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Medicines Technology Landscape

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List of abbreviations

ACTG	AIDS Clinical Trials Group
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARVs	Antiretrovirals
CAB	Community advisory board
CDC	Centers for Disease Control and Prevention
CHAI	The Clinton Health Access Initiative
CPTR	Critical Path to TB Drug Regimens Initiative
CREATE	Consortium to respond effectively to the AIDS TB epidemic
CTB²	Consortium for TB Biomarkers
DDI	Drug-drug interaction
DOT	Directly observed therapy
DOTS	Directly observed therapy–short course
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility testing
DS-TB	Drug-susceptible tuberculosis
E	Ethambutol
EBA	Early bactericidal activity
EDCTP	European and Developing Countries Clinical Trials Partnership
EOI	Expression of Interest
FDA	U.S. Food and Drug Administration EMA: European Medicines Agency
FDC	Fixed dose combination
FLM(s)	First-line medicine(s)
GCP	Good clinical practice
GDF	The Stop TB Partnership's Global Drug Facility
GLI	World Health Organization's Global Laboratory Initiative
GLC	World Health Organization's Green Light Committee
H	Isoniazid
HIV	Human immunodeficiency virus
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
IPT	Isoniazid preventive therapy
LTBI	Latent TB infection
MDR-TB	multidrug-resistant tuberculosis
MSF	Médecins Sans Frontières
NIAID	U.S. National Institute of Allergies and Infectious Diseases
NIH	U.S. National Institutes of Health
NTP	National treatment program
OBR	Optimized background regimen
OST	Opioid substitution therapy
PI	Protease inhibitor
PIP	Pediatric investigational plan
PK	Pharmacokinetics
POC	Point-of-care
PPM	Private-public mix
PQ	Prequalified
QA	Quality-assured
R	Rifampicin
R&D	Research and development
SLM(s)	Second-line medicine(s)
STAG	World Health Organization's Strategic and Technical Advisory Group
TAG	Treatment Action Group
TB Alliance	The Global Alliance for TB Drug Development
TB CAB	Global Tuberculosis Community Advisory Board
TB	Tuberculosis
TBTC	Tuberculosis Trials Consortium
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide

Foreword

In 2009, the medicines used to treat tuberculosis (TB) cured the disease in approximately 87% of people who had smear-positive, drug-sensitive TB (DS-TB) (World Health Organization 2011b). However, this statistic does not account for smear-negative or extrapulmonary TB; nor does it account for drug-resistant TB (DR-TB), which is cured only 30% to 80% of the time (Orenstein 2009, Dheda 2010). Furthermore, even with smear-positive, drug-sensitive TB, a number of challenges exist in implementing and adhering to the WHO-approved regimens, so that success rates are often much lower than the global target of 85% (World Health Organization 2011b). There is an urgent need for new medicines and new regimens to improve the standard-of-care in TB treatment.

This report describes key areas of need in the TB medicines landscape, how novel and repurposed compounds in the pipeline are being developed to address these needs, and the regulatory and research challenges to the development and approval of these new medicines. Additionally, this report highlights the key shortcomings in the market that hinder the successful uptake of novel compounds and regimens.

Currently, isoniazid prevention therapy (IPT) is used to treat latent tuberculosis (LTBI) and to prevent TB in people with HIV. Although it has been shown to be effective, reducing the risk of contracting TB up to 67% in people with HIV (World Health Organization 2008b), adherence is challenging due to its side effects, lack of data on the durability of its preventive effect, and the long duration of treatment, which lasts 6-36 months, or more (World Health Organization 2010c, World Health Organization 2012b).

The duration of treatment for both DS- and DR-TB is also a significant challenge. Current regimens for DS-TB require taking multiple pills for six months, and DR-TB regimens can last for 18-24 months or longer and require even more daily medications. The length of treatment makes adherence difficult, and lapses in adherence can lead to the development of further DR-TB.

Existing medicines to treat DR-TB are difficult to tolerate, have toxicity issues and have limited efficacy, with cure rates falling far below the global treatment goal of 85%. The emergence of TB that is resistant to all available first- and second-line medicines highlights the need for novel medicines to which the TB bacteria will not be cross-resistant. Since adding a novel medicine to an existing ineffective regimen is likely to breed resistance to the new compound, it is also critical to develop wholly new regimens.

Additionally, there is inadequate access to these second-line medicines. Poor market forecasting and underutilization of procurement mechanisms means that medicines are not made available in countries with high TB burdens. Even when ordered, stockouts of second-line medicines often occur in the public sector. Furthermore, the private sector frequently does not use quality-assured procurement mechanisms, and so many of the WHO-recommended second-line medicines are not consistently available to patients treated there.

If novel regimens for DS- or DR-TB were approved, this could cause a significant shift in market dynamics. However, in order for these regimens to be commercially viable, drug-drug interaction studies must be performed between the medicines in the regimen to evaluate how they affect one another's efficacy and safety. Additionally, a significant amount of the population that uses TB medicines may also use opioid substitution therapy

(OST) or antiretrovirals (ARVs), so it is critical that interactions between these compounds and novel TB medicines be evaluated in order for novel compounds or regimens to be marketable in these sizable populations.

Finally, medicines must be produced at appropriate doses for children with TB. In 2010, the WHO released guidelines that updated the recommended pediatric doses for TB medicines. The pediatric first-line fixed-dose combinations (FDCs) on the market do not match these updated doses, and appropriate single doses of first-line medicines do not exist in child-friendly formulations. Additionally, second-line medicines have not been rigorously studied in children.

The novel and repurposed medicines in the pipeline are being developed to address these areas of unmet need, with proposed indications for LTBI, DS- and DR-TB. Some medicines are also being studied for use in shortened and novel regimens. The first of the new medicines is expected to be approved in 2012, at the earliest, through accelerated approval processes in some countries.

In summary, there is a need for the development and uptake of novel and repurposed TB medicines that:

- Shorten the duration of treatment for LTBI, DS-TB, and DR-TB;
- Improve cure rates for DR-TB;
- Interact safely and effectively with other TB medicines, ARVs, and medicines used in OST; and
- Are studied and developed for pediatric TB treatment.

In order to accomplish this, several hurdles must be cleared in research and development (R&D), the regulatory process, and the TB medicines market. Currently, TB R&D suffers from a lack of funding and insufficient infrastructure. Regulatory guidances do not provide enough clarity on the proposed integration of new TB medicines into current regimens, and approval processes and requirements vary among nations, making the development of new medicines even more time-consuming and expensive. Expedited conditional approval and compassionate use approval guidelines are unclear, as well.

Fragmented and unregulated markets make it challenging to forecast demand for TB medicines. There is poor planning at the national level for medicines procurement in many countries, and many cases of TB are undetected due to flawed diagnostics and inadequate case finding. These factors make it difficult to assess the need for TB medicines and to generate competition among manufacturers and suppliers. There is a substantial need to unite the private and public sectors through public-private mix programs (PPMs) in order to consolidate medicines purchasing, regulate quality, and accurately forecast demand, which will stimulate the TB medicines pipeline. Engaging regulatory bodies in this process will provide guidance and support for the production and sale of new TB treatments.

Executive summary

Background

In 2010, the World Health Organization (WHO) estimated that there were 8.8 million incident and 12 million prevalent cases of TB disease. It is estimated that tuberculosis (TB) killed 1.45 million people in 2010, including 320,000 women and 350,000 people with HIV, making it the leading cause of death among people with HIV. The global estimates for the 2009 cohort of patients showed a treatment success rate of 87% for smear-positive, DS-TB (World Health Organization 2011b). This statistic only applies to treatment of TB patients whose disease was detected via the sputum smear microscopy test, the most commonly used TB diagnostic. Omitted are treatment results for smear-negative pulmonary disease (in which there are too few bacteria in the sputum to be detected) and extrapulmonary disease (in which the disease occurs outside the lung). Extrapulmonary TB and smear-negative TB are more common among children and those who are HIV-positive. The treatment success rate is also much lower for DR-TB cases. Drug resistance cannot be identified by the smear test. In 2006, WHO estimated that only 20% of the TB cases worldwide were detected by sputum smear microscopy (World Health Organization 2006a). Thus, it is not surprising that in 2010 only 6.2 million cases of TB were reported to worldwide national TB programs (NTPs), leaving 30% of the world's TB cases unreported (World Health Organization 2011b).

TB treatment has challenges related to its duration, interactions with other medications, and ensuring treatment adherence. Many high-burden countries have treatment success rates lower than the global target of 85%, and the rate can be as low as 55% (World Health Organization 2011b). The current TB treatment regimens for DR-TB are less effective, and cure rates range from 30% to 80% depending on the severity of drug resistance (Orenstein 2009, Dheda 2010).

Rationale

The goal of this report is to provide TB stakeholders with an assessment of the TB medicines landscape so as to identify opportunities to improve market dynamics and ensure accessibility of safe and effective TB treatment.

To understand the challenges of current and future TB treatment, this landscape analysis describes:

- The current TB medicines available to treat TB infection and disease;
- The shortcomings of current treatments and the need for new TB treatments;
- The new TB medicines being developed and how they may address current challenges in TB treatment;
- The research and regulatory challenges impacting uptake of new TB medicines and what key players are doing to address these challenges; and
- Opportunities for market-based interventions to promote the development and uptake of new TB medicines.

