (public-sector only), based on reporting to WHO, (3) comprised approximately:

- 6.2 million courses of first-line treatment of TB in adults;[2] and
- 55,597 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. (1)

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, the GDF procured 242,490 courses of paediatric TB treatment in 2010 (74) and 187,996 courses in 2011 (7) with donor funding, but this procurement mechanism is thought to reach only one in five children with TB. The remainder are either untreated, or treated with adult medicines (e.g., crushed or split tablets). (19)

Value estimates

For the 2013-15 period, an estimated $1 billion per year will be needed for TB care and control in lower-middle-income countries; this figure excludes funding needed for services related to TB/HIV co-infection. This is roughly twice the amount of current funding levels, but still much less than donor funding for malaria ($2 billion in 2010) or HIV ($6.9 billion in 2010). (3) However, TB medicines represent only a fraction of overall costs. (3)

The total value of the TB medicines market in 2011 (public and private sectors), based on a model created by UNITAID, is estimated to be approximately $700m, including:

- $430 million for first-line treatment of TB in adults; and
- $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 the value of treatments for TB in children, due to lack of data. While the GDF procured paediatric TB treatments worth $2,715,829 in 2010, (74) the total market is uncertain. However, if up to 1 million children need TB treatment annually, and assuming an average first-line regimen costs roughly $30, the potential market for paediatric TB medicines could be up to $30 million. With these assumptions, but only 327,000 cases of paediatric TB reported to national TB programs **in 2011, the actual value of all paediatric TB medicines was probably less than $10 million**.

2 Based on global case detection rate reported in the WHO Global TB Report 2012: an approximate indication of the proportion of all incident TB cases that are diagnosed, reported to national treatment programmes, and started on treatment.

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, the GDF supplies quality-assured TB medicines for both the donor-funded segment (i.e., for countries included in donor grants) and direct procurement for countries. The GDF not only represents an important mechanism for supply of TB medicines, but also provides technical assistance, supply chain management, and other services. Nevertheless, GDF is only one of many critical stakeholders that buy TB medicines. (2) Indeed, in 2010, 13 of 22 high-burden countries reported procuring domestically manufactured first-line TB medicines. (75)

Provision of TB medicines in the private sector is thought to be significant, especially in high-burden countries such as Pakistan, India, Indonesia, Philippines (and China, in terms of absolute number of patients). (1) **However, visibility on the private-sector market segment is poor**: private-sector market size, treatment patterns and other dynamics have been examined in ten 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. (1) (75) Figure 5 and Figure 6 show the estimated value of the global markets for TB and MDR-TB medicines in 2011 (unless specified otherwise), based on the best available data, with a breakdown by procurement channel.

Figure 5. Value of the 2011 first-line TB medicines market, by procurement channel

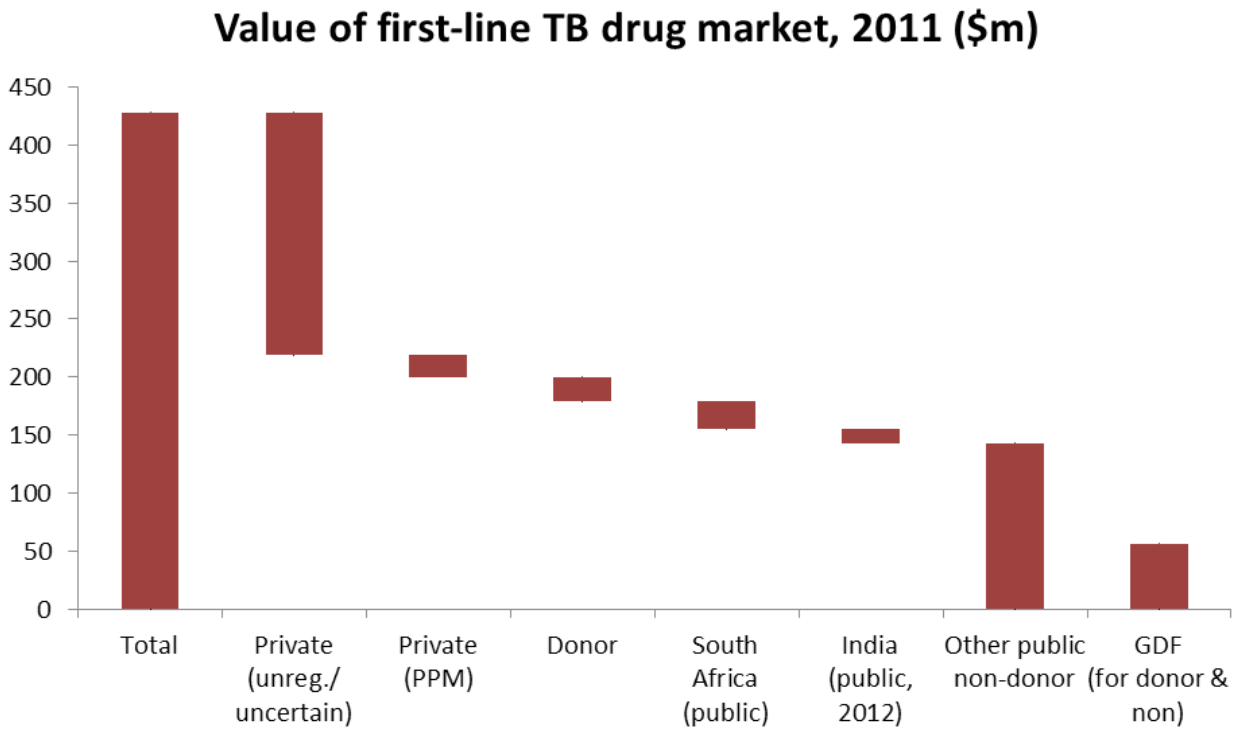
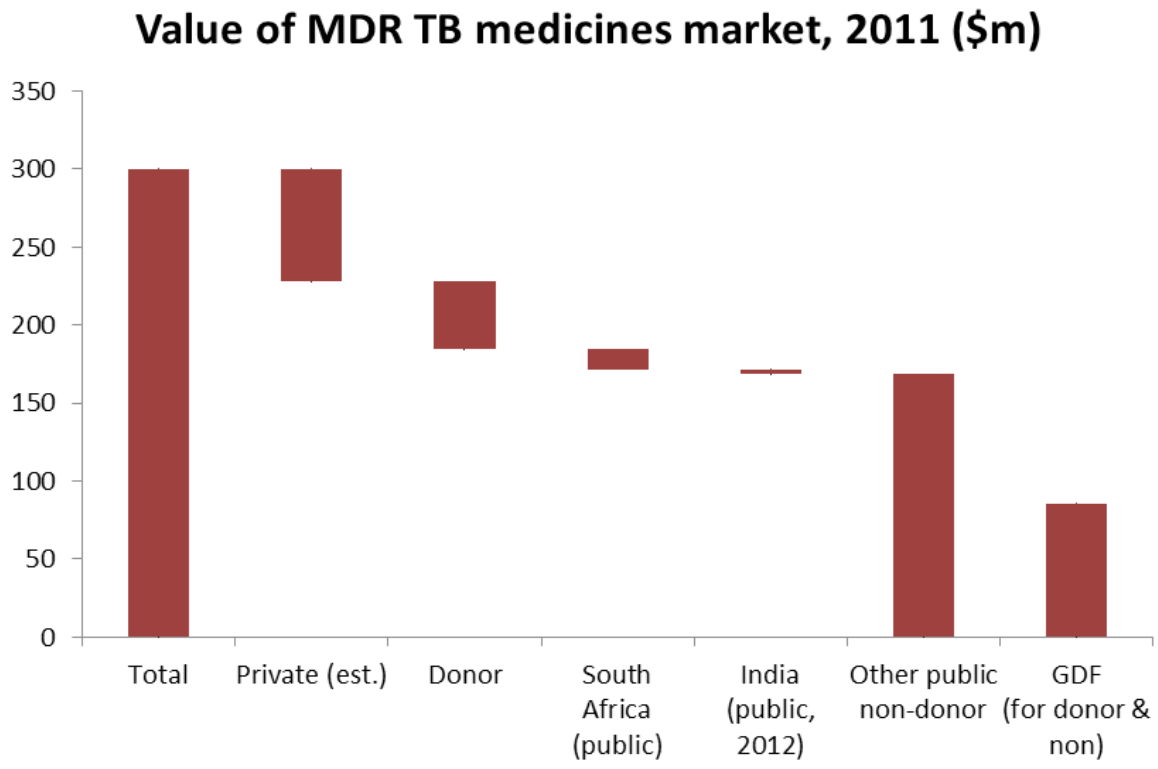


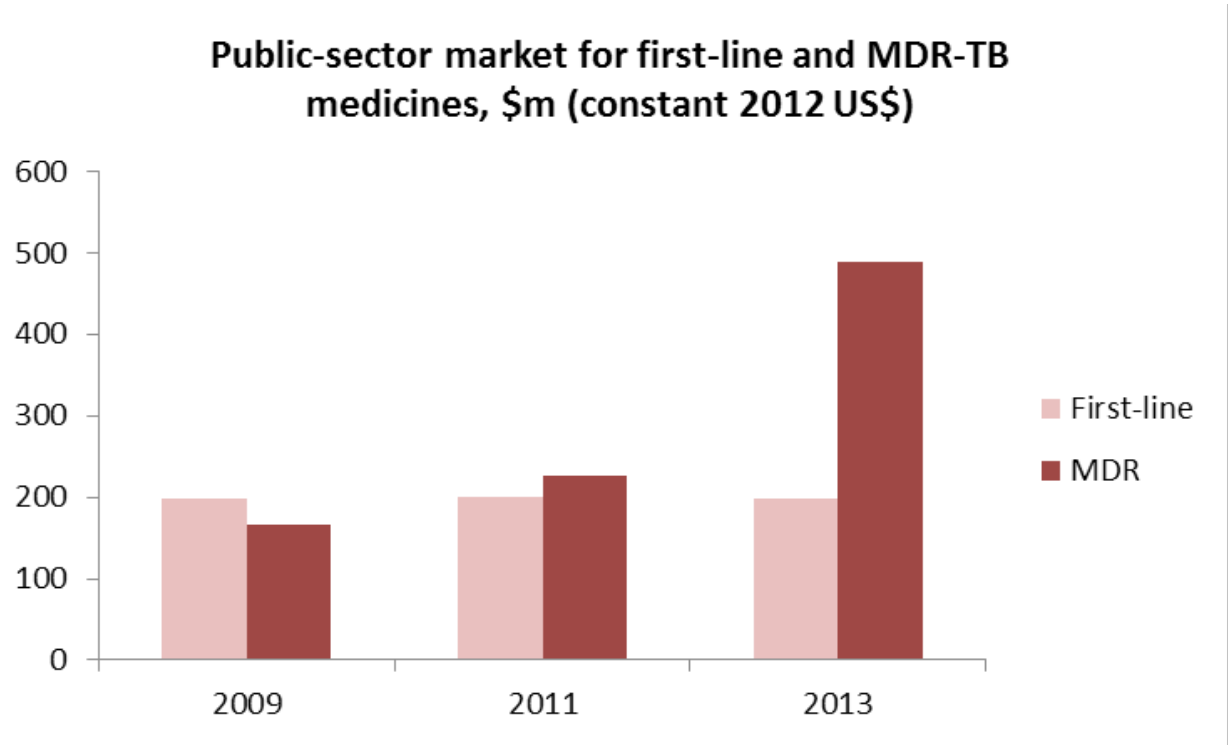
Figure 6. Value of the 2011 MDR-TB medicines market, by procurement channel



Notes: *Total market approximated from build-up of various procurement channels, as described in Appendix A.*

While the market for first-line TB medicines is relatively stable, analysis of public-sector procurement projections suggest high potential for growth in the MDR-TB medicines market. Figure 7 illustrates directional trends in the value of public-sector procurement of first- and second-line TB medicines.