Some sections in this report have been adapted from the TAG Pipeline Report 2012, which includes regularly updated review of the latest developments in TB medicines (http://www.pipelinereport.org). This UNITAID report is intended to complement the TAG Pipeline Report, with particular emphasis on market issues (as above) and treatment in low- and middle-income countries.

Key Findings

The field of TB research and development (R&D) has recently seen promising activity with approval and rollout of the most rapid test for TB ever developed – GeneXpert, progression of two promising TB medicine candidates into late-stage clinical trials, and increasing focus on developing potent new combinations of TB medicines; however, the TB R&D field is still underdeveloped. Due to costs and infrastructure requirements for its operation, GeneXpert cannot serve as a point-of-care (POC) test for most clinics in high TB burden areas, and the existing TB diagnostics pipeline is unlikely to provide a better candidate soon. Similarly, despite recent progress in TB medicine development, the clinical pipeline for TB medicines is far from robust, with only six novel and second-generation candidates. Moreover, the current late-stage candidates have primarily been evaluated in addition to a standardized regimen rather than as part of an entirely novel regimen. Thus, even if approved, the majority of these candidates would not radically alter the treatment paradigm as necessary to dramatically shorten TB treatment and combat the development of drug resistance.

Access to an accurate, inexpensive POC diagnostic test for TB is crucial – both for detecting individual TB cases and for correctly determining and documenting the true burden of TB. This would facilitate forecasting of a stable market for TB medicines, which could, in turn, stimulate more interest in developing new medicines and treatment regimens for TB. These new medicines and regimens are urgently needed to shorten and simplify treatment, address the growing problem of DR-TB, and better treat TB-infected children and people with HIV.

In order to develop and ensure access to better TB medicines, other obstacles also need to be addressed. These include research challenges like insufficient clinical trial capacity, unclear regulatory requirements for new treatment regimens, and the need to identify biomarkers that can predict cure, treatment failure, and relapse. Underpinning all of these research challenges is the need for increased funding for TB research: TB research faced a shortfall of almost US$1.4 billion in 2010, according to the annual targets set by the *Global Plan to Stop TB 2011-2015* (Jiménez-Levi 2012).

Market and access challenges also require attention. The public-sector market for TB medicines is fragmented, with the Stop TB Partnership's Global Drug Facility purchasing medicines for less than one-fifth of the public sector, and countries often purchasing medicines that are not quality assured. The quality of medicines and

their appropriate use is even more problematic in private-sector markets, where data, though scarce, indicate inappropriate dosing and regimens of TB medicines.

Stakeholders including the World Health Organization, the Global Drug Facility, the Global Alliance for TB Drug Development, the Clinton Health Access Initiative (CHAI), and Médecins Sans Frontières are working to increase the currently insufficient uptake of quality-assured medications; nonetheless, more work is essential. Increasing the uptake of public-private mix programs, driving accurate demand forecasting, pooling procurement to increase purchasing power and reduce prices, and encouraging competition among manufacturers are all necessary to ensure high-quality, low-priced TB medicines. Only by harmonizing public- and private-sector efforts to motivate TB diagnostic and medicine research, build research capacity, clarify regulatory guidance, and coordinate medicine procurement processes will the necessary effective medicines be accessible to protect the 8.8 million people who develop TB each year (World Health Organization 2011b).

Methodology

Findings from peer-reviewed literature and policy documents were combined with a survey of key institutions focused on improving TB treatment and the accessibility and rational use of TB medicines. The key informant survey does not capture the work of all institutions addressing TB treatment research and accessibility issues, though key informants were asked to identify other relevant institutions working on these issues. Most agencies identified were already surveyed for this analysis, indicating that the survey for this analysis reached most key institutions. Research for this report was conducted in 2012; information presented is up to date as of August 2012.

Introduction

The following report describes the TB medicines landscape, and identifies opportunities where market-based interventions can improve TB care by promoting the development and uptake of novel and repurposed medicines.

Section 1 outlines the existing medicines used in TB treatment, and identifies key areas of unmet need according to the current standard-of-care. Medicines in the pipeline are described, with a focus on how they are being developed to address these treatment needs. Section 2 goes on to discuss the R&D and regulatory challenges to the development of new TB medicines, and describes challenges in market that hinder the purchasing and competitive pricing of quality-assured TB medicines. Section 3 summarizes the key findings of this document.

In order to promote the uptake of new TB medicines, it is necessary to improve market forecasting through a better point-of-care (POC) diagnostic and intensified efforts to find TB cases. Consolidated purchasing in the public and private sectors, which can be accomplished in part through PPM programs, is also needed. Additionally, increased R&D and funding are necessary to maintain a strong pipeline of TB medicines, and regulatory agencies must be engaged to guide the integration of these novel medicines or regimens into the treatment paradigm. Through these interventions, it may be possible to incentivize the development of a robust TB medicines pipeline and the purchase of quality-assured medications, and to successfully improve the standard-of-care for TB.

Section 1:
Current products and the pipeline for TB medicines

This section outlines the current state of TB treatment. Section 1.1 describes the existing standard-of-care, including information on WHO-recommended first- and second-line medicines for TB. Section 1.2 outlines five key challenges in TB treatment, and Section 1.3 describes medicines in the pipeline and how they may address these five areas of unmet need. Finally, Section 1.4 describes the research challenges that hinder the development of novel TB medicines.

1.1 What is the current standard of care for TB?

The long-term goal of TB treatment is to prevent or cure disease, preserve life, improve and maintain health, prevent relapse, and prevent drug resistance from emerging. The short-term goal is to reduce infectiousness and restore health. Infectiousness is often measured by conversion from sputum smear positive to sputum smear negative or culture positive to culture negative.

In the years since the advent of TB treatment, clinical trials have yielded three basic principles upon which recommendations for treatment are based:

1. Regimens for treatment of TB disease must contain multiple medicines to which the organisms are susceptible;
2. The medicines must be taken together at appropriate dosing intervals; and
3. Therapy must continue for a sufficient period of time to ensure cure.

If any of these principles is not adhered to, the risk of treatment failure and the development of drug resistance increase.

The following sections describe the different types of TB infections and the medicines used to treat each of these, as well as the patent and licensure states of these medicines. Tables 1 and 2 summarize first-line medicines (FLM) and second-line medicines (SLMs) currently used in TB treatment.

1.1.1 Types of TB infection

Latent TB

Latent TB infection (LTBI) is a condition in which the immune system has successfully contained the TB bacilli and prevented disease. Each person who is latently infected with TB is a potential future case of TB disease. It is therefore vital to prevent the progression of latent TB infection to active disease.

Isoniazid is one of the two most powerful medicines used in first-line TB treatment regimens. It is highly effective in killing actively replicating TB bacteria and has been shown to reduce the risk of LTBI progressing to active disease when taken daily for 6-12 months. Data comparing the two regimens of daily isoniazid preventive therapy (IPT) did not show a significant difference in efficacy between the 6- and 12-month regimens, so WHO strongly recommends a 6-month regimen of daily IPT (World Health Organization 2010b). It is important

to remember that IPT is for people who are infected with TB but are not suffering any signs or symptoms of the disease and are well; someone who has symptoms consistent with TB may have TB or some other respiratory illness causing symptoms and disease and should not undergo IPT.

Recent clinical data demonstrate that a 12-week regimen of isoniazid and rifapentine given weekly as directly observed therapy (DOT) is equivalent in efficacy to a nine-month regimen of daily isoniazid without DOT, which was previously the standard-of-care in the US. Furthermore, the 12-week regimen has higher rates of completion than the nine-month alternative. Based on this data, the Centers for Disease Control and Prevention issued a statement in December 2011 that a 12-week, weekly DOT regimen of isoniazid and rifapentine is recommended as equivalent to a nine-month daily regimen of isoniazid in people who are twelve years old or above and are otherwise healthy, including people living with HIV who are not on ARVs (Centers for Disease Control and Prevention 2011b).

For people with HIV, IPT has been shown to significantly reduce incidence of TB disease, both before, and when taken in combination with, antiretroviral therapy (ART). Combined ART and IPT are more effective in reducing TB incidence than either treatment used individually (Golub 2007). WHO recommends at least 6-36 months of daily IPT for HIV-positive persons who are latently infected with TB to reduce the risk of developing active TB disease (World Health Organization 2010c, World Health Organization 2012b). The recommendation of 36 months – based on data that suggest that this duration of IPT significantly reduces the incidence of TB disease among people with HIV, particularly among those who were tuberculin skin test positive – is conditional because it is based on a single study (Samandari 2011). Other studies comparing a six-month regimen to regimens lasting three or six years offer conflicting evidence. One study suggests that there are no significant differences in efficacy, while another proposes that the longer duration of treatment may be better at reducing TB infection, but only while the subjects continue to take isoniazid, and that the adherence challenges of a longer regimen make it equivalent in efficacy to a shorter one (Swaminathan 2010, Martinson 2011).

Active TB disease

Active TB disease occurs when TB breaks out of latency and causes disease. Some individuals – usually infants and young children, and some people with HIV – may progress to active disease right after being infected with TB.