Figure 7. Value of TB medicines procured in the public sector, projected trends from 2009-2013



Sources and notes: *Based on interpretation of data reported to WHO; (3) actual tender data from South Africa; (4) (5) and estimates based on number of cases. See Appendix A for additional detail. MDR-TB market trends in particular should be interpreted as directional only, and with caution, due to the high price and price variation for MDR-TB regimens; small base of reported data; and reliance on extrapolation.*

6.2. Market for first-line TB medicines to treat drug-susceptible 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. Over 6 million first-line TB treatment courses are required for treatment delivered through the public sector alone.[3] As shown in Figure 5, the global market for first-line TB medicines is estimated to be approximately $430 million, with minimal change between 2009 and 2013. First-line TB medicines include isoniazid, rifampicin, pyrazinamide, ethambutol; two-, three- and four-component FDCs of these drugs; and injectable streptomycin (used for retreatment patients). A standard regimen of quality-assured first-line treatment, comprising two months of daily isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by four months of daily isoniazid and rifampicin, costs roughly $20-$40. (76) (3)

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 5). Indeed, a recent publication on the role of the GDF suggests that changes in market share may reflect increased provision of first-line TB medicines by national governments' own public-sector programmes. (2) However, there is wide variation in levels of domestic funding. In Brazil, Russia, South Africa and China, nearly all (>95%) funding for TB care and control is from domestic sources.[4] Outside Brazil, Russia, 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, (7) 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 28-41% of the total between 2006 and 2013. In Afghanistan, Bangladesh, the Democratic Republic of the Congo, Ethiopia and Myanmar—high-burden countries that are also low-income—over 70% of TB funding is expected to be supplied by donors in 2013. (3)

Overall, procurement of public- and donor-funded first-line TB medicines is estimated to be approximately $200 million, or nearly half of the total market in 2011 (Figure 5). Of this, about 90% ($180 million) reflects public (non-donor-funded) first-line TB medicines procurement. For example, the South African Government plans to spend nearly $50 million, on at least 1.5 million first-line TB treatment courses, over two years.[5] (4) (5) Indian Government purchases include over 1 million first-line TB treatment courses in one year.[6] (6) Analysis of PQR data shows Global Fund procurement of first-line TB medicines worth $18 million in 2011. With the Global Fund responsible for 88% of all donor funding, (3) this suggests donor-funded procurement of first-line TB medicines totalled at least $21 million in 2011.

The GDF reported 2011 procurement of first-line TB medicines worth nearly $57 million. (7) A recent 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. (2)

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 $230 million in 2011 (Figure 5). (1) 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 recent study of first-line TB medicines isoniazid and rifampicin showed that over 9% of all private-sector TB drugs tested were of substandard quality. (77) (Refer to Box 3 for further detail.) 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

3 Based on global case detection rate reported in the WHO Global TB Report 2012 (2): an approximate indication of the proportion of all incident TB cases that are diagnosed, reported to national treatment programmes, and started on treatment

4 Funding for overall TB care and control, including provision and delivery of appropriate first-line medicines. Estimated public spending on first-line drugs only is shown in Figure 7.

5 Based on analysis of tender data for the period 1 August 2011 to 31 July 2013

6 Based on analysis of tender data for the period 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

programme standards, are still limited in scope in many countries, accounting only a fraction of the estimated private market for first-line TB medicines (Figure 5). (75) More work is needed to improve visibility on private-sector market dynamics, particularly in the unregulated private segment.

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**. Refer to Box 3 and Box 4 for further detail.

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 $22 from the GDF (76) (3), $23-$32 through South African Government tenders7 (4) (5), and $11 through Indian Government tenders.8 (6) Average costs reported to WHO are up to $40 for low- and lower-middle income countries, and $50 for upper-middle-income countries. Prices can vary partly due to costs such as freight, inspection, agent fees and insurance. (3) According to WHO, low- and lower middle-income countries report an average cost of up to $40, and upper middle-income countries report an average cost of $50.

Fixed-dose combinations

Public sector programs in all but one of the high-burden countries use FDC medicines to treat TB. (75) 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). (21) 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. The GDF promotes standardized patient treatment through use of FDCs and patient kits. GDF reports that two- and four-component fixed-dose combination products accounted for over 60% (by value) of first-line TB medicines procured by GDF in 2011. (7) Analysis of South African Government procurement shows a similar preference for FDCs, with 73% FDC vs. 27% loose pills (by value) for contracts awarded for the period 1 August 2011 to 31 July 2013. (4) (5)

Competition

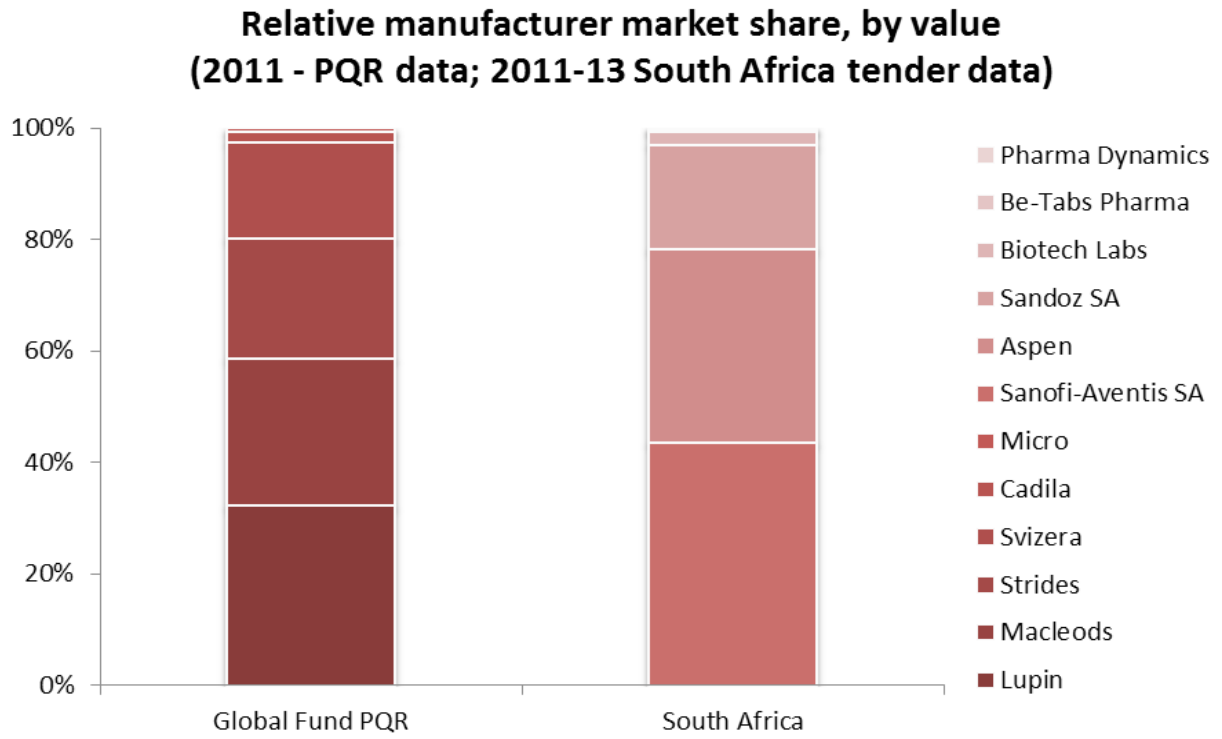
Manufacturer market share is concentrated, with different manufacturers meeting demand from various procurers. Four manufacturers—Lupin, Macleods, Strides, and Svizera—account for over 97% of 2011 first-line TB medicines purchases reported in the Global Fund PQR (used as a proxy for donor-funded procurement). Three manufacturers—Sanofi-Aventis South Africa, Aspen, and Sandoz—account for 97% of first-line TB medicines contracts awarded by the South African Government for the period 1 August 2011 to 31 July 2013. Notably, there is no apparent overlap in manufacturers serving the donor-funded and South African Government markets (refer to Figure 8).

For procurement of first-line TB medicines, the Indian Government awarded contracts almost exclusively to Sandoz in 2010-11 (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 2012-13 (100% market share, by value). The switch from Sandoz to Lupin may have been driven by price. Sandoz won the 2010-11 contracts with bid prices of 6% less than Lupin's. However, by 2012-13, Sandoz bid prices had increased sharply, exceeding Lupin's by 7-9%. Contracts in 2012-13 were awarded to Lupin. Refer to Figure 9.

7 delivered price; equivalent to $20-$28 (excluding 14% VAT). Based on analysis of contracts awarded by the South African government for the period 1 August 2011 to 31 July 2013, for a standard first-line regimen with 2- and 4-component fixed-dose combination products.

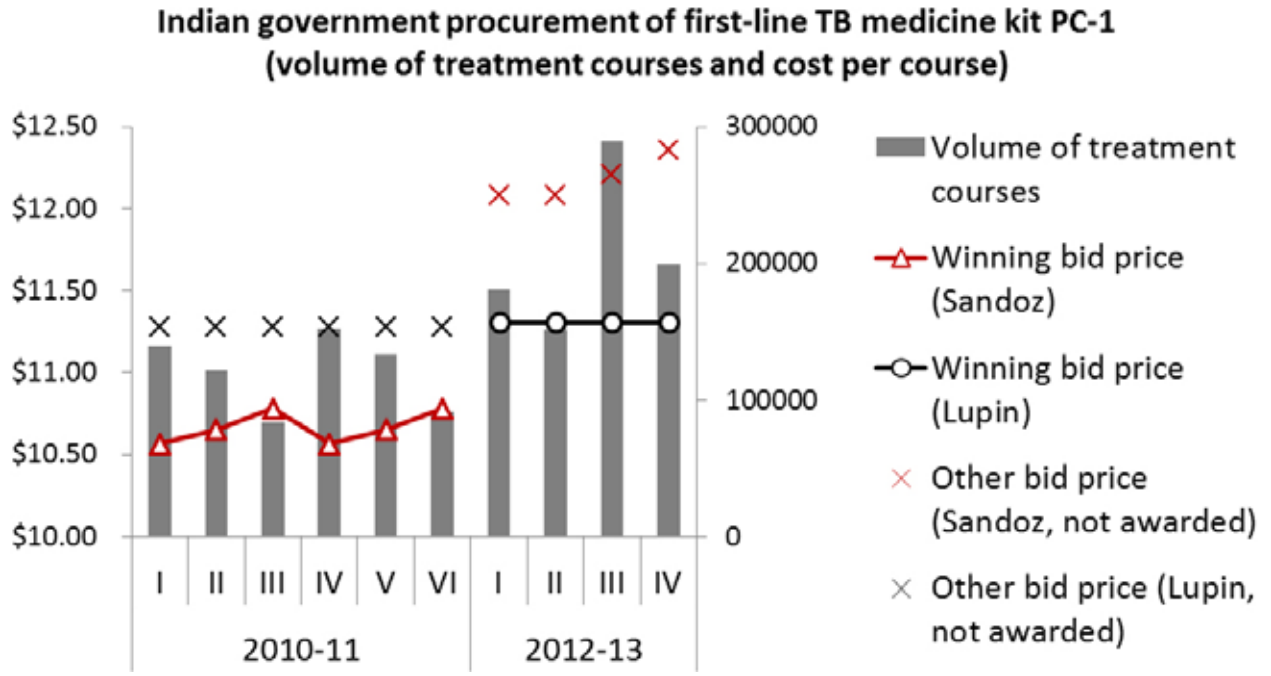
8 Price excludes 5% VAT and sales tax. Based on analysis of Indian government purchases of first-line TB medicines from 1 April 2012 to 31 March 2013, for patient kits of multi-blistered tablets. Procurement through RITES with Indian government funds, including World Bank loans. Excludes GDF procurement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

Figure 8. Relative market share of first-line TB medicines manufacturer, by value, Global Fund vs. South African Government procurement



Sources and notes: Global Fund PQR: *UNITAID analysis of the Global Fund's PQR database, 2011 transactions, excluding those pending verification.* **South Africa:** *Analysis of Bid HP01-2011TB (4) & HP01-2011TB/01 (5), Supply and delivery of Anti-Tuberculosis Medicines to the Department of Health for Period 01 August 2011 to 31 July 2013. Used exchange rate as of 16 July 2011 (date first contract signed): 6.8915 ZAR = 1 USD (x-rates.com).*

Figure 9. Indian Government procurement of first-line TB medicine kit, contract volume and prices



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 = 1 USD (x-rates.com). Unit prices shown exclude 5% VAT and sales tax. (6)*

Quality assurance of first-line TB medicines can vary by product and manufacture (refer to Box 3). Appendix B, 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 quality assured by WHO Prequalification, a stringent regulatory authority, or the Expert Review Panel (ERP) hosted by WHO on behalf of the Global Fund.

Recent shortages have threatened supply of isoniazid in some countries (e.g., India, United States). (78) 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 multidrug-resistant (MDR) TB

6.3.1. Introduction

The MDR-TB medicines market segment is small and fragmented. From a manufacturer perspective, market potential is low: although quality-assured MDR-TB medicines are much more expensive than those used for first-line treatment ($4,000-6,000 vs. $22 per regimen), (76) and treatment duration is longer (20-24 vs. 6 months), (21) (79) volumes are extremely low. In 2011, only 55,597 patients were enrolled on second-line treatment (80)—fewer than 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 less than 4% of the total.[9] This small market is further fragmented by many procurement channels (described below) and a wide range of complex treatment regimens, in which various products and formulations are combined.

2011 WHO guidance outlines principles of MDR-TB treatment. (79)[10] In practice, however, standardization of treatment is minimal. A recent survey of Chinese hospitals found widespread variation in TB treatment, including 19 different regimens for MDR TB. (81) GDF reports 18 different leading regimens across 18 countries, again pointing to limited potential to consolidate demand. (7)

6.3.2. Buyers of MDR-TB medicines

In 2011, national governments were significant purchasers of MDR-TB drugs, as shown in Figure 6. WHO data suggest that, overall, national treatment programmes account for about three-quarters of all spending (by value) on MDR-TB drugs and management. [11] (3) 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[12] and are actively scaling up care for MDR TB. Indeed, just three of these countries—India, China, and the Russian Federation—accounted for almost 60% of the estimated 310,000 MDR-TB cases in 2011. (3) Tender data show that, for the period 1 August 2011 to 31 July 2013, the South African Government alone procured $25.5 million of MDR-TB medicines. Donors also play a critical role in the procurement of MDR-TB medicines: in 2011, the GDF reported procurement of over $82 million of grant-funded MDR-TB medicines, including $63 million for the Global Fund and $16 million for UNITAID.[13] A recent publication estimated that GDF procurement, for both donor-funded and public non-donor segments, accounts for 31.7% of all reported MDR-TB cases, or 4.2% of estimated cases (by volume). (2) 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). (2)

Provision of medicines in the private sector is thought to be less significant for MDR TB than for drug-sensitive TB, with many MDR-TB drugs and even some drug classes not available. (76) 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 (including hospitalization for the duration of treatment in some countries), the private sector may refer MDR-TB patients back to the public sector. A study using 2006 data estimated the value of medicines purchased for MDR-TB in five countries to be $37 million, but these estimates are plagued by uncertainty about the percentages of these drugs being used for other indications. (82) 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 3 and Appendix B, Table A 2 for further detail.

9 i.e., 310,000 estimated cases of MDR-TB / 8,700,000 estimated cases of DS-TB in 2011. (2)

10 an intensive phase, lasting at least 8 months, should include four MDR-TB medicines, including an injectable; treatment should include pyrazinamide, a fluoroquinolone (preferably later-generation), ethionamide or prothionamide, cycloserine or PAS; total duration should be at least 20 months (WHO 2011 MDR treatment guidelines)

11 Funding for 'TB care and control' includes spending on both drugs and programmatic aspects of MDR TB

12 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. (2)

13 This exceeds the value of donor-funded segment estimated from PQR data in Figure 2 ($39 million Global Fund, $44 million all donors), likely due to reporting differences. It should also be noted that the GDF 2010 annual report shows direct purchase of SLDs far outpacing grant purchases of SLDs (41.2 million vs. 15.9 million in 2010), as countries transitioned from grants to Global Fund or other sources of funding.

Box 3. Quality assurance of TB medicines

Quality of medicines can be regulated by bodies including National Drug Regulatory Authorities or 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. (83) 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 Food & Drug Administration (US FDA) or European Medicines Agency (EMA).[14] 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.[15] (84) (85) Likewise, the Global Drug Facility procures only quality-assured medicines—e.g., approved by WHO PQ, a stringent regulatory authority, or ERP. Despite these requirements, quality-assured MDR-TB medicines are thought to make up only 13% of the total market. (86) National governments procuring medicines often require local regulatory approval, for which requirements and stringency vary by country. TB medicines purchased through the private sector are often of variable or unknown quality. For example, a recent study of first-line TB medicines isoniazid and rifampicin showed that over 9% of private-sector TB drugs were 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[16]). (77)

In summary, variation in quality requirements can fragment TB medicines markets. For example, an insufficient number of quality-assured versions can concentrate supplier power, limit competition, and increase prices.

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 Box 4 for further detail.

14 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.

15 If the Expert Review Panel 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.

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

Box 4. Variation in formulations of TB medicines

Medicines used in MDR-TB treatment are highly variable. While first-line TB treatment involves a total of up to five drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin), standard MDR-TB therapy requires choosing four to six drugs from a possible 18 second-line agents indicated by WHO. Moreover, quality-assured second-line drugs are available as more than 25 unique products eligible for procurement by the Global Drug Facility. The broader market includes even more product variations depending on different quality standards, formulation types and packaging. Thus many possible permutations of regimens are ordered by purchasers of MDR-TB drugs. The high-burden MDR-TB countries are currently estimated to use upwards of 40 unique standard MDR-TB regimens in their public programs.

Some of the variation is necessary to account for different populations and dynamic patient needs. For example, the "strain W" of MDR-TB from the 1990's New York City outbreak was kanamycin-resistant but capreomycin-susceptible. As such, capreomycin was favoured in the regimen construction in this case, but would not be valid for another strain with documented capreomycin resistance. Similarly, individual patients often need to switch medications due to adverse reactions or if resistance to one drug is developed.

However, some of the existing variation in MDR-TB medicines is non-essential. There are three levels of non-essential variation:

1. Packaging—i.e., superficial variation at the inner packaging level for an identical drug product. For example, cycloserine 250mg is available in a blister pack or jar. Variation in packaging would require relatively little effort to change or harmonize.

2. Dosage form—i.e., variation in dosage form of a given drug in contexts without strong evidence or need for one over the other. For example, kanamycin is available as a powder (to be reconstituted) or as a solution for injection. Such variation would require relatively low to moderate efforts to change or harmonize.

3. Regimen—i.e., variation between drugs chosen for standard regimens in contexts without strong evidence or need for one over the other. For example, either injectable agent amikacin or kanamycin can be used as part of a recommended treatment regimen. Such variation is expected to be more difficult to change or harmonize.

Non-essential variation is a significant challenge in the context of a relatively small market. It diminishes the total potential market size for a given drug and adds complexity to the overall market operations. The smaller, more complicated volumes reduce the incentives for suppliers to participate and limits their ability to produce efficiently. On the country level, it exacerbates the challenges of forecasting, supply chain management and scale-up planning. It should be emphasized that unique patient or operating circumstances require tailored products, but the prevalent levels of alternatives observed in the market likely contain non-essential variation and this should be addressed. Identifying and addressing non-essential variation can help bring stability to the market, since harmonizing orders will consolidate and help build demand for key drugs and also help simplify the landscape.

Making these changes requires committed engagement to affect guideline, procurement, and country-level product administration decisions. This must be coordinated with simultaneous collaboration with multilateral agencies and suppliers concerned with guidelines and production in the global market. While not identical, the simplification and evolution of HIV guidelines and antiretroviral medicines procurement over the last 10 years could offer valuable lessons on the potential harmonization.

Source: *Sana Mostaghim, Clinton Health Access Initiative*

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 quality-assured, standard regimen including capreomycin costs approximately $4,000-6000[17] per patient from GDF. (87) (76) National treatment programmes often pay less: in 2011, based on country data reported to WHO, MDR-TB drugs cost national treatment programmes $1200-$3800 per patient. For 2013, national programmes in low-income countries plan to budget $2600 per patient; upper-middle-income countries, $4700. (3) 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.

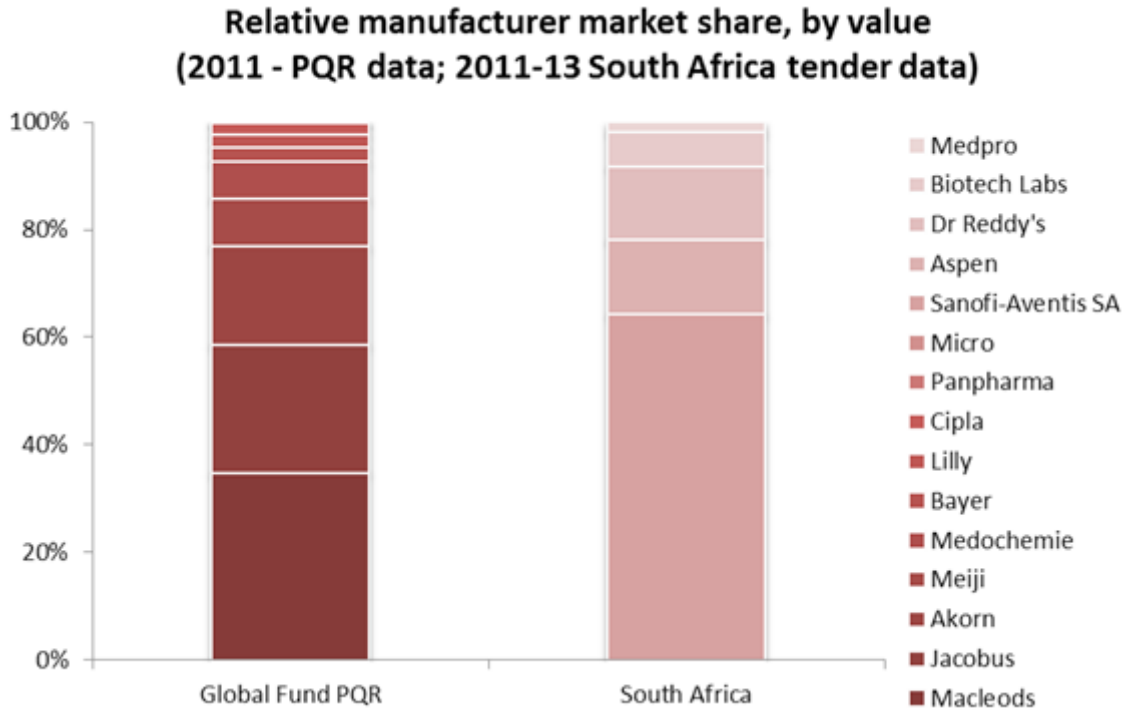
For example, differences in quality requirements hinder direct price comparisons: quality-assured medicines procured by GDF are typically more expensive than those without quality assurance (but ineligible for procurement with donor funds; refer to Box 3). Components of MDR-TB regimens appear to be procured by the Indian Government at roughly one-third of the GDF price for quality-assured products. Quality-assured kanamycin from the GDF is $0.83/vial (powder for injection, 1 g vial) (87), while the Indian Government procured non-quality-assured product from Vital Healthcare at $0.26/vial (excluding 5% VAT and sales tax) in 2011-12. (6)

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 10 (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.

17 Costs can be lower—$2850—if kanamycin is used instead of capreomycin

Figure 10. 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—e.g., Jacobus supplies the same PASER product to GDF and South Africa via a local distributor.* **Global Fund PQR:** *UNITAID analysis of the Global Fund's PQR database, 2011 transactions, excluding those pending verification.* **South Africa:** *Analysis of Bid HP01-2011TB & HP01-2011TB/01, Supply and delivery of Anti-Tuberculosis Medicines to the Department of Health for Period 01 August 2011 to 31 July 2013. Used exchange rate as of 16 July 2011 (date first contract signed): 6.8915 ZAR = 1 USD (x-rates.com).*

Appendix B, Table A 2 summarizes MDR-TB medicine formulations in the WHO Model List of Essential Medicines and/or WHO standard treatment guidelines, and the of formulations with quality assured by WHO Prequalification, a stringent regulatory authority, or the Global Fund Expert Review Panel. For MDR-TB medicines with few quality-assured 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.

Up to 95% of the overall cost of quality-assured MDR-TB regimens is driven largely by four MDR-TB medicines: capreomycin, PAS, moxifloxacin,[18] and cycloserine. (76) Together with kanamycin, these four MDR-TB medicines accounted for over 80% (by value) of MDR-TB medicines procured with Global Fund funding in 2011. Issues affecting these key products include:

- capreomycin: price, quality and supply instability;
- PAS: demand fragmentation and supply instability;
- moxifloxacin: emergence of generic alternatives; and
- kanamycin: quality and supply instability.