Drug-susceptible TB

Drug-susceptible TB (DS-TB) can be cured by first-line treatment. A combination of medicines, typically a four-drug regimen, is required to get adequate short- and long-term killing of DS-TB bacteria. There are two phases of treatment: an intensive phase and a continuation phase. The intensive phase of treatment is designed to kill actively growing and semidormant bacteria. This dramatically reduces bacillary burden and usually eliminates infectiousness within a couple of weeks. The continuation phase eliminates (sterilizes) the body of most or all residual bacteria and greatly reduces treatment failures and relapses. After an effective intensive phase of treatment, the numbers of bacteria are low and there is less chance of selecting drug-resistant bacteria; therefore, fewer medicines are needed during the continuation phase. The 2010 WHO TB treatment guidelines recommend:

- New patients with pulmonary TB receive two months of isoniazid (H)/rifampicin (R)/pyrazinamide (Z)/ethambutol (E), followed by four months of isoniazid and rifampicin (2HRZE/4HR).
- Patients with extrapulmonary TB are to be treated with the same regimens as those with pulmonary TB. Due to a high risk of disability or death, the length of treatment is extended to 9-12 months for TB meningitis. As treatment response is hard to monitor when TB infection is of the bones and joints, a nine-month treatment regimen is recommended. Cotreatment with corticosteroid is recommended for TB meningitis and pericarditis (unless drug resistance is suspected), and streptomycin should replace ethambutol in the treatment of TB meningitis (World Health Organization 2010f).
- Retreatment regimens add streptomycin during the intensive two-month treatment phase, followed by one month of isoniazid/rifampicin/pyrazinamide/ethambutol, followed by five months of isoniazid/rifampicin/ethambutol (2HRZES/1HRZE/5HRE).[1]

1 A person who experiences incomplete treatment or relapse after first-line therapy is referred to as a retreatment case and receives a five-drug intensive regimen. This, however, is controversial since if drug resistance has emerged, simply adding a fifth drug will only lead to further resistance. Therefore, it would be wise to use drug-susceptibility testing before retreatment to guide appropriate therapy.

An inadequate regimen may select for drug-resistant bacteria, particularly in patients with high bacillary counts – indicated by smear-positive TB – due to the high likelihood of preexisting resistance mutations among a large bacillary population that would result in the emergence of drug resistance while on therapy.

Drug-resistant TB

Pathogens such as *Mycobacterium tuberculosis* can develop resistance to the medicines used to treat them when people (i) do not complete a full course of treatment, (ii) are inconsistent about taking their medications, and/or (iii) have not been prescribed an appropriate treatment regimen. When the full course of treatment is not completed, the weakest and most drug-susceptible forms of the microbe are killed first, leaving room for drug-resistant forms to grow. TB drug resistance can also be transmitted. Persons who have never been treated for TB may find themselves with limited treatment options if they became infected with a drug-resistant strain. Suspected drug-resistant cases should be confirmed by drug susceptibility testing (DST) whenever possible. DST is inaccessible to most people with TB, however, as it requires specialized laboratories and is expensive (Syed 2011).

There are two types of drug-resistant TB:

- Multidrug-resistant TB (MDR-TB), which is no longer susceptible to the two most important FLMs, isoniazid and rifampicin; and
- Extensively drug-resistant TB (XDR-TB), which is resistant to isoniazid, rifampicin, fluoroquinolones (broad-based antibiotics used to treat a variety of bacterial infections), and any second-line injectable medicine.

Treatment of DR-TB can last from 18 to 24 months and sometimes longer. TB treatment regimens used to treat drug-resistant organisms may be individualized (designed on the basis of previous TB treatment history and individual DST results) or standardized (designed on the basis of representative drug resistance surveillance data), depending on the availability of DST and on national policy. Standardized regimens vary by region, but the WHO recommends that they include at least pyrazinamide, a fluoroquinolone, an injectable agent (not including streptomycin, which is not recommended for the treatment of DR-TB), a thioamide, and either cycloserine or p-aminosalicyic acid (PAS) (if cycloserine cannot be used) (World Health Organization 2011c). Please refer to Table 1 for a comparison of the medicines used in standardized regimens for DS-TB and DR-TB.

Table 1 Medicines Used in WHO-Recommended Standardized Regimens for DS- and DR-TB.

Medicine	DS-TB	DR-TB
Isoniazid	✓	
Rifampicin	✓	
Pyrazinamide	✓	✓
Ethambutol	✓	
Fluoroquinolone		✓
Injectable Agent		✓
Thioamide		✓
Cycloserine or PAS		✓

Some DR-TB regimens are standardized until DST results are available, and then treatment is individualized based on results. Individualized regimens are more efficacious but they require a higher level of laboratory infrastructure and the availability of skilled medical professionals. Cure rates for MDR-TB may reach 80% in the best-run health systems but usually hover between 50 and 60% (World Health Organization 2011g, Orenstein 2009), and can drop to 30% or below for XDR-TB patients who are HIV-negative (Dheda 2010, World Health Organization 2012a). Many, especially those with HIV, die before diagnosis.

Since 2006, cases of XDR-TB have been reported that are resistant to all first- and second-line TB medicines, and in some instances, are resistant to all available TB medicines. These cases have been called totally drug-resistant TB, although the term is not entirely appropriate, given that the drug stocks may vary from place to place, and that additional medicines (both current and future) may yet be effective in these patients. Cure rates for these strains can be extremely low, as seen with a 13% cure rate in one cohort of XDR-TB patients in Brazil, some of whom were resistant to second-line oral bacteriostatic agents and agents of unclear efficacy, as well as standard first- and second-line medicines (World Health Organization 2012a).

Please refer to Tables 2a-2c below for a summary of information on WHO-recommended first- and second-line medicines for the treatment of DS-TB and DR-TB.

Table 2a. Medicines Used in TB Treatment: First-line Oral Agents

	Isoniazid (H)	Rifampicin (R)	Ethambutol (E)	Pyrazinamide (Z)	Rifabutin	Rifapentine
Class		Rifamycin			Rifamycin	Rifamycin
WHO Drug Group Classification	First-line oral agent	First-line oral agent	First-line oral agent	First-line oral agent	First-line oral agent	First-line oral agent
Indication per SRA-approved label	DS-TB	DS-TB	DS-TB	DS-TB	Disseminated MAC disease in patients with HIV	DS-TB
WHO-recommended use	DS-TB	DS-TB	DS-TB	DS-TB	DS-TB in patients taking protease inhibitors; may be useful for those on opioid substitution therapy	None
Essential Medicines List	Yes – adults and children	Yes – adults and children	Yes – adults and children	Yes – adults and children	Yes – adults	No
Mode of action	Inhibits synthesis of cell wall	Inhibits RNA synthesis	Inhibits cell wall synthesis	Mechanism undetermined; may inhibit fatty acid synthase	Inhibits RNA synthesis	Inhibits RNA synthesis
Launch year*	1952	1963	1968	1956	1996	1998
Strength of Grades of Recommendation Assessment, Development, and Evaluation (GRADE) evidence**	High	High	High	High	No recommendation	No recommendation
Critical side effects	Skin rash, jaundice, hepatitis	Skin rash, jaundice, hepatitis, acute renal failure	Impairment of sight, hepatitis	Skin rash, jaundice, hepatitis, gout	Skin rash, chest pain, severe headache, muscle aches, flu-like symptoms, vision disturbances, jaundice	Skin rash, hives, swelling of mouth/face/lips/tongue, irregular heartbeat, diarrhea, fever, jaundice, nausea, vomiting, anorexia, may damage fetus in pregnant women

Table continued on next page

	Isoniazid (H)	Rifampicin (R)	Ethambutol (E)	Pyrazinamide (Z)	Rifabutin	Rifapentine
Critical interactions	May increase toxicity of acetaminophen, some antidepressants, benzodiazepines, anticoagulants, disulfiram, theophylline, and anticonvulsants	May reduce effects of some antiretrovirals, methadone, oral contraceptives, other compounds processed by cytochrome p450 enzyme	May interact with aluminum hydroxide	May interact with probenecid	May interact with oral contraceptives, antidiabetics, antimalarials, anticoagulants, or heart disease medications	May interact with antiretrovirals, oral contraceptives, anticonvulsants, heart medication, anticoagulants, antifungals, barbiturates, corticosteroids, beta blockers, hypoglycemics, methadone, antidepressants
Prequalified fixed-dose combinations (FDCs) for adults	Yes – available in HE, HRZE, HRE, HRZ, HR	Yes – available in HRZE, HRE, HRZ, HR	Yes – available in HE, HRZE, HRE	Yes – available in HRZE, HRZ	No	No
Pediatric formulations* **	Yes	Yes	Yes	Yes	No	No
WHO prequalified suppliers	Two suppliers – Micro Labs Ltd., Macleods Pharmaceuticals Ltd. (Available in FDCs from five suppliers – Macleods Pharmaceuticals Ltd., Lupin Ltd., Sandoz Pty Ltd., Wyeth Pakistan Ltd., Cadila Pharmaceuticals Ltd.)	None (Available in FDCs from four suppliers – Wyeth Pakistan Ltd., Lupin Ltd., Sandoz Pty Ltd., Macleods Pharmaceuticals Ltd.)	Three suppliers – Cadila Pharmaceuticals Ltd., Macleods Pharmaceuticals Ltd., Lupin Ltd. (Available in FDCs from five suppliers – Macleods Pharmaceuticals Ltd., Wyeth Pakistan Ltd., Lupin Ltd., Sandoz Pty Ltd., Cadila Pharmaceuticals Ltd.)	Three suppliers – Micro Labs Ltd., Cadila Pharmaceuticals Ltd., Macleods Pharmaceuticals Ltd. (Available in FDCs from four suppliers – Wyeth Pakistan Ltd., Lupin Ltd., Sandoz Pty Ltd., Macleods Pharmaceuticals Ltd.)	None	None

Notes: *Year in which medicine was approved by a stringent regulatory authority, although not necessarily for TB indication; **based on WHO's system to evaluate clinical trials GRADE; ***indicates pediatric formulations approved by a stringent regulatory authority or prequalified by WHO. None of these pediatric formulations are of the correct dosages recommended per WHO's Rapid Advice: Treatment of Tuberculosis in Children (2010).