Cycloserine, while a cost driver of MDR-TB treatment, has a relatively secure quality-assured supply of finished pharmaceutical product.

Product-specific issues are analysed in this section, based on available data. Supply issues affecting several MDR-TB medicines include availability of API. Lack of API sources and small volumes jeopardise the viability

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

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.

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

Active pharmaceutical ingredients (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 is not gathered systematically. API production for MDR-TB medicines can be complex, technically challenging, environmentally unfriendly, and scale- and capital-intensive (e.g., capreomycin API requires a sterile fermentation process). Up to 80% 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 quality-assured 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.

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 lower number of API manufacturers. Data from interviews[19] revealed that low overall demand, high volatility of demand, complex production processes, and more rewarding opportunities in other API markets make **MDR-TB API a rather unattractive market for new entrants**.

Prices

Many factors can drive high prices of MDR-TB drugs, including production at less than minimum efficiency scale, lack of competition in an API or finished product market, and high transaction costs. Empirical models[20] confirm that the **degree of competition at the API stage is strongly correlated with finished product price**. Keeping other factors constant, MDR-TB medicines with fewer quality-assured API suppliers tend to have higher prices. Payment terms are one of the most important determinants of finished product price: **prices are 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.

Source: *Prashant Yadav, William Davidson Institute, analysis for UNITAID (88)*

Capreomycin

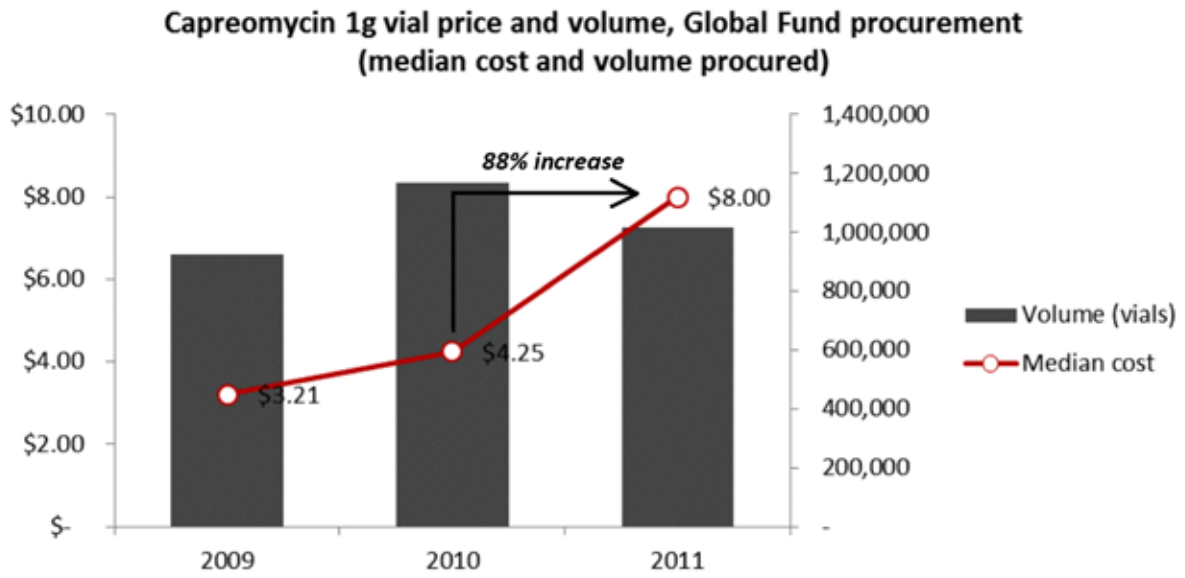
Issues with technology transfer and supplier transitions have compromised market function for capreomycin. Capreomycin prices for donor-funded procurement nearly doubled between 2010 and 2011, as developer Eli Lilly exited the market, selling its license to Akorn and ending subsidized pricing of the injectable drug. (86) In 2003, Eli Lilly committed to transfer its technology to companies in high TB burden countries. Four generic manufacturers (Aspen, Hisun, Akorn and Vianex) were recipients of Lilly's technology transfer. (89) To date, two finished product manufacturers and one API manufacturer have received stringent regulatory authority approval, and two finished product manufacturers have submitted dossiers for WHO prequalification. Upon Lilly's exit in mid-2011, however, Akorn became the only approved capreomycin manufacturer. (90)[21] Following capreomycin approval in Spain in early 2012, Vianex became a second approved manufacturer, and prices dropped 32% as a result. (91) (76) Figure 11 and Figure 12 illustrate directional price and volume trends over time, based on analysis of Global Fund's PQR database. (Due to limitations in available data for 2012, the price drop noted above is not evident in these figures.)

19 Quasi-structured interviews with current or potential API manufacturers for MDR-TB medicines

20 Models used finished product prices from the Global Fund PQR database (using data until 2010)

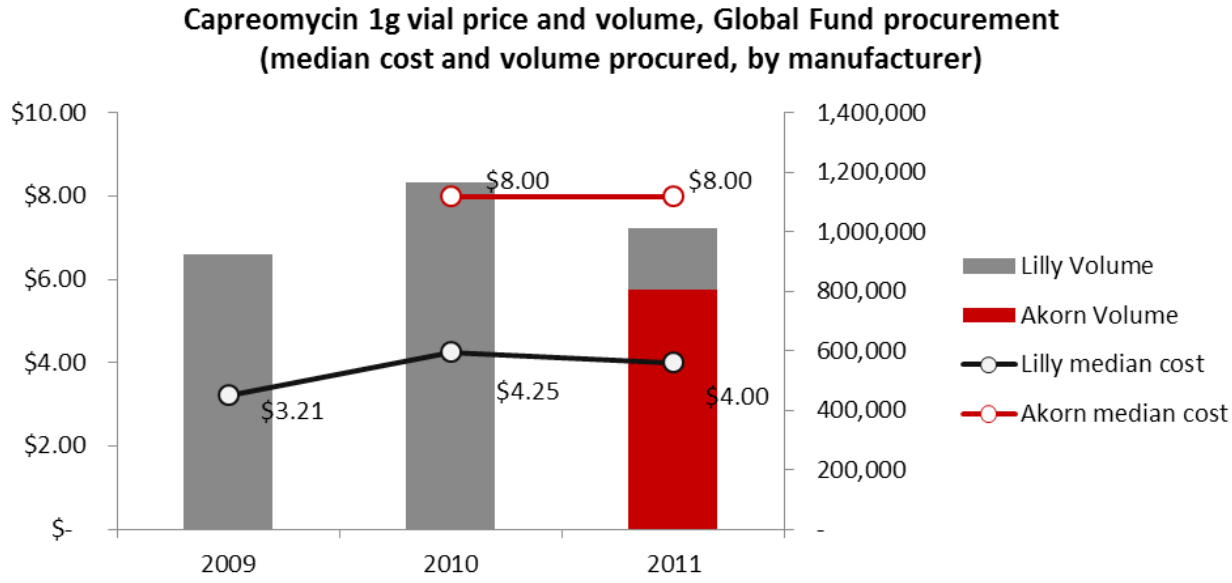
21 Macleods, Aspen and Hisun have submitted to WHO Prequalification of Medicines, but were not approved as of 8 April 2013.

Figure 11. Capreomycin price and volume trends, 2009-2011 (Global Fund data)



Source: *UNITAID analysis of the Global Fund's PQR database, 2009-2011 transactions, excluding those pending verification.*

Figure 12. Capreomycin price and volume trends, 2009-2011, by manufacturer (Global Fund data)



Source: *UNITAID analysis of the Global Fund's PQR database, 2009-2011 transactions, excluding those pending verification.* **Notes:** *Eli Lilly supplied GDF at a subsidized price of $4.00 until exiting the market and exhausting its stock. GDF now sources from Akorn, at $8.00 per vial, or Vianex, a second quality-assured manufacturer as of 2011, at $5.34 per vial. (76) Preliminary PQR data for 2012 suggest an alternate price of $5.53 (median)—likely from Vianex.*

The South African Government sources capreomycin from a single local manufacturer, Aspen, (4) (5) at a delivered price of over $12 per 1 g vial. Adjusted to exclude 14% VAT, this is still over 30% higher than the 2011 weighted average cost to GDF of the Akorn product, and over 2.5 times higher than that of the 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. (92) Additional suppliers (Macleods, Aspen,

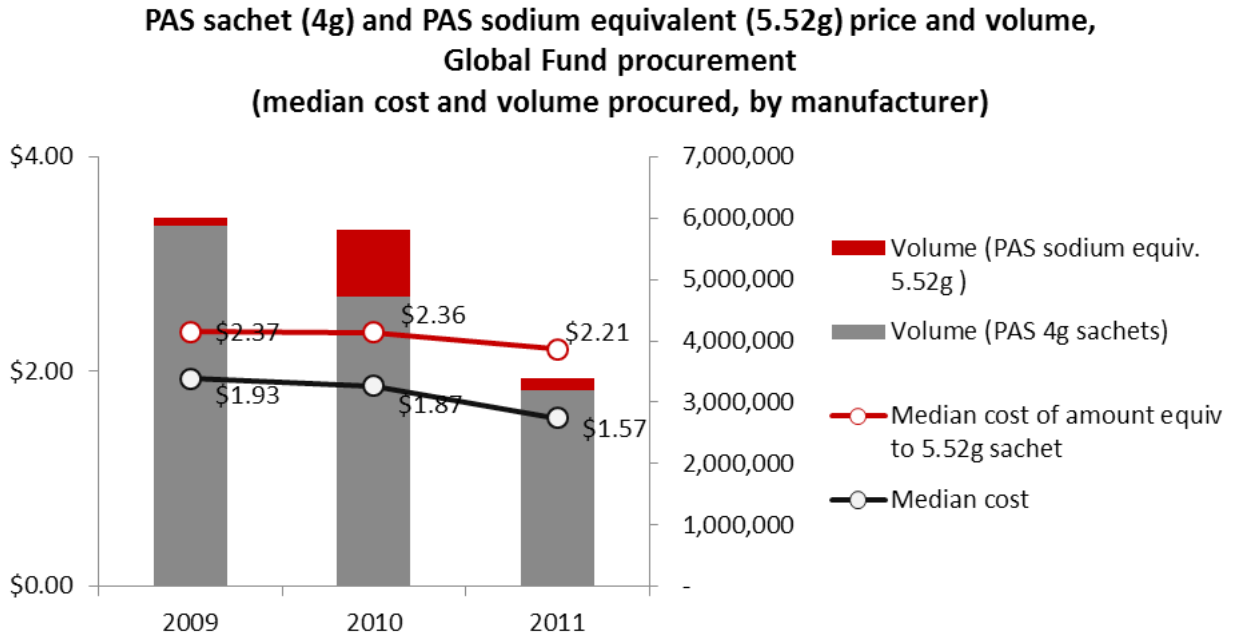
Hisun) have applied to WHO prequalification and may soon diversify quality-assured sources of finished product. (76) However, national government procurement and API production challenges may continue to affect capreomycin price and supply.

In 2011, procurers faced insufficient quantities of capreomycin due to Lilly's exit and Akorn's challenges with scale-up. In addition, there is only one quality-assured API supplier: Hisun in China. While alternative API manufacturers do exist, none has been approved by a stringent regulatory authority or WHO PQ. A complex, sterile fermentation process is required to produce capreomycin API, (76) and preliminary estimates suggest that API contributes over 20% of the finished product cost. Initial process and economic modeling suggests that manufacturing changes to optimize scale and improve efficiency of capreomycin API and finished pharmaceutical product production may generate significant cost savings. (88) Refer to Box 5.

PAS and PAS sodium

The supply of PAS products is vulnerable: despite WHO prequalification of three suppliers, the demand for PAS products is fragmented across multiple formats that are not easily interchangeable (e.g., due to different cold chain requirements). Only one quality-assured manufacturer (Jacobus) supplies PAS, and only two (Macleods and Olainfarm) supply PAS sodium. (76) PAS 4 g sachets make up the bulk of procurement funded by The Global Fund. PAS sodium (60% w/w) is available in 9.2 g sachets and 100 g containers of granules, and in 5.52 g sachets of powder for solution. Following WHO prequalification 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 (vs. 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." (79) Figure 13 illustrates directional volume and price trends, based on analysis of Global Fund's PQR database.

Figure 13. PAS and PAS sodium price and volume trends, 2009-2011, by manufacturer (Global Fund data)



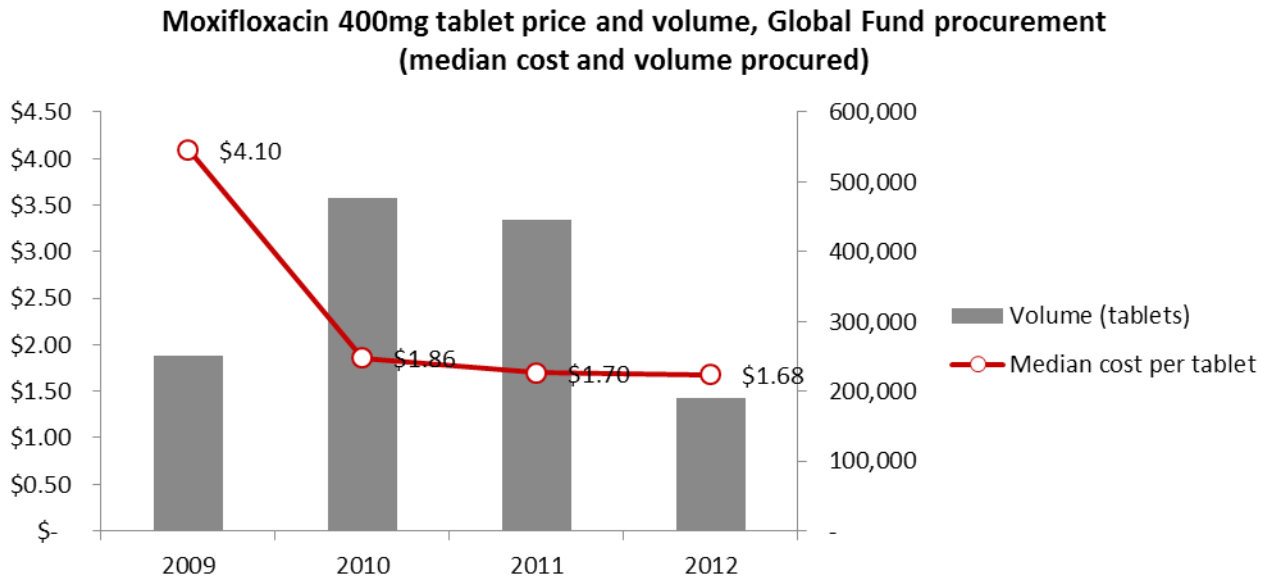
Source: *UNITAID analysis of the Global Fund's PQR database, 2009-2011 transactions, excluding those pending verification.* **Notes:** *5.52 g PAS sodium is equivalent to 4 g PAS. PQR reports procurement of PAS sodium in 100 g containers; figures were adjusted to reflect amount equivalent to PAS 4 g. Most countries procure only PAS; very few procure both PAS and PAS sodium (Kazakhstan in 2009, Pakistan in 2010). Medecins sans Frontieres (MSF) reports prices of approximately $1.5 across PAS products: PAS 4 g sachet (Jacobus), 9.2 g sachets of PAS sodium 60% w/w granules (Macleods), and 5.52 g sachets of PAS sodium powder for solution (Olainfarm). (76)*

Moxifloxacin

Following the expiry of Bayer's basic patent in most countries, **the price of moxifloxacin has steadily decreased with the increased availability of quality-assured generics**; refer to Figure 14 for directional volume and price trends, based on analysis of Global Fund's PQR database. Cipla received WHO prequalification for its generic moxifloxacin product in November 2010, and quickly gained market share at the expense of Bayer; refer to Figure 15 and Figure 16 for directional trends evident from analysis of available transactions in the Global Fund's PQR data. Additional sources of quality-assured generic moxifloxacin are becoming available, reinforcing downward price trends and supply security:

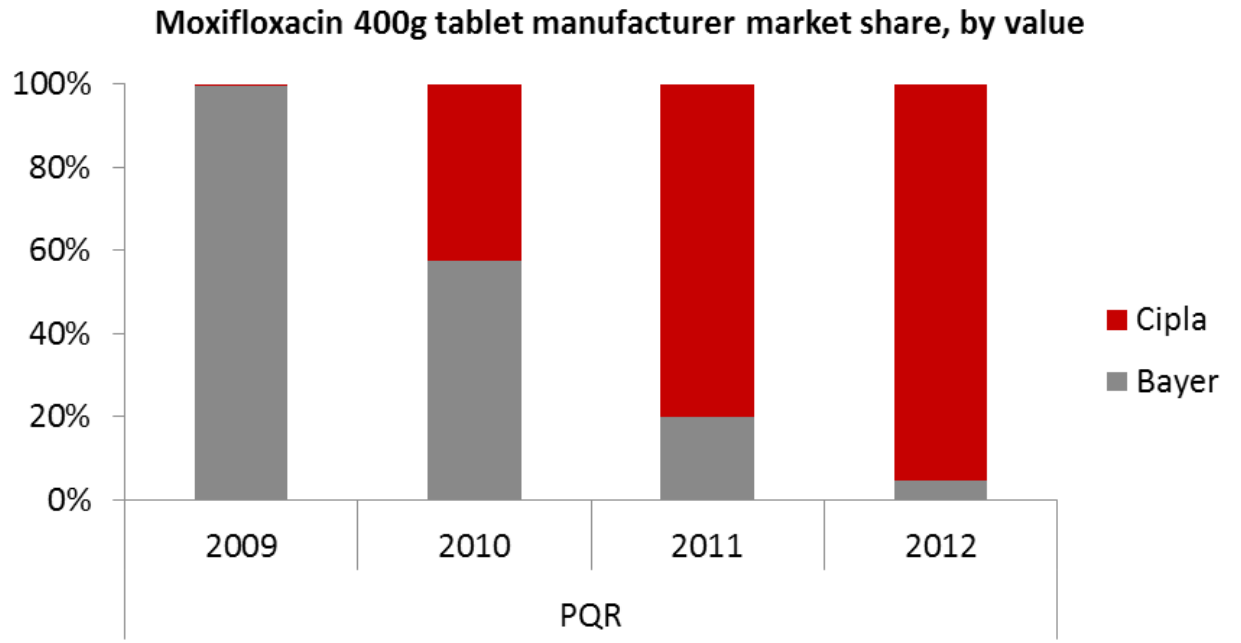
- The GDF and Global Fund approved Macleods' generic product in 2012 (joint expert panel review pending WHO prequalification). (76)
- In India, a key patent blocking generic production was rejected, opening the market for increased generic competition. Generic moxifloxacin is already marketed in Russia. (76)
- In its most recent tender (2011-13), the South African Government procured 6.6 million tablets of generic moxifloxacin, worth $3.5 million, from manufacturer Dr Reddy. (4) (5) This suggests a per-tablet delivered price of $0.52, or $0.46 excluding 14% VAT.

Figure 14. Moxifloxacin price and volume trends, 2009-2011 (Global Fund data)



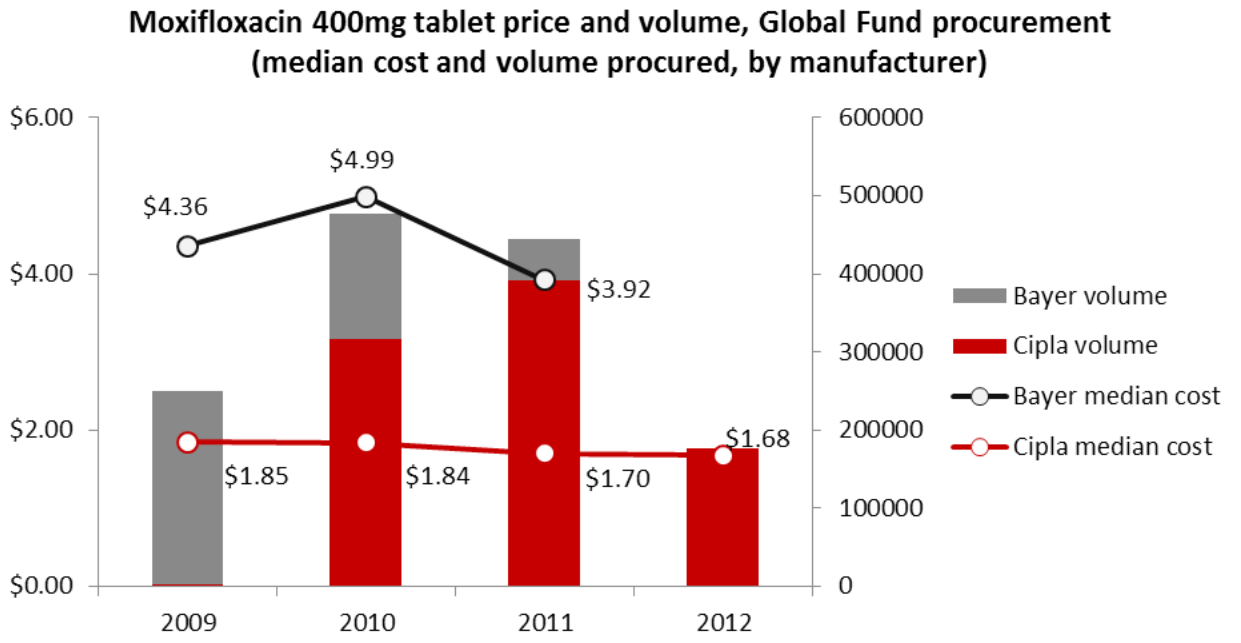
Source: *UNITAID analysis of the Global Fund's PQR database, 2009-2012 transactions, excluding those pending verification.* **Notes:** *Partial data only for 2012; included to show continuation of directional trends.*

Figure 15. Market shift toward generic moxifloxacin, 2009-2012 (Global Fund data)



Source: *UNITAID analysis of the Global Fund's PQR database, 2009-2012 transactions, excluding those pending verification.* **Notes:** *Partial data only for 2012; included to show continuation of directional trends.*

Figure 16. Moxifloxacin price and volume trends, 2009-2012, by manufacturer (Global Fund data)

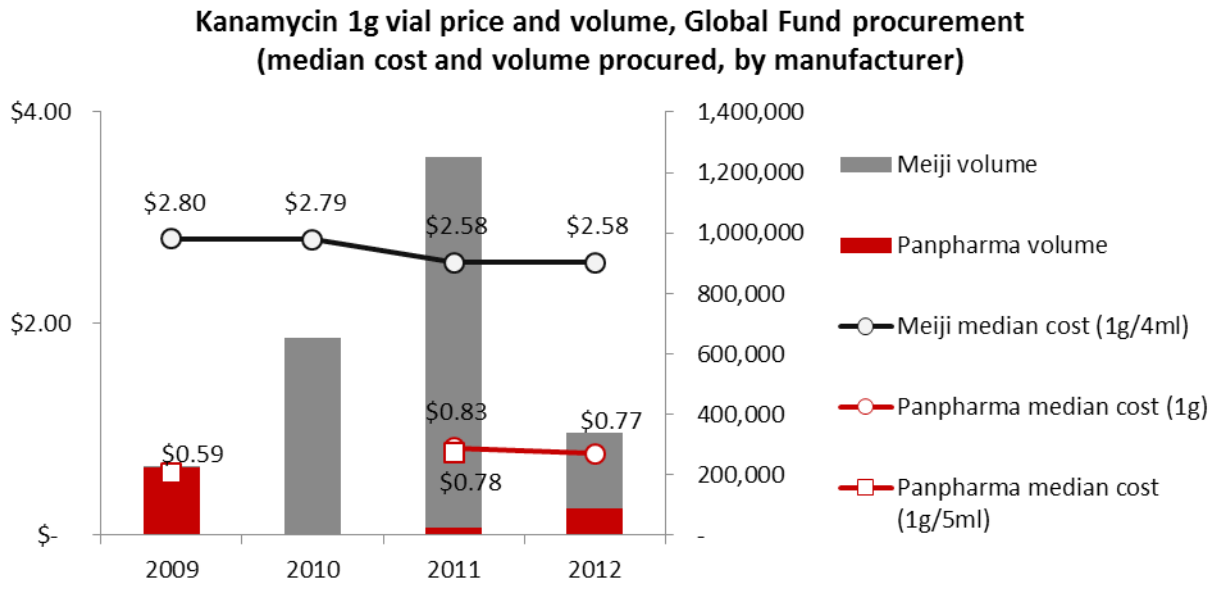


Source: *UNITAID analysis of the Global Fund's PQR database, 2009-2012 transactions, excluding those pending verification.* **Notes:** *Partial data only for 2012; included to show continuation of directional trends.*

Kanamycin

Kanamycin, like capreomycin, has been subject to price and supply instability linked to API production. GDF sources quality-assured kanamycin, approved by stringent regulatory authorities, from Panpharma (France) and—since 2010—Meiji (Japan). Quality-assured kanamycin supply was disrupted in 2009 when an API manufacturer relocated. GDF identified Meiji as an alternative supplier of quality-assured kanamycin, but at a higher price. Figure 17 illustrates the supply and price volatility caused by these disruptions (from 2009). A steady supply of quality-assured kanamycin API is needed to stabilize the finished product market, but few manufacturers are capable of producing the API, which requires specialized fermentation processes and sterile conditions. Supply instability in the finished product therefore persists. (76) Preliminary estimates suggest that API makes up 10% of the finished product cost. If this is the case, then scope for reductions in the finished product price may be lower than for products where API drives more of the finished product price. (88) Refer to Box 5 for further discussion of market issues related to MDR-TB APIs.