Sources: AIDSinfo; DrugBank; Drugs.com; Institute of Medicine 2000; Knox 2011; McNeeley 2011; Medline Plus; PubMed Health; Report of an informal consultation on missing priority medicines for children 2011; Roehr 1998; Search Medica Rx; Stop TB Partnership/World Health Organization 2009; TB Online 2011a, 2011b; Treatment Action Group 2011; U.S. Food and Drug Administration 2011c; Van Niekerk 2011; Wishart 2006, 2008; World Health Organization 2010e, 2010f, 2010g, 2011d, 2011h, 2011i.

Table 2b. Medicines Used in TB Treatment: Second-line Medicines – Injectables and Fluoroquinolones

	Streptomycin (S)	Amikacin	Kanamycin	Capreomycin	Ofloxacin	Levofloxacin	Moxifloxacin
Class	Aminoglycoside	Aminoglycoside	Aminoglycoside	Polypeptide	Fluoroquinolone	Fluoroquinolone	Fluoroquinolone
WHO Drug Group Classification	Injectable agent	Injectable agent	Injectable agent	Injectable agent	Fluoroquinolone	Fluoroquinolone	Fluoroquinolone
Indication per SRA-approved label	Broad-spectrum antibiotic	Broad-spectrum antibiotic	Broad-spectrum antibiotic	DR-TB	Broad-spectrum antibiotic	Broad-spectrum antibiotic	Broad-spectrum antibiotic
WHO-recommended use	Extrapulmonary TB, retreatment regimens	DR-TB	DR-TB	DR-TB	DR-TB	DR-TB	DR-TB
Essential Medicines List	Yes – adults and children	Yes – adults and children	Yes – adults and children	Yes – adults and children	Yes – adults and children	Yes – adults and children	No
Mode of action	Inhibits protein synthesis	Inhibits protein synthesis	Inhibits protein synthesis	Thought to inhibit protein synthesis, induces some abnormal protein production	Inhibits DNA replication and transcription	Inhibits bacterial DNA replication and transcription	Inhibits bacterial DNA replication and transcription
Launch year	1944	1957	1957	1967	1990	1996	1999
Strength of GRADE evidence	No recommendation	Medium	Medium	Medium	High	High	High
Critical side effects	Skin rash, deafness, dizziness, decreased urine output	Vertigo, ringing in ears, hearing loss, reversible kidney damage, damages fetus in pregnant women	Vertigo, ringing in ears, hearing loss, reversible kidney damage, damages fetus in pregnant women	Vertigo, ringing in ears, hearing loss, kidney damage	Anorexia, nausea, vomiting, dizziness, headache, mood changes, tendonitis, tendon rupture, caffeinelike effect	Anorexia, nausea, vomiting, dizziness, headache, mood changes, tendonitis, tendon rupture, caffeinelike effect	Anorexia, nausea, vomiting, dizziness, headache, mood changes, tendonitis, tendon rupture, caffeinelike effect
Critical interactions	May interact with other ototoxic or nephrotoxic drugs, may damage fetus in pregnant women	May interact with other nephrotoxic or ototoxic drugs, neuromuscular blocking drugs, diuretics	May interact with lithium, diuretics, methotrexates, anti-inflammatory or anti-pain drugs, anticolitis drugs, immunosuppressants, antiviral drugs, cancer medication, neuromuscular blocking drugs, other nephrotoxic or ototoxic drugs	May interact with lithium, methotrexate, pain medications, antiarthritis drugs, anticolitis drugs, immunosuppressants, antiviral drugs, cancer medication, other ototoxic and nephrotoxic drugs	May interact with antacids, anticoagulants, antidepressants, antipsychotics, caffeine, cyclosporine, diuretics, heart medication, anti-inflammatory drugs, vitamins	May interact with antacids, anticoagulants, antidepressants, antipsychotics, cyclosporine, diuretics, antidiabetics, heart medication, anti-inflammatory drugs, vitamins	May interact with antacids, anticoagulants, antidepressants, antipsychotics, diuretics, heart medication, anti-inflammatory drugs, vitamins
Pediatric formulations	Yes	Yes	No	No	No	Yes	No
WHO prequalified suppliers	None	One supplier – Cipla Ltd.	None	None	One supplier – Cipla Ltd.	One supplier – Cipla Ltd.	One supplier – Cipla Ltd.

Sources: DrugBank, Drugs.com, Institute of Medicine 2000; Knox 2011; Médecins Sans Frontières/International Union Against Tuberculosis and Lung Disease 2011; Medline Plus; PubMed Health; Search Medica Rx; TB Online 2011a, 2011b; Treatment Action Group 2011; U.S. Food and Drug Administration 2011c; Wishart 2006, 2008; World Health Organization 2010e, 2010f, 2010g, 2011c, 2011d, 2011h, 2011i.

Table 2c. Medicines Used in TB Treatment: Second-Line Oral Bacteriostatic Agents and Agents of Unclear Efficacy

	Ethionamide	Prothionamide	Cycloserine	Terizidone	P-aminosalicylic acid	Linezolid	Thioacetazone
Class	Thioamide	Thioamide	D-alanine analog	D-alanine analog	Salicylic acid -anti-folate	Oxazolidinone	
WHO Drug Group Classification	Oral bacteriostatic second-line agent	Oral bacteriostatic second-line agent	Oral bacteriostatic second-line agent	Oral bacteriostatic second-line agent	Oral bacteriostatic second-line agent	Agent with unclear role in treatment of DR-TB	Agent with unclear role in treatment of DR-TB
Indication per SRA-approved label	DR-TB	DR-TB	DR-TB	DR-TB	DR-TB	Broad-spectrum antibiotic	DR-TB
WHO-recommended use	DR-TB	DR-TB	DR-TB	DR-TB	DR-TB	DR-TB	DR-TB
Essential Medicines List	Yes – adults and children	No	Yes – adults and children	No	Yes – adults and children	No	No
Mode of action	Inhibits protein synthesis	Inhibits protein synthesis	Inhibits cell wall synthesis	Inhibits cell wall synthesis	May inhibit cell wall synthesis, inhibits folic acid synthesis	Inhibits protein synthesis	Interferes with cell wall synthesis
Launch year	1966	2005	1955	1970s	1944	2000	1946
Strength of GRADE evidence	Medium	Medium	Medium	No GRADE recommendation	Medium	No GRADE recommendation	No GRADE recommendation
Critical side effects	Anorexia, salivation, nausea, abdominal pain, diarrhea, central nervous system impairment, hepatitis, damages fetus in pregnant women	Anorexia, salivation, nausea, abdominal pain, diarrhea, central nervous system impairment, hepatitis, damages fetus in pregnant women	Neurological and psychiatric disturbances including depression, headaches, anxiety, aggression psychosis, paranoia, dizziness, slurred speech, convulsions; nausea, vomiting, skin allergies	Neurological and psychiatric disturbances including depression, headaches, anxiety, aggression, psychosis, paranoia, dizziness, slurred speech, convulsions; nausea, vomiting, skin allergies	Fever, rash, itchiness, anorexia, nausea, vomiting, stomach pain	Headache, nausea, vomiting, insomnia, constipation, rash, dizziness, tongue discoloration, taste alteration, oral thrush	Nausea, vomiting, diarrhea, anorexia, rash, aches, vision disturbances, seizures, mood changes, fever, jaundice, blood cell deficiencies, severe cutaneous hypersensitivity

Table continued on next page

	Ethionamide	Prothionamide	Cycloserine	Terizidone	P-aminosalicylic acid	Linezolid	Thioacetazone
Critical interactions	May interact with ethanol, other antituberculosis drugs (including cycloserine, isoniazid, and rifamycins)	May interact with cycloserine, rifamycins, ethanol	May interact with ethanol, antiseizure drugs, other antituberculosis drugs (including ethionamide, prothionamide, isoniazid)	May interact with ethanol, antiseizure drugs, other antituberculosis drugs (including ethionamide, prothionamide, isoniazid)	May interact with rifampicin, vitamin B12, digoxin, salicylates, aminosalicylates, probenecid, anticoagulants, ammonium chloride	May interact with MAO inhibitors, antidepressants, antipsychotics, Parkinson's disease drugs, restless leg syndrome drugs, headache drugs, stimulants, allergy drugs, ADHD drugs, pain medications	Unavailable; isoniazid/thioacetazone may interact with pain medication, steroids, oral contraceptives, heart medication, thyroid medication, antimalarials, chemotherapy drugs, muscle relaxants, psoriasis drugs, arthritis drugs, immunosuppressants, blood pressure drugs, antialcoholism drugs, antipsychotics, antibiotics, other ototoxic or nephrotoxic drugs
Pediatric formulations	No	No	No	No	No	Yes	No
WHO prequalified suppliers	Two suppliers – Macleods Pharmaceuticals Ltd., Cipla Ltd.	None	Two suppliers – Aspen Pharmacare Ltd., Macleods Pharmaceuticals Ltd.	None	Two suppliers – OlainFarm JSC, Macleods Pharmaceuticals Ltd.	None	None

Sources: Alahari 2007; DrugBank; Drugs.com; Institute of Medicine 2000; Knox 2011; Médecins Sans Frontières/International Union Against Tuberculosis and Lung Disease 2011; Medline Plus; PubMed Health; Search Medica Rx; TB Online 2011a, 2011b; Treatment Action Group 2011; U.S. Food and Drug Administration 2011c; Wishart 2006, 2008; World Health Organization 2008a, 2010e, 2010f, 2010g, 2011c, 2011d, 2011h, 2011i.

1.1.2 Current Patent and Licensing Status for TB Medicines

The medicines used in first-line treatment – isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) – are no longer under patent and can be reproduced by generic medicine developers. As a result, the cost of a six-month regimen of the combination HRZE is less than US$20 (Médecins Sans Frontières/International Union Against Tuberculosis and Lung Disease 2011). However, the costs to the health system and those to the patient vary widely by country and setting. A 2008 study from Lusaka, Zambia, has found that "[t]he median total patient costs for diagnosis and 2 months of treatment was US$24.78 ... per patient – equivalent to 47.8% of patients' median monthly income" (Aspler 2008). In Rio de Janeiro, Brazil, "Costs per completed treatment were US$194 for patients and US$189 for the health system in SAT [self-administered therapy] facilities, compared to US$336 and US$726 in DOT [directly observed therapy] facilities" (Steffen 2010). Meanwhile, a systematic review from China found that "[l]ow income patients, defined at household or district level, pay a total of US$149 to 724 (RMB 1241 to 5228) for medical costs for a treatment course; as a percentage of annual household income, estimates range from 42% to 119%. One national survey showed 73% of TB patients at the time of the survey had interrupted or suspended treatment" (Long 2011).

Rifapentine and rifabutin – medicines that may be used in place of rifampicin in some cases – are also off patent. The inventor of rifapentine, Sanofi-Aventis, has reinvested in the development of the medicine even though it no longer holds exclusive rights and is working to broaden the medicine's TB indication to increase future use in preventive therapy and for the full duration of treatment of active TB. In August 2009, several months after WHO added rifabutin to the Essential Medicines List, CHAI negotiated an agreement with Pfizer to sell rifabutin at US$1 per dose, a 60% cost reduction (Clinton Health Access Initiative 2009). A six-month regimen of rifabutin now costs $90 (TB Online 2011b). Rifabutin is particularly indicated as a substitute for rifampicin among HIV-positive persons receiving ART containing a boosted protease inhibitor (PI) while undergoing first-line TB treatment, though in some cases the rifabutin or PI dose must be adjusted (Centers for Disease Control and Prevention 2007). These recent developments have the potential to make rifapentine and rifabutin potentially more accessible once more data are available on how best to use them. Currently, the Global Drug Facility does not procure rifapentine or single-dose rifampicin pills (Stop TB Partnership 2011a) and costs vary among countries. The cost for one rifapentine tablet ranges from $2 (W. MacKenzie, personal communication, 23 November 2011) to $3.63, and the cost of a single dose 150 mg rifampicin tablet in South Africa varies from R0.58 (approximately US$0.07) in the public sector to R1.29 (approximately US$0.15) in the private sector (TB Online 2011b). By comparison, one tablet of 150 mg rifampicin costs approximately $2.57 in Zambia (Pham and Bartlett 2010). When procured through the U.S. Veterans Administration, a 300 mg rifampicin tablet costs $0.58 in the United States (W. MacKenzie, personal communication, 23 November 2011). Please refer to Table 3 for a summary of this information.

Table 3. Varying costs of rifamycins among countries

	Rifampicin 150 mg (US$)	Rifampicin 300 mg (US$)	Rifabutin 150 mg (US$)	Rifapentine 150 mg (US$)
United States	--	$0.58	$1.00	$2.00 – 3.63
South Africa	$0.07 – 0.15	--	--	--
Zambia	$2.57	--	--	--

Most of the medicines used in second-line treatment are not licensed for a TB indication by stringent regulatory authorities, though some – para-aminosalicylic acid, capreomycin, ethionamide, and cycloserine – were approved by the U.S. Food and Drug Administration (FDA) in the 1950s and '60s (Institute of Medicine 2000). These medicines are included in WHO treatment guidelines because of the unmet medical need of DR-TB treatment. Introduced in the 1990s, the fluoroquinolones ciprofloxacin, ofloxacin, and levofloxacin were approved by the FDA in 1990, 1990, and 1996, respectively, but as broad-spectrum antibiotics and not for TB (Institute of Medicine 2000). Bayer's first U.S. patent on Avelox (generic name: moxifloxacin) expired in December 2011 (U.S. Patent and Trademark Office 2011). Its second U.S. patent extends through March 2014, shortly before

which Teva Pharmaceuticals USA, Inc. will begin selling a generic form of the medicine (Bayer 2008). For the SLMs that still have patents, the status will vary from country to country based on when the patents were granted and the country-specific rules. Patents do not seem to be the pressing issue that is preventing more manufacturers from producing these medicines. The absence of clear demand for quality-assured (QA) medicines is a greater factor preventing more manufacturers from entering the TB field and from engaging in robust competition to reduce the cost of SLMs.

1.2 What are the challenges of current TB treatment?

Current treatment strategies and vaccines are not sufficient to reach the Stop TB Partnership's goal of eliminating TB by 2050. Depending on whether it is for DS- or DR-TB, treatment takes from six months to two years to complete, requires patients to take multiple pills (in some cases at different times of day), and causes a range of side effects from mild nausea to severe (and potentially irreversible) side effects like deafness. Cure rates for DS-TB may reach 95% within well-controlled research settings, but this is not the case for the majority of locations. Many patients access their care in settings where actual cure rates do not reach the global treatment target of 85% and are lower than 60% because of poor TB-control programs (World Health Organization 2010c). Patients may find themselves relapsing or failing treatment because they did not receive adequate support to complete their regimen or were not given the appropriate regimen. The situation for DR-TB is more dismal and is exacerbated by HIV. One of the main barriers to increasing the cure rate for TB is a need for better medicines and a shorter treatment regime. In the absence of new medicines, there is a need for better data on how best to use current medicines, especially in patients coinfected with HIV and in children.

Improved treatment options are especially important because the only TB vaccine currently used, the Bacille Calmette Guérin vaccine, does not protect children from pulmonary TB, loses its efficacy by the time those vaccinated reach adolescence, and is not recommended for children with HIV (Wingfield 2011). To effectively reduce TB disease and deaths, vastly improved diagnostics are also needed to identify those in need of treatment.

A number of significant challenges in TB treatment that require attention are discussed below, including:

- Implementation of isoniazid prevention therapy to treat LTBI;
- Long duration of treatment for both DS- and DR-TB;
- Drug-drug interactions among TB medicines, and between TB medicines and ARVs and OST;
- Low cure rates for DR-TB; and
- Treatment of pediatric patients with TB.

1.2.1 Implementation challenges of IPT

Despite WHO's recommendation and evidence showing IPT to be a valuable intervention to reduce the incidence of TB disease by decreasing the risk of contracting TB up to 67% in people with HIV (World Health Organization 2008b), its implementation is poor throughout the world (World Health Organization 2010b). Approximately one-third of the population, or over two billion people worldwide, are estimated to be infected with LTBI (World Health Organization 2006a). However, given that LTBI is asymptomatic, people with latent infection do not seek care. Moreover, programmatic efforts to identify and treat close contacts of TB cases, or people with HIV, are often limited: in 2010, only 178,000 HIV-positive people – less than 1% of people with HIV – were offered IPT (World Health Organization 2010c, World Health Organization 2011b). Isoniazid preventive therapy is, by its very nature, a therapy for healthy people – or at least those without active TB disease – making the long duration of treatment, side effects, and uncertainty of durability an adherence challenge. Another barrier to its implementation is provider uncertainty over the ability to exclude active TB due to poor diagnostics. Few countries have policies providing IPT to people who are latently infected with TB. Of those that do have a policy, a small minority consistently implement it. WHO data from 2007 show that 100 countries had a national IPT policy, but only 29% successfully carried it out (World Health Organization 2009).

1.2.2 Duration of treatment

Treatment for DS-TB lasts six months and involves taking multiple pills, which presents a challenge for adherence. This is further compounded in patients with DR-TB, who have a higher pill burden and experience more side effects. Side effects and pill burden are especially important factors for patients coinfected with HIV. As pa-

tients with TB often feel better once on treatment, ensuring full compliance for a 6-month regimen is extremely challenging. Regimens for latent infection and active disease last anywhere from 6 to 36 months and WHO recommends every dose of DR-TB treatment and the intensive phase of first-line treatment be given as DOT as opposed to self administration (World Health Organization 2010f).

1.2.3 Drug-drug interactions

There are limited data on the drug-drug interactions of most TB medications with treatments for other diseases or conditions, particularly with ART and opioid substitution therapy (OST).

Rifampicin was the first medicine in the rifamycin class, which also includes rifabutin and rifapentine. These medicines kill nonreplicating persistent organisms – those trapped inside cells and lung cavities – which are not easily accessed by many other medicines; thus, rifampicin-based regimens are much more potent than non-rifampicin-based regimens for DS-TB. However, because rifampicin induces the cytochrome p450 liver enzyme, it speeds the metabolism and removal of many other medicines from the body, including certain key antiretrovirals (ARVs), such as the nonnucleoside reverse transcriptase inhibitors and PIs (Centers for Disease Control and Prevention 2007; World Health Organization 2010f). The magnitude and duration of rifampicin exposure determines the level of interaction. Insufficient concentrations of ARVs are likely to lead to the emergence of drug-resistant HIV.

Drug use is associated with an increased risk of being latently infected with TB and having TB disease (Deiss 2009). Reasons may include malnutrition, marginal housing, and poor housing conditions like overcrowding and bad ventilation. Unfortunately, despite the increased risk for TB among drug users, TB programs do not adequately address preventing and treating the disease in this population.

For some drug users who are dependent on opioids – a class of drugs that includes heroin, opium, morphine, and codeine – there are medications that may be used to help prevent withdrawal symptoms and reduce craving. Methadone and buprenorphine are the most studied and commonly used medications for OST. However, it appears that rifampicin and rifapentine lower the levels of methadone and buprenorphine, requiring a significant adjustment in the dosages of OST. No interactions have been reported between methadone or buprenorphine and rifabutin; as such, rifabutin may be considered as an alternative, but there are limited data available to support this recommendation (Brown 1996, McCance-Katz 2011). There are little to no data on interactions between OST and other TB medicines, particularly for DR-TB.

1.2.4 Poor cure rates for MDR-TB and XDR-TB

Cure rates for MDR-TB are typically between 50 and 60% (World Health Organization 2011g, Orenstein 2009); the cure rate for XDR-TB can be much lower, falling beneath 30% (Dheda 2010, World Health Organization 2012a). Most of the medicines used to treat DR-TB are not licensed for TB by stringent regulatory authorities but are used in treatment because they have shown activity through clinical practice as opposed to randomized, controlled clinical studies. Therefore much of the data guiding dosing, safety and toxicity, and drug-drug interactions in adults and children are based on anecdotal evidence.

1.2.5 Pediatric challenges

Children, particularly infants and children under five years of age, are at much higher risk for being latently infected and developing more severe disease. There is insufficient evidence to guide clinicians in determining appropriate treatment for children, especially for those with DR-TB. There are considerable differences in national recommendations in pediatric medicine dosing, and many children receive subtherapeutic levels of TB medicines (Ramachandran 2011). After revising its formulary in 2009, WHO issued *Rapid Advice: Treatment of Tuberculosis in Children* in 2010 to provide a framework for accurate dosing of first-line treatments for children (World Health Organization 2010e). While the principles of treatment in children and adults are the same, the dosages are not (Graham 2010). Children and adults metabolize medicines differently; therefore, doses for children cannot simply be determined by scaling down the adult dose per kilogram (Ramachandran 2011).

The 2010 WHO guidelines accounted for these differences and updated the recommended dosages of the FLMs isoniazid, rifampicin, pyrazinamide, and ethambutol. These updated doses have also received support from the European Medicines Agency (EMA) (European Medicines Agency 2012). Unfortunately, implementing these

new recommendations is challenging for national programs because child-friendly formulations (e.g. crushable, dispersible, or scored tablets or capsules) of current single-dose medicines do not exist for the new dosing recommendations. The pediatric fixed-dose combination (FDC) formulations available on the market today are not tailored to deliver the new dosages, and complex interim dosing guidelines using the current unsuitable FDC have hindered the implementation of these recommendations and present operational challenges. It is vital that manufacturers produce a new FDC for DS-TB in children, but there is hesitancy to move forward until clear guidance is given for its composition (i.e., the number of medicines and dosages for each medicine included in the FDC). Formulation challenges are also significant and need to be resolved to manufacture FDCs that meet the new WHO dosing guidelines. No children have been included in studies of SLMs, and as a result there are no clinical trials data guiding how to use these medicines in children. Treatment providers have encouraged the WHO to establish recommendations for the composition of a new FDC for pediatric first-line treatment that corresponds to the new pediatric dosing guidelines. Once the agreed new FDC formulations are on the WHO Prequalification Expression of Interest (EOI) list for drug manufacturers, manufacturers will need to be engaged to start production of these FDCs as quickly as possible.

1.3 How is the pipeline addressing the gaps in current treatment regimens?

To address some of the challenges of TB treatment, current medicines are being repurposed and new compounds are being developed. Six new compounds from existing and novel medicine classes are being evaluated in phase II and III clinical trials, and existing medicines that have been used off-label to treat TB and other bacterial infections are being repurposed to shorten treatment duration, reduce adverse events, and improve treatment outcomes. Two of these novel compounds were being considered for regulatory approval as of August 2012.

This section describes these repurposed and novel compounds, as well as novel TB regimens being studied. Figure 1 illustrates the stage to which each compound has advanced in the development pipeline, and the chemical classes to which each belongs. Tables 4-6 provide summaries of their development and the ways in which these medicines may affect the current landscape of TB care.

Additionally, this section explains how these compounds might be able to address the five key challenges in TB treatment previously discussed – IPT implementation, duration of treatment, drug-drug interactions, poor cure rates for DR-TB, and pediatric TB treatment.

Figure 1: Pipeline of TB medicine development (Mendel 2012)

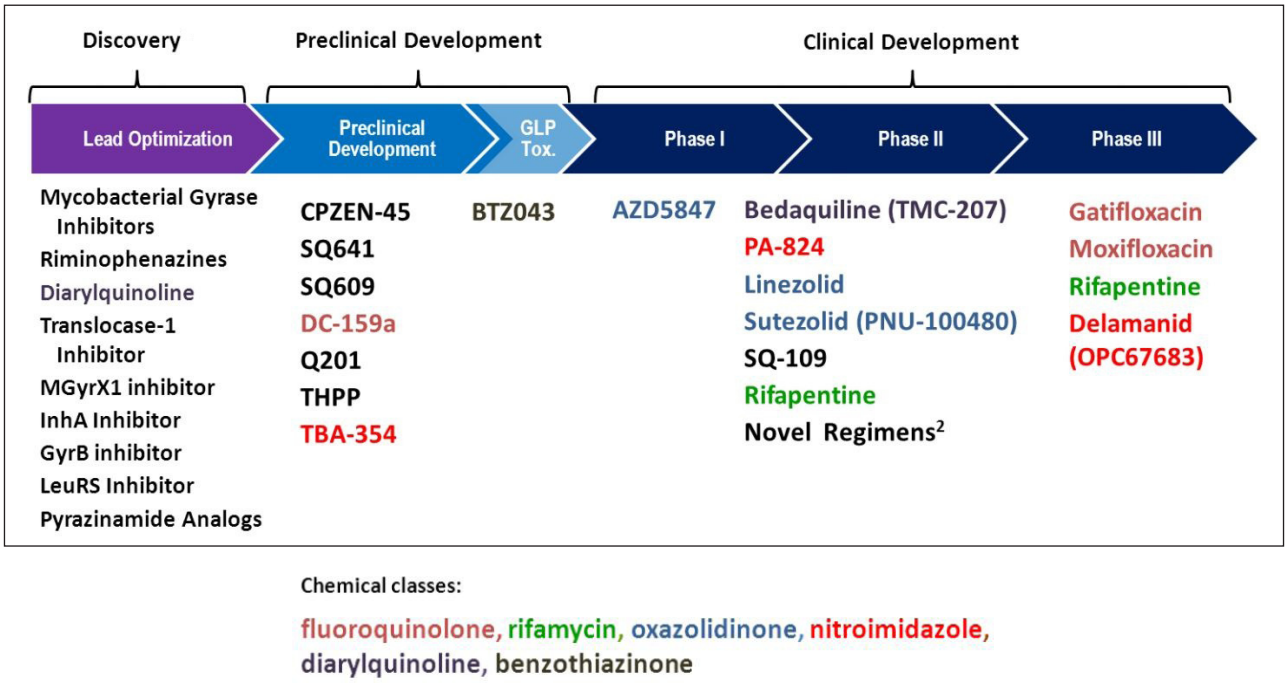


Table 4. Existing Medicines (Approved and Unapproved for a TB Indication) Being Repurposed to Improve TB Treatment (as of August 2012)

Medicine	Class	Selected Sponsors	Phases of Development	Proposed Indications	Strategy
Rifapentine	Rifamycin	CDC/TBTC‡; NIAID+++; ACTG*; IMPAACT**; Sanofi-Aventis; FDA ++; EDCTP+; INTERTB†; Johns Hopkins University	Phases I – III	LTBI DS-TB	Treatment shortening (replace rifampicin, supplement isoniazid in IPT)
Rifampicin (high dose)	Rifamycin	Harvard University; Radboud University; NIAID+++; EDCTP+; INTERTB†; Universitas Padjadjaran	Phase II	DS-TB TB Meningitis	Treatment shortening (replace standard rifampicin)
Rifabutin	Rifamycin	CDC/TBTC ‡; Pfizer; French National Agency for Research on AIDS and Viral Hepatitis	Phases I – Phase IV	DS-TB	Reduce drug-drug interactions with selected ARVs (replace rifampicin)
Gatifloxacin	Fluoroquinolone	Gatifloxacin for TB (OFLOTUB) Study Team WHO/TDR ‡‡‡; IRD†††	Phase III	DS-TB/ DR-TB	Treatment shortening (replace other fluoroquinolones)
Clofazimine	Riminophenazine	TB Alliance; IUATLD ††; MRC-U.K. ‡‡	Phase II [planned]	DS-TB/DR-TB	Treatment shortening (novel regimens with PA-824 and TMC-207)
Moxifloxacin	Fluoroquinolone	Universitas Padjadjaran; TB Alliance; Bayer; MRC-U.K. ‡‡; EDCTP+; KEMRI***; INTERTB†; CDC/TBTC‡; IUATLD ††; University College, London; Johns Hopkins University	Phases II - III	DS-TB TB Meningitis	Treatment shortening (replace ethambutol or isoniazid)

* AIDS Clinical Trials Group

‡ Centers for Disease Control and Prevention/TB Trials Consortium

\+ European and Developing Countries Clinical Trials Partnership

††† French Institut de Recherche pour le Développement

† International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis

†† International Union Against Tuberculosis and Lung Disease

** International Pediatric Maternal Adolescent AIDS Clinical Trials Group

*** Kenya Medical Research Institute

+++ National Institutes of Allergy and Infectious Diseases

‡‡ British Medical Research Council

++ U.S. Food and Drug Administration

‡‡‡ World Health Organization-based Special Programme for Research and Training in Tropical Diseases

Sources: ClinicalTrials.gov 2011a, 2011b, 2011d, 2011e, 2011f, 2012b, 2012f, 2012g, 2012h, London School of Hygiene and Tropical Medicine 2011, Mendel 2012.

Table 5. Novel and Second-generation Compounds (as of August 2012)

Medicine	Class	Sponsor	Phase	Indication	New Combination Study	Estimated Date of Regulatory Approval
AZD5847	Oxazolidinone*	AstraZeneca	Phase IIa *one study recruiting*	TBA	No	2017
PNU-100480 (sutezolid)	Oxazolidinone*	Pfizer	Phase IIa *one study completed*	DR-TB	No	2016 2018
SQ 109	Diamine*	Sequella/ PanACEA	Phase II *one study completed*	DS-TB DR-TB	No	2015 2017
PA-824	Nitroimidazole**	TB Alliance	Phase II *one study not yet recruiting, three completed*	DS-TB DR-TB	Yes (NC001, NC002, NC003)	2015 2017
OPC-67683 (delamanid)	Nitroimidazole**	Otsuka	Phase III *one study recruiting* Phase II *two studies completed, one ongoing*	DR-TB	No	2012 (Filed for approval in Europe in late 2011, decision pending; accelerated approval anticipated in some countries)
TMC207 (bedaquiline)	Diarylquinoline**	TB Alliance/ Janssen Janssen	Phase II *three studies ongoing, two completed*	DS-TB DR-TB	Yes (NC001, NC003)	2012 (Filed for approval in the U.S. in 2012, accelerated approval in some countries)

* Second-generation medicine; ** New medicine class.

NB: strategy not included in this table because strategies are not yet developed for the majority of the novel and second-generation compounds.

Sources: ClinicalTrials.gov 2011c, 2012a, 2012c, 2012d, 2012e, 2012i, 2012j

Table 6. Repurposed, Novel, and Second-generation Medicines by Indication and Potential Regimen Implications

Medicine	Indication						In Clinical Development As Part of Novel Regimen	Notes
	LTBI	DS-TB	DS-TB: shorten treatment	DS-TB: reduce drug-drug interactions	DR-TB	TB Meningitis		
Rifapentine*	✓	✓	✓					Medicines in the rifamycin class are in various stages of development to optimize treatment for latent TB and for active, DS-TB by replacing or increasing the dosage of rifampicin. MDR-TB is, by definition, resistant to rifampicin, and therefore these drugs are not in development for DR-TB.
Rifampicin (high dose)*		✓	✓			✓		
Rifabutin*		✓		✓				
Moxifloxacin*		✓	✓		✓	✓	✓	In development for DS- and DR-TB in combination with: 1) Pyrazinamide, PA-824
Gatifloxacin*		✓	✓		✓			Gatifloxacin is not being developed as part of a novel regimen; the OFLOTUB study, for example, is evaluating whether gatifloxacin can replace ethambutol to shorten first-line treatment.
Clofazimine*		✓			✓		✓	In development for DS- and DR-TB in combination with: 1) PA-824, TMC-207 2) TMC-207, pyrazinamide 3) PA-824, pyrazinamide, clofazimine
TMC207 (bedaquiline)		✓			✓		✓	In development for DS- and DR-TB in combination with: 1) PA-824, pyrazinamide 2) PA-824, clofazimine 3) Pyrazinamide, clofazimine 4) PA-824, pyrazinamide, clofazimine
PA-824		✓		✓	✓		✓	In development for DS- and DR-TB in combination with: 1) Moxifloxacin, pyrazinamide 2) TMC-207, clofazimine 3) TMC-207, pyrazinamide, clofazimine
SQ109		✓			✓			These new medicines in development have not yet been tested as part of a novel combination, nor have their sponsors indicated plans to do so.
OPC-67683 (delamanid)				✓	✓			
AZD5847 ‡								
PNU-100480 (sutezolid)					✓			

* Existing/repurposed medicine.
‡ AstraZeneca has not yet announced the proposed indication for AZD5847.

1.3.1 Novel and repurposed compound development and patent information

AstraZeneca Pharmaceuticals and Pfizer each have a second-generation compound from the oxazolidinone class of medicines. AstraZeneca has yet to announce whether it will be pursuing AZD5847 for DS-TB and/or DR-TB, while Pfizer is developing PNU-100480 for DR-TB. These compounds are still in early clinical development but have been shown to be well tolerated and appear superior to previous oxazolidinones (e.g., linezolid). Recently released results from a phase IIa early bactericidal activity (EBA) study showed PNU-100480 to reduce the mycobacterial burden in sputum, and to be safe and reasonably well-tolerated (Wallis 2012).

Sequella's SQ109 is a distant cousin of ethambutol – a medicine used in first-line treatment to prevent the development of isoniazid-resistant TB. The company is working with collaborators from Africa and Eastern Europe to evaluate SQ109 for both DS-TB and DR-TB. Sequella recently completed a phase II EBA trial and is planning on initiating further phase II and III studies in 2012. Sequella will be conducting some studies in 2012 and 2013 in collaboration with the AIDS Clinical Trials Group (ACTG), and will be collaborating with the Maxwell Biotech Venture Fund to conduct a phase II/III study in patients with DR-TB in late 2012, as well (G. Horwith, personal communication, 18 April 2012).

PA-824 comes from a new class of medicines known as nitroimidazoles and is licensed by the Global Alliance for TB Drug Development (TB Alliance) from the former biotech company Chiron. The TB Alliance is developing PA-824 as one component of novel three-medicine regimens including moxifloxacin, pyrazinamide, clofazamine, and bedaquiline to be tested for treatment of both DS-TB and DR-TB. Data from a recent phase II study of this regimen have shown it to be as good as the standard of care of HRZE (Diacon 2011a). Because this regimen does not include isoniazid or rifampicin it may be useful for both DS-TB and some forms of MDR-TB and may be compatible with ARVs.

The TB Alliance does not plan to hold a patent for PA-824. To make PA-824 accessible, the TB Alliance may attempt to stimulate competition between generic manufacturers that will commit to producing the medicine based on quality standards (M. Spigelman, personal communication, 19 October 2011).

The two novel compounds that are farthest along in the clinical development pipeline are delamanid (formerly known as OPC67683) from Otsuka Pharmaceuticals and bedaquiline (formerly known as TMC207) from Janssen Infectious Diseases BVBA (a subsidiary of Johnson & Johnson formerly known as Tibotec). Otsuka filed with the EMA in the fourth quarter of 2011 for accelerated approval for a DR-TB indication (M. Destito, personal communication, 11 July 2012), and expects to receive a decision sometime in 2013. Janssen filed with the FDA in 2012 for accelerated approval for a DR-TB indication, as well (Johnson & Johnson 2012).

Delamanid comes from the same class of medicines as PA-824, the nitroimidazoles. Final data from its phase IIb clinical trial showed that patients on an optimized background regimen (OBR) plus 100 mg and 200 mg delamanid had higher rates of sputum culture conversion at two months than patients on OBR plus placebo, with 45.4% and 41.9% converting on delamanid versus 29.6% on placebo (Gler 2012). Otsuka has initiated a phase III study, moving the product into the next phase of development based on the successful phase IIb results. It is promising to see that people on ARVs, often excluded from TB treatment trials, are included in this study. The company has initiated its pediatric investigational plan and is working on an appropriate formulation for children. The company is in the process of applying for a patent for delamanid and is planning to produce the medicine itself. As of August 2012, the company had not made any further decisions on how it would ensure global access and affordability to QA medicine. Otsuka recently applied for accelerated approval for treatment of DR-TB in Europe through the EMA, and has not revealed any other plans for phased introduction of delamanid into the global market.

Bedaquiline is the first compound from a new class of medicines called diarylquinolines, and is being considered for treatment of LTBI as well as DS-TB and DR-TB. Phase II data show that when added to a standard background MDR-TB regimen, the medicine could shorten time to culture conversion and increased the number of culture conversions (D. F. McNeeley, personal communication, 25 October 2010). Janssen Therapeutics, formerly Tibotec, is finalizing data from a phase IIb study of bedaquiline in patients with DR-TB, and recently published two-year follow-up data from an early phase II trial, indicating that bedaquiline shortened time to culture conversion, with lower rates of acquired resistance to other TB medicines (Diacon 2012). An analysis of another ongoing, open-label study in people with smear-positive, confirmed MDR- or XDR-TB also demonstrated promising results, with 81% sputum conversion at 24 weeks (Haxaire 2011). Janssen is the first com-

pany to provide access to its compound preapproval, and has initiated a compassionate use program to provide access to bedaquiline to XDR- or pre-XDR-TB patients who have no other treatment options and are ineligible to participate in any other bedaquiline study. The compassionate use program is currently providing bedaquiline to at least 48 patients in 12 countries, in response to individual requests from health care providers on behalf of their patients. France alone accounts for half of these patients (M. Haxaire-Theeuwes, personal communication, 29 March 2012). A phase III study is in development and will evaluate bedaquiline with the nine-month regimen used in the Bangladesh study described below (replacing gatifloxacin with high-dose levofloxacin) as background regimen (M. Haxaire-Theeuwes, personal communication, 30 September 2011).

Janssen has granted the TB Alliance rights to develop bedaquiline for DS-TB. After completing dose-finding studies, the TB Alliance is pursuing the compound as a potential building block for future regimen change. A recent study found evidence that the combination of pyrazinamide – a medicine that is able to kill TB bacteria inside of cells – and bedaquiline appeared to have greater bactericidal activity than HRZE (Diacon 2011b).

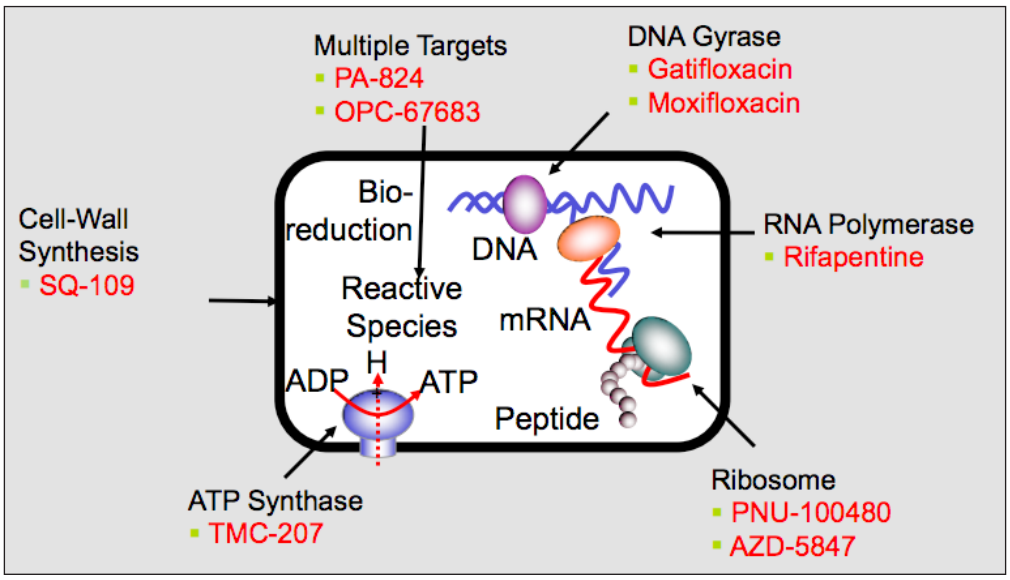
Janssen has patented bedaquiline. The TB Alliance is not holding any patents for this medicine. To make the medicine accessible and affordable, Janssen is in the process of transferring manufacturing expertise of the active pharmaceutical ingredient and the finished product to low-cost manufacturers in India. The company is also open to exploring other options to reduce costs and to work with WHO, the Stop TB Partnership's Global Drug Facility (GDF), and other global players to increase access to QA medicines that are used in a rational manner (M. Haxaire-Theeuwes, personal communication, 24 October 2011). Janssen is planning to file for approval in 2012 with the FDA, the EMA, and the Chinese and South African regulatory authorities for the phased introduction of the medicine. In 2013 the company will file in India after it receives the U.S. Certificate of Pharmaceutical Product (a requirement for India). Following that, it will initiate the next phase of introducing bedaquiline broadly in high- as well as low-TB-burden countries (M. Haxaire-Theeuwes, personal communication, 23 November 2011).

As of June 2012, no information is available about whether companies conducting studies to repurpose existing medicines will patent the medicine for its new indication or new formulation. For instance, although Sanofi Aventis plans to develop new pediatric formulations of rifapentine, no information is available about whether it will patent the new formulation of the medicine.

1.3.2 Novel regimens

Although a combination of medicines is required to cure TB, medicine development has traditionally evaluated one new compound at a time by adding an experimental medicine to a standardized regimen. The FDA has expressed concern that this model of medicine development is unethical given the risk for the emergence of resistance and rendering the new compound ineffective (Woodcock 2011), and has released the draft *Guidance for Industry: Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination* (U.S. Food and Drug Administration 2010) to facilitate the development of novel combination therapies rather than sequential medicine development. There are several challenges to this approach, not limited to different timelines of medicine development, the hesitation of sponsors to work together and share data, and the lack of appropriate drug-drug interaction data to guide dosing regimens in such studies. However, given the diverse mechanisms of action of the medicines in the pipeline, new regimens comprised of these medicines have significant potential in treating and preventing the development of DR-TB, and shortening treatment time for both DS- and DR-TB. Please refer to Figure 2 for more information on these mechanisms of action.

Figure 2: Mechanisms of action of novel and repurposed TB medicines in the pipeline (Mendel 2012).



PA-824, the above-described novel nitroimidazole in development by the TB Alliance, was tested in a phase II EBA study with moxifloxacin and pyrazinamide as part of a unique regimen (PaMZ) that is made of medicines that are not recommended for use in high-burden settings. This trial is called new combination study 001 (NC001). In 2012, PA-824 will be further tested as part of PaMZ and as part of additional novel regimens (studies NC002 and NC003), in combination with moxifloxacin, bedaquiline, pyrazinamide, and clofazimine (Table 5 and Table 6) (Mendel 2012). Rifapentine and moxifloxacin are being tested together as replacements for rifampicin and ethambutol in the intensive phase of TB treatment (ClinicalTrials 2011b). However, based on existing information and current clinical trials, none of the other novel, second-generation, or repurposed medicines in the pipeline appears to be in development for integration into new regimens. Rather, they are being tested against optimized background regimens. If they are effective and go to market, they will likely be launched as an additive to current regimens. We therefore anticipate that the launch of these novel products will not significantly alter TB market dynamics, with the exception of PA-824 and bedaquiline, which have the potential to be marketed as components of novel regimens.

1.3.3 How repurposed and novel medicines can address key treatment challenges

The following sections outline how medicines in the pipeline may address the areas of unmet need in TB treatment. Please refer to Tables 4-6, above, for more information on the studies currently underway with these compounds, as well as the proposed indications for each medicine.

Improving implementation of IPT

Repurposed/existing medicine: isoniazid

Available clinical evidence clearly demonstrates the benefit of IPT in reducing TB disease. Yet many countries do not have clear guidelines for programmatic implementation of IPT, and research indicates that in high-burden settings, IPT may need to be administered for much longer durations than existing guidelines recommend (Lawn 2012). Implementation research has been gathering evidence on how best to scale up IPT in HIV-prevalent settings. The THRio study evaluated the provision of IPT among HIV-positive persons using public-sector HIV clinics in Brazil and showed that IPT reduced TB incidence by 13% overall, and by 36% among patients who visited the clinic at least once per year, while in those two study populations TB deaths decreased by 11% and 27%, respectively (Durovni 2011). Data from the study have been cited as the rationale for expanding integration of IPT with ART and placing responsibility for IPT on national AIDS programs (NAPs). As a result of the study, the Brazilian NAP promulgated a policy requiring HIV clinics to take responsibility for screening patients for active TB and providing IPT to patients testing positive with a tuberculin skin test. The NAP has included IPT and other TB medicines in the system that controls medicines used to treat HIV and HIV-related

opportunistic infections. This is an important step, because it means that the HIV clinics will take ownership of TB prevention and treatment as an essential component of HIV and help the services becoming more integrated (L. Eldred, personal communication, 2011).

Botswana is another country that has integrated IPT into its HIV healthcare system, with similar success. A study from 2004-2006 demonstrated 86% adherence to the IPT regimen, and less than 0.2% of almost 2,000 participants developed TB. As a step toward increased national IPT implementation, some countries may be able to follow Botswana's lead in first initiating an IPT pilot program prior to rollout of its national program. Botswana used this program as an opportunity to evaluate any potential problems with the system, and to fine-tune its TB screening process (FHI 360 2011).

Shortening length of treatment

Repurposed/existing medicines: rifamycins and fluoroquinolones

A number of studies are underway that evaluate treatment-shortening regimens for LTBI and DS- and DR-TB.

Rifamycins

Because rifapentine has been shown to have superior bactericidal activity to the other rifamycins, rifampicin and rifabutin, the Tuberculosis Trials Consortium (TBTC), a research consortium funded by the Centers for Disease Control and Prevention (CDC) is evaluating its potential to shorten regimens for LTBI and active disease.

The recently completed PREVENT TB trial – also referred to as TBTC Study 26 – showed that 12 weeks of once-weekly rifapentine with isoniazid given as DOT was as effective as and had better completion rates than the standard self-administered 9-month daily regimen of IPT in treating LTBI (Centers for Disease Control and Prevention 2011a, Sterling 2011). TB programs in countries with low TB burden – where much of TB control is geared toward treating LTBI – are considering inclusion of the 12-week regimen in treatment guidelines for HIV-negative adults. In the US, the CDC recently endorsed the 12-week regimen as equivalent to the nine-month regimen in otherwise healthy adults who are 12 years old or above, including