Figure 17. Kanamycin price and volume trends, 2009-2012, by manufacturer (Global Fund data)



Source: *UNITAID analysis of the Global Fund's PQR database, 2009-2012 transactions, excluding those pending verification.* **Notes:** *Partial data only for 2012; included for kanamycin to show apparent re-emergence of Panpharma supply. 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 1 transaction) and Panpharma 2011 price (4 transactions).*

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 3). Biotech Laboratories (Pty) Ltd., a local South African manufacturer supplying ten countries in southern Africa, supplies kanamycin at a delivered price of $1.73 per 1 g injection, 3 ml vial, or $1.51 excluding 14% VAT—41% lower than the 2012 weighted average cost to GDF from Meiji (as reported in the Global Fund's PQR data), but 94% higher than the Panpharma product.

Cycloserine

When 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, 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 both Aspen and Chao Center are WHO-prequalified suppliers of cycloserine; in addition, cycloserine from Dong-A was prequalified in early 2013. Additional manufacturers are currently under review by WHO prequalification.[22] Preliminary estimates suggest that API makes up 38% of the finished product cost, indicating potential to optimize scale and improve efficiency of production. (88) Refer to Box 5 for further discussion of market issues related to MDR-TB APIs.

22 As this report was going to press, the WHO Prequalification of Medicines Programme announced the prequalification of cycloserine produced by Biocom.

Even in currently functional markets, vertical integration could be a potential future threat, but more work is needed to understand the likely net impact on market dynamics. For example, if a quality-assured API manufacturer develops capacity to produce finished product, that integrated manufacturer may realize manufacturing efficiencies leading to potential to reduce costs—but is also likely to discontinue API supply to other, competitor finished product manufacturers, therefore limiting competition.

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 as many as 1 million children needing treatment each year, very few cases of paediatric TB are detected and treated. In 2011, only 327,000 cases of paediatric TB were reported to national TB programs. (3)

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. However, this estimate assumes that the case detection rate in adults (66% of all cases are detected) also applies to children—i.e., that the 327,000 cases of paediatric TB reported to national TB programs suggests a total of 490,000 estimated cases. Actual figures are likely much higher due to challenges in diagnosing TB in children. (3)

Detection of TB in children is poor for a range of reasons. The most common sample used to diagnose TB, sputum, 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. (72) (73) 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 recently announced funding for 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. (93) 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, 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 paediatric TB leads to underdiagnosis of children, which in turn amplifies uncertainty on the burden of disease and demand for TB medicines. The burden of paediatric TB was estimated by WHO for the first time in 2012 (3), accounting for 6% of TB cases, but most experts agree it is more likely 10-15% of the global burden. (94) 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 (95) (96) on Standardized Clinical Case Definitions and Standardized Research Methods, 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 are currently under review: an update of 2006 WHO Guidance for national TB programs on management of TB in children, and the Stop TB Partnership Childhood TB Sub-group Childhood TB Roadmap.

Use of existing technology specifically for children, and with alternative specimen types (97) (98) (99) (100) is starting to be evaluated, but more studies are needed. Initial reports on the Xpert MTB/RIF assay showed lowered sensitivity in children versus adults, as expected. But more recent studies (101) (102) (72)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. Based on emerging data, the Strategic and Technical Advisory Group for Tuberculosis has recommended that WHO evaluate the Xpert MTB/RIF assay for diagnosing paediatric and extra-pulmonary TB with subsequent policy refinement. Two promising studies, (103) focused on culturing alternate specimen types, are ongoing. An Oxford University study in Vietnam 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 detail on technology and market issues related to TB diagnostics, refer to the *UNITAID 2013 Tuberculosis Diagnostics Landscape,* available at: http://www.unitaid.org/resources/publications/technical-reports.

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 $30, the potential market for paediatric TB medicines could be up to $30 million. With these assumptions, but only 327,000 cases of paediatric TB reported to national TB programs **in 2011, the actual global market for paediatric TB medicines was probably less than $10 million**.

Approaches to treating 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 3 for detail. In contrast to adult medicines, however, there is a discrepancy between products that are recommended by WHO and those that are WHO-prequalified or approved by stringent regulatory authorities. That is, several quality-assured FDCs of TB medicines are WHO-prequalified or available under GDF's 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; (104) (105) 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; (26) refer to Table 4. However, many diverse approaches to paediatric TB treatment persist. Of 34 countries surveyed in early 2012, half had adopted the new paediatric dosing recommendations—but even among these, efforts are impeded by the lack of appropriate medicines. Various combinations of adult FDCs and loose pills are still used to achieve recommended paediatric doses. (19)

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 do exist regarding procurement of TB medicines specifically for children by the GDF and South Africa. The GDF reported procurement of 242,490 paediatric treatment courses in 2010 (74) and 187,996 in 2011[23] (7)—a majority of the 327,000 cases of paediatric TB reported to national TB programs in 2011, but only approximately 20% of the total if 1 million children need treatment each year. Figure 18 illustrates the number of paediatric TB treatment courses procured by GDF, including those funded by UNITAID. In its most recent tender for TB medicines, the South African Government procured at least $1.9 million worth of paediatric TB medicines.[24] Refer to Table 5.

23 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. (6)

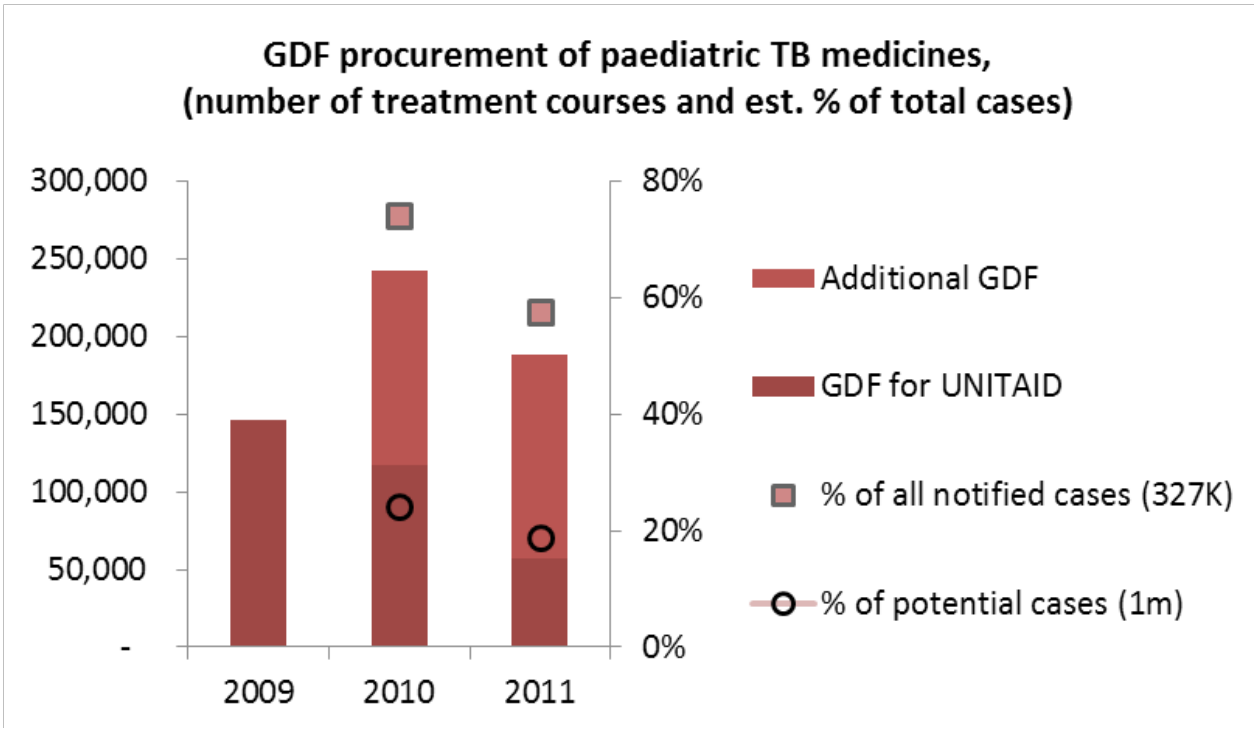
24 For the 2FDC dispersible, intent for use in children was evident from dose, formulation, and description of selected product (Rimactazid Paed 60/60). For the ethambutol 100 mg tablet, intent for use in children was assumed based on would-be pill burden in adults—i.e., based on the GDF standard treatment regimen, the adult daily dose of ethambutol is 825 mg; it is unlikely that 100 mg tablets would be used to achieve this daily dose. 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. 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]).

Table 4. Quality-assured TB medicines included in WHO guidance on dosing for children using currently available fixed-dose combinations

Product	Manufacturer	Quality assurance
Rifampicin 60 mg + isoniazid 30 mg (2FDC) dispersible	Lupin, Macleods	WHO prequalified
Rifampicin 60 mg + isoniazid 60 mg (2FDC) dispersible	Macleods	WHO prequalified
Rifampicin 150 mg + isoniazid 150 mg (2FDC) dispersible	N/A	Available under GDF Quality Assurance policy
Rifampicin 150 mg + isoniazid 75 mg (2FDC) tablet	Macleods, Strides, Lupin, Arcolab , Svizera, Sandoz	WHO prequalified
Rifampicin 60 mg + isoniazid 30 mg + pyrazinamide 150 mg (3FDC) dispersible	Lupin, Macleods	WHO prequalified
Rifampicin 150 mg + isoniazid 75 mg + ethambutol 275 mg (3FDC) tablet	Lupin, Svizera, Macleods	WHO prequalified
Rifampicin 150 mg + isoniazid 75 mg + pyrazinamide 400 mg + ethambutol 275 mg (4FDC) tablet	Macleods, Strides Arcolab , Svizera, Sandoz, Lupin, Wyeth Pakistan	WHO prequalified

Source: WHO Dosing instructions for the use of currently available fixed-dose combination TB medicines for children (26); list of WHO-prequalified medicines (90). **Notes:** additional prequalified formulations are available—e.g., rifampicin 150 mg + isoniazid 150 mg (2FDC) tablet from Lupin, prequalified 29 Jan 2013—but are not included in WHO guidance on dosing for children. Prior to prequalification, rifampicin 60 mg + isoniazid 60 mg (2FDC) dispersible was previously also available under the GDF Quality Assurance policy.

Figure 18. GDF procurement of paediatric TB medicines (number of treatment courses and percentage of total cases)



Sources: *GDF annual reports; UNITAID grant performance data; WHO Global TB report 2012.* **Notes:** *For both 2010 and 2011, calculated percentage of notified cases uses number of notified cases from 2011 from WHO Global TB report (2010 data not available). In addition to curative paediatric courses, UNITAID also funded preventive paediatric courses: 173,620 in 2010 and 89,304 in 2011. GDF figures are for overall procurement of paediatric treatment courses and do not distinguish between curative and preventive treatments. GDF reported procurement of paediatric TB treatments worth $2,715,829 in 2010 and $1,222,757 in 2011 - of which UNITAID-funded paediatric TB medicines accounted for $1,222,757 in 2011 (per annual reports).*

Table 5. South African procurement of paediatric TB medicines, 2011-2013

Product	Value of procurement ($US, delivered price)	Volume of procurement (tablets)
Rifampicin 60 mg + isoniazid 60 mg (2FDC) dispersible	1,405,790	19.6 million (partial component of 58,333 intensive courses)
Ethambutol 100 mg tablet	540,956	10 million (partial component of 29,762 intensive courses)

Sources and notes: *Analysis of South African tender data; figures shown reflect delivered prices, excluding 14% VAT. Refer to Appendix A for additional detail on calculations.*

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. In addition, differences in quality requirements can further complicate direct price comparisons; refer to Box 3. Limited available data, however, show significant apparent differences in cost of select paediatric medicines by procurement channel. Quality-assured rifampicin 60 mg + isoniazid 60 mg (2FDC) dispersible from the GDF is $0.036/dispersible tablet (87), while the South African Government procured at $0.063/dispersible tablet (excluding 14% VAT). Quality-assured ethambutol 100 mg tablet from the GDF is also $0.036/dispersible tablet (87), but $0.047/tablet when procured by the South African Government.

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 1 August 2011 to 31 July 2013, Sandoz SA, Ltd. is the exclusive supplier for South African Government procurement of the two paediatric formulations listed above. The GDF, on the other hand, procures WHO-prequalified rifampicin 60 mg + isoniazid 60 mg (2FDC) dispersible from Macleods, and other products from the manufacturers shown in Table 4.

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.

6.5.1. Market shortcomings related to MDR-TB medicines

Availability: MDR-TB regimens are complex, expensive, long (20-24 months, including eight months of injections), and can cause severe side effects. (106) ***Reasons:*** Market incentives are limited: second-line drugs target a small population (diminished further by underdiagnosis), with little return on investment. Drug resistance evolves, making new drug development high-risk. The typical approach to TB drug development—one medicine at a time—means development of entirely novel regimens is long and challenging.

Affordability: Quality-assured MDR-TB drugs are expensive (e.g., $4,000-$6,000+ per treatment course for a standard 24-month regimen including 8 months' injectable capreomycin.) (87) (76) ***Reasons:*** Increased manufacturing costs 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. (107) Competition is limited: few suppliers exist for finished products and active ingredients. Prices have increased due to manufacturer exit (e.g., Eli Lilly; capreomycin, cycloserine) and product shortages (e.g., kanamycin). (86) Moxifloxacin remains under patent in certain countries. (76)

Quality: Quality-assured medicines make up only a small fraction 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). (2) TB medicines purchased by the private sector or National TB Programs are often of variable or unknown quality. ***Reasons:*** A small quality-assured market limits incentives for producers to invest in stringent regulatory approval. Procurement by the private sector or national TB programmes 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 receive appropriate treatment. (3) ***Reasons:*** Low availability of DST—<4% of patients (new, bacteriologically-positive cases) had access in 2011 (3)—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 programs 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). (108) ***Reasons:*** Limited number of suppliers exist, especially of API. 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 those for adults: a 6-month course of quality-assured, first-line TB drugs costs 40% more ($22 for adults but $30 for children), (87) despite containing less active ingredient. ***Reasons:*** Few suppliers exist for quality-assured formulations. A small market and fragmented demand increase risk for manufacturers, as do higher costs in product development (e.g., formulation, dosing, safety) and greater complexity in manufacturing.

Quality: Only one in five children with TB received quality-assured drugs via the GDF, meaning many children are receiving drugs of unknown quality in non-standard doses (e.g., split adult FDC). ***Reasons:*** No appropriately-dosed FDC is on the market (i.e., an FDC that corresponds to the dosing recommended in the 2010 guideline update). A majority of the market is served by private-sector and non-donor public-sector TB drugs procurement, which is typically non-quality assured.

Acceptability/Adaptability: No appropriately-dosed, quality-assured, paediatric FDC on the market consistent with 2010 WHO treatment guideline revision. Delays in needed paediatric trials for novel medicines (≥7-year lag between adult and paediatric formulations, despite requirement for submission of plan for paediatric development). In second-line drugs, only amakacin and levofloxacin exist in paediatric formulations, but are not widely available. ***Reasons:*** The small, fragmented quality-assured 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 have long lead times (e.g., for the first half of 2012, the GDF reported a median lead time of 146 days for the GDF/UNITAID Paediatric Project). (108) ***Reasons:*** There is a limited number of quality-assured 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 are 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 hard 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 related to DS- and MDR-TB medicines

TB medicines markets are a challenging area in which to intervene. The range and complexity of shortcomings related to MDR-TB medicines markets suggest that multiple interventions may be appropriate for UNITAID and other stakeholders to consider—i.e., a combination of broad and targeted market-based approaches to alleviate market shortcomings. Given close links between market segments (e.g., APIs and finished pharmaceutical products; diagnostics and medicines), potential interventions are often interdependent, with complementary approaches in multiple areas necessary to ensure success. UNITAID also recognizes the importance of non-donor procurers of TB medicines, with many patients seeking care from programmes funded by country governments

or in the private sector. As such, potential interventions in TB medicines markets must ensure a coordinated approach across multiple key stakeholders.

Potential opportunities may include work to:

- **Consolidate demand for TB medicines by aligning different segments of the market, through mechanisms such as harmonizing quality standards and other requirements across different procurers or engaging with government or private-sector stakeholders in TB medicines markets in novel ways**. As noted above, the already small market for MDR-TB medicines is fragmented by many procurement channels—each of which may be subject to specific quality, regulatory, tender standards and requirements (see Figure 6 and Box 3). Market approaches that harmonize or consolidate demand for quality-assured products, growing this market segment beyond medicines procured with donor funds, could increase market incentives for manufacturers to engage and, ultimately, improve access to better-quality drugs for more patients. Potential opportunities may include alignment with government purchasers, especially those in middle-income countries including Brazil, Russia, India, China, or South Africa; collaboration with manufacturers, especially those based in high-burden countries, to improve quality standards and thus availability of quality-assured TB medicines; and engagement with private-sector stakeholders, with mechanisms to facilitate appropriate use of quality-assured TB medicines at affordable prices.

  Reducing the complexity of MDR-TB treatment could facilitate demand consolidation. Within WHO treatment guidelines, there is a high degree of variation in specific TB treatment options that can be used for an individual patient. Some of this variation is clinically necessary. However, some variation stems from a lack of data on particular drug choices (e.g., kanamycin versus capreomycin). Additional clinical data could establish the necessary evidence base to identify priority TB medicines and/or regimens around which to focus the market—still within WHO treatment guidelines. Finally, some of the variation may be non-essential and unlinked to clinical needs (e.g., interchangeable packaging options, dosage forms, or equivalent regimens; see Box 4). Inventory and review of current quality, regulatory, and tender processes, standards and requirements may identify opportunities to streamline or rationalize duplicates. Such activities could facilitate consolidation of demand for TB medicines and facilitate efforts to improve market dynamics.
- **Improve demand forecasts for TB medicines, reducing the risk in production planning and enabling more efficient manufacture and supply management.** 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 (vs. 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.
- **Support complementary means to verify quality at the point of care,** such as development of new tools to confirm medicine quality. While prospective quality assurance mechanisms can assess the inherent quality of a particular product, tools to verify the quality of medicines at the point of care may supplement these—particularly given the multiple quality standards for TB medicines that can exist, as noted in Box 3 and Sections 6.2.2 and 6.3.3.
- **Reduce supply vulnerability through robust procurement processes and supply chain improvements** through mechanisms to stabilize the market (e.g., new supply chain mechanisms such as product 'banks' or stockpiles to cushion demand volatility).
- **Enhance the function and efficiency of specific product markets through mechanisms to assure demand or provide technical assistance.** Interventions to identify production efficiencies could reduce the cost of operating, and eventually stimulate competition or enable price reductions. Design of market interventions should account for unique considerations of different market segments—API vs. finished product, or for specific products.

  The economics of API markets are different from those of finished product markets. For example, there are lower margins and greater economies of scale in production of API than of finished products. 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 prod-

ucts 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**. The **interdependence and 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 market and public health impact 'downstream'.

- **Facilitate improved manufacturing processes for MDR medicines to lower costs, improve quality, and support supply security through mechanisms such as process chemistry changes, production and scale efficiencies.** Market intelligence could help prioritize interventions by highlighting areas of greatest potential—e.g., where margins are particularly high, suggesting scope for process or other improvements.
- **Support manufacturers with an interest in producing quality-assured TB medicines but without the necessary technical expertise, through technical assistance to support technology transfer, quality manufacturing or increased production capacity.** Technology transfer or production capacity issues have impacted the availability or price of capreomycin, PAS sodium, and kanamycin. Interventions to reduce barriers to entry could encourage greater competition, stimulating price reductions and expanded access, especially where the potential of generics has not been fully realized.
- **Support appropriate access to new medicines to improve TB treatment and encourage further innovation.** Market approaches could facilitate appropriate use of new and emerging TB medicines and regimens by: increasing visibility and control over private-sector usage patterns; decreasing availability of poor-quality or incomplete TB regimens; and fostering more stable, competitive markets for TB medicines.

  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). Market approaches for 'repurposed' medicines—including some already used for TB, even without a formal indication in TB—have different trade-offs. For example, increased access to repurposed TB medicines may require tools to monitor resistance. On the other hand, work with repurposed medicines could also leverage opportunities such as untapped potential for increased generic competition.

  To complement market approaches supporting entry and appropriate use of new TB medicines, work may be needed to increase detection, enrolment and support for people with MDR TB—e.g., through technical assistance, expansion or integration of public-private partnerships, and further diagnostic development and scale-up.

6.6.2. Potential opportunities for market intervention related to paediatric TB medicines

The current UNITAID grant to TB Alliance aims to map the paediatric market; develop deliver new appropriately-dosed, quality-assured, fixed-dose TB medicines for children; and drive policy and regulatory change to scale-up treatment. Until then, UNITAID remains committed to supporting treatment of children with TB through its extended engagement with the GDF, and open to other, complementary market interventions in this space. Potential opportunities in the paediatric TB medicines market may include interventions to:

- **Consolidate demand, negotiate prices, and scale up quality-assured medicines.** *[NB: most relevant once new quality-assured, paediatric formulations are available ~2-3 years]*.
- **Incentivize development and facilitate uptake of novel TB diagnostics appropriate for children.** Possible components to support improved diagnosis may include: scale-up of currently available technology specifically for paediatrics; scale-up with alternate specimen types; consideration of a small sub-segment of paediatric TB such as TB/HIV; support to establish evidence for paediatric TB with new technologies.
- **Develop mechanisms to accelerate paediatric trials of novel compounds/regimens.** An intervention designed to reduce the significant lag time in development of paediatric formulations of new and emerging TB medicines and regimens—including some of those described in Section 5.2—could extend the benefit of new developments to children with TB.

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Appendix A. Additional detail on methods for select figures and tables

Figure 5. Value of the 2011 first-line TB medicines market, by procurement channel

Sources and notes: Total market approximated from build-up of various procurement channels, estimated as follows. **Private:** estimated total private market volumes by extrapolating total number of patient treatments procured in private sector from literature. (1) Derived estimates of the portion of the private market treated through PPM programmes (vs. 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 (2011) (3)] x [% of patients accessing TB treatment in the private sector]. (75) 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. UR Tanzania: PPM coverage known to be minimal (12 physicians only), but not quantified; assumed negligible. Applied estimates of PPM coverage (as % of private sector) to estimate range of patient treatments procured through PPM programmes vs. 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 ($40) to size PPM and unregulated/uncertain market segments by value. Chart reflects midpoint of value estimate for PPM market segment ($19 million); and balance of overall total private market ($209 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 TB Report 2012. **Public non-donor:** extrapolation of data reported to WHO from 99 countries accounting for 85% of global DS-TB cases receiving treatment (WHO Global TB Report 2012 (3)); for South Africa only, used actual tender data (50% of two-year tender for TB medicines). **South Africa:** Analysis of Bid HP01-2011TB & HP01-2011TB/01, Supply and delivery of Anti-Tuberculosis Medicines to the Department of Health for Period 01 August 2011 to 31 July 2013 (4) (5). Used exchange rate as of 16 July 2011 (date first contract signed): 6.8915 ZAR = 1 USD (x-rates.com). Assumed 50% of tender would roughly approximate 2011 value of TB medicines. **India:** Analysis of Indian Government purchases of TB medicines in FY 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. (6) **GDF:** data from 2011 Annual Report. (7)

Figure 6. Value of the 2011 MDR-TB medicines market, by procurement channel

Sources and notes: WHO estimates a total 2011 market of over $300 million for MDR-TB medicines. (3) Total market approximated from build-up of various procurement channels, estimated as follows. **Private:** $37 million in private-sector sales were reported for five countries only in 2007; (1) assumed additional $35 million private sector worldwide based on global market estimates of $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 TB Report 2012. **Public non-donor:** extrapolation of data reported to WHO from 99 countries accounting for 29% of MDR-TB cases receiving treatment; (3) for South Africa only, used actual tender data (50% of two-year tender for TB medicines, 2011-2013). **South Africa:** Analysis of Bid HP01-2011TB (4) & HP01-2011TB/01 (5), Supply and delivery of Anti-Tuberculosis Medicines to the Department of Health for Period 01 August 2011 to 31 July 2013. Used exchange rate as of 16 July 2011 (date first contract signed): 6.8915 ZAR = 1 USD (x-rates.com). Assumed 50% of tender would roughly approximate 2011 value of TB medicines. **India:** Analysis of Indian Government purchases of TB medicines in FY 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. (6) NB: Revised National TB Control Programme annual report cited 2nd-line TB medicines expenditure at 22% of budget; with a 2011-12 budget of $73.6 million (400.00 Rs in crore), this amounts to $16.2 million, but may include medicines funded by the Global Fund. **GDF:** data from 2011 Annual Report. (7). 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. (2)

Figure 7. Value of TB medicines procured in the public sector, projected trends from 2009-2013

First-line market trends reflect: extrapolation of data reported to WHO from 99 countries accounting for 85% of global DS-TB cases receiving treatment; (3) actual tender data from South Africa; (4) (5) and estimates based on number of cases on treatment for Russia and other countries accounting for 6% of total cases. (3) MDR-TB market trends reflect: extrapolation of data reported to WHO from 99 countries accounting for 29% of MDR-TB cases receiving treatment; (3) actual tender data from South Africa; (4) (5) and estimates based on number of cases on treatment for Russia and other countries accounting for 27% of total cases. (3) **MDR-TB market trends in particular should be interpreted as directional only, and with caution, due to the high price and price variation for MDR-TB regimens; small base of reported data; and reliance on extrapolation.**

Table 5. South African procurement of paediatric TB medicines, 2011-2013

Analysis of South African tender data: Bid HP01-2011TB & HP01-2011TB/01, Supply and delivery of Anti-Tuberculosis Medicines to the Department of Health for Period 01 August 2011 to 31 July 2013. Used exchange rate as of 16 July 2011 (date first contract signed): 6.8915 ZAR = 1 USD (x-rates.com). To calculate number of treatment courses, referred to paediatric dosing tables 3a, 3b. Weight band 20-30 kg: recommend 2x RH 60/60, in both intensive (56-day) and continuation (112-day) phase; 5.5x ethambutol 100 (as part of 4FDC) in intensive phase only. (26) VAT for delivered prices reported in South African tender data = 14%; excluded in figures shown in table.

Calculations referenced in Section 6.4.3

GDF prices from online catalogue. (87) South African Government prices derived from analysis of South African tender data: Bid HP01-2011TB & HP01-2011TB/01, Supply and delivery of Anti-Tuberculosis Medicines to the Department of Health for Period 01 August 2011 to 31 July 2013. (4) (5) Used exchange rate as of 16 July 2011 (date first contract signed): 6.8915 ZAR = 1 USD (x-rates.com). VAT for delivered prices reported in South African tender data = 14%; excluded in figures cited.

Calculations referenced in Section 6.2.3

Calculated prices of product PC-1, kit containing medicines for two months' intensive-phase treatment, followed by four months' 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 multi-blister 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.

Appendix B. Quality assurance of TB medicines

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

Drug	Formulation	Strength	WHO-prequalified options	SRA-approved options	ERP options	Total QA options
Isoniazid (H)	tablet/capsule	300 mg	3	4	0	7
Rifampicin (R)	capsule	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	0	3
		500 mg	3	4	0	7
Ethambutol (E)	coated tablet/ capsule	200 mg	0	0	0	0
		275 mg	0	0	0	0
		400 mg	0	2	0	2*
Streptomycin	powder for injection (vial)	1 g	0	4	0	4
		0.75 g	0	0	0	0
HR	coated tablet/ capsule	75 mg/150 mg	5	0	1	6
		150 mg/150 mg	1	0	0	1
		150 mg/300 mg	0	2	0	2**
HE	coated tablet/ capsule	150 mg/400 mg	3	0	0	3
HRE	coated tablet/ capsule	75 mg/150 mg/275 mg	3	0	0	3
HRZ	coated tablet/ capsule	150 mg/150 mg/500 mg	0	0	0	0
		75 mg/150 mg/400 mg	0	0	0	0
HRZE	coated tablet	75 mg/150 mg/400 mg/275 mg	6	0	0	0

Sources and notes: *List derived from 11th Expression of Interest for WHO PQ (reflects formulations in WHO Model List of Essential Medicines and/or WHO standard treatment guidelines). (109) Number of prequalified options for each medicines/formulation/strength from WHO list of prequalified medicines (22 May 2013). (90) ERP: Expert Review Panel, hosted by WHO on behalf of the Global Fund; QA: quality assured; SRA: stringent regulatory authority. Refer to Box 3 for additional context. * Table reflects* film-coated *tablets only; also available as tablets (four WHO-prequalified options, five SRA-approved options). ** Table reflects* film-coated *tablets only; also available as tablets (one SRA-approved option) and capsules (one WHO-prequalified option, one SRA-approved option).*

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

Drug	Formulation	Strength	WHO-prequalified options	US FDA or EMA-approved options	ERP options	Total QA options
Amikacin	solution for injection	500 mg/2g vial	2	2	0	4
	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	3	2	2	7
Ethionamide	tablet/capsule	250 mg	4	1	0	5
Kanamycin	powder for injection	1 g vial	0	1	0	1*
		500 mg vial	0	1	0	1
Levofloxacin	tablet/capsule	250 mg	2	17	1	20
	tablet	500 mg	2	17	1	20
		750 mg	0	17	0	17
Moxifloxacin	tablet/capsule	400 mg	2	5	2	9**
Ofloxacin	tablet/capsule	200 mg	3	2	1	6
		400 mg	2	2	1	5
Prothionamide	tablet/capsule	250 mg	1	2	2	5
PAS	sachets, granules	4 g	0	2	0	2
PAS sodium	jar, granules	100 g	1	0	0	1
	sachets, granules	4 g	0	0	0	0
		9.2 g	1	0	0	1
	powder for oral soln	sachets	1	0	0	1
Terizidone	tablet/capsule	250 mg	0	1	0	1
		300 mg	0	0	0	0

Sources and notes: *List derived from 11th Expression of Interest for WHO PQ (reflects formulations in WHO Model List of Essential Medicines and/or WHO standard treatment guidelines). (109) Number of prequalified options for each medicines/formulation/strength from WHO list of prequalified medicines (22 May 2013). (90) Additional formulations may be under review by WHO PQ, or have approval by a stringent regulatory authority—e.g., capreomycin: two versions (Akorn, Macleods) are under review by WHO PQ, and two versions (Akorn, Vianex). (76) ERP: Expert Review Panel, hosted by WHO on behalf of the Global Fund; QA: quality assured; SRA: stringent regulatory authority. *Also available as solution for injection (4 SRA-approved options in different concentrations). **Multiple SRA-approved registrations from Bayer (e.g., prior to centralized EMA registration); considered one product.*

Appendix C. Patents on selected new and pipeline TB medicines

The table below provides an overview of patents on several new and pipeline TB medicines in high burden TB and high burden MRD-TB countries. It should be noted that the patent status of a particular product in a particular country is subject to change, thus, this table only provides an indication[1].

Table A 3. Overview of patents on selected new and pipeline TB medicines

	bedaquiline	delamanid	SQ-109	AZD5847	sutezolid	PA-824
Afghanistan	n/a	n/a	n/a	n/a	n/a	n/a
Armenia	patent(s) granted	n/a	patent(s) granted	patent(s) pending	n/a	n/a
Azerbaijan	patent(s) granted	n/a	patent(s) granted	patent(s) pending	n/a	n/a
Bangladesh	n/a	patent(s) pending	n/a	n/a	n/a	n/a
Brazil	patent(s) pending	patent(s) pending	n/a	no patents found*	patent(s) granted	n/a
Bulgaria	patent(s) granted	patent(s) granted	patent(s) pending	patent(s) pending	patent(s) pending	n/a
Belarus	patent(s) granted	patent(s) granted	patent(s) granted	patent(s) pending	n/a	n/a
Cambodia	n/a	n/a	n/a	n/a	n/a	n/a
China	patent(s) granted	patent(s) granted	patent(s) granted	patent(s) pending	patent(s) granted	n/a
DR Congo	n/a	n/a	n/a	n/a	n/a	n/a
Estonia	patent(s) granted	patent(s) granted	patent(s) pending	patent(s) pending	patent(s) pending	n/a
Ethiopia	n/a	n/a	n/a	n/a	n/a	n/a
Georgia	n/a	n/a	n/a	n/a	n/a	n/a
India	patent(s) granted	patent(s) granted	patent(s) granted	no patents found*	no patents found*	no patents found
Indonesia	patent(s) pending	patent(s) pending	n/a	patent(s) pending	n/a	n/a
Kazakhstan	patent(s) granted	n/a	patent(s) granted	patent(s) pending	n/a	n/a
Kenya	patent(s) granted	n/a	n/a	n/a	n/a	n/a
Kyrgyzstan	patent(s) granted	n/a	patent(s) granted	patent(s) pending	n/a	n/a
Lithuania	patent(s) granted	patent(s) granted	n/a	patent(s) pending	patent(s) pending	n/a

1 The information in Table A3 should not be considered a complete or authoritative source of patent information on the listed compounds. It provides a snapshot at a particular point in time based on the information available to UNITAID. UNITAID does not accept any responsibility for the accuracy of data, nor guarantee that it is complete or up-to-date.

	bedaquiline	delamanid	SQ-109	AZD5847	sutezolid	PA-824
Latvia	patent(s) pending	patent(s) granted	n/a	patent(s) pending	patent(s) granted	n/a
Moldova	patent(s) granted	n/a	patent(s) granted	patent(s) pending	n/a	n/a
Mozambique	patent(s) granted	n/a	n/a	n/a	n/a	n/a
Myanmar	n/a	n/a	n/a	n/a	n/a	n/a
Nigeria	n/a	n/a	n/a	n/a	n/a	n/a
Pakistan	patent(s) pending	patent(s) pending	n/a	n/a	n/a	n/a
Philippines	patent(s) granted	patent(s) granted	n/a	patent(s) pending	patent(s) pending	n/a
Russia	patent(s) granted	patent(s) granted	patent(s) granted	patent(s) pending	patent(s) pending	n/a
South Africa	patent(s) granted	patent(s) pending	patent(s) granted	patent(s) pending	patent(s) pending	n/a
Tajikistan	patent(s) granted	n/a	patent(s) granted	patent(s) pending	n/a	n/a
Tanzania	patent(s) granted	n/a	n/a	n/a	n/a	n/a
Thailand	patent(s) pending	patent(s) pending	n/a	n/a	n/a	n/a
Uganda	patent(s) granted	n/a	n/a	n/a	n/a	n/a
Ukraine	patent(s) granted	patent(s) granted	n/a	patent(s) pending	n/a	n/a
Uzbekistan	n/a	n/a	n/a	n/a	n/a	n/a
Vietnam	patent(s) pending	patent(s) pending	n/a	patent(s) pending	n/a	n/a
Zimbabwe	patent(s) granted	n/a	n/a	n/a	n/a	n/a

Sources and notes: *Summarized from reviews of the patent landscapes of bedaquiline, delamanid, SQ-109, AZD5847, sutezolid and PA-824 prepared by the Initiative for Medicines, Access & Knowledge (I-MAK) for UNITAID. Patent searches were conducted in the first half of 2013 (except for bedaquiline, were searches were conducted in June 2011).*

*Patent(s) granted = one or more patents have been granted; patent(s) pending = one or more patent application(s) have been filed/are pending; no patents found = the searches conducted did not reveal patents or patent applications (however, patent applications may not have been published yet at the time of the search, and/or may have been missed); * data for a more recent patent application are not available; n/a = data not available.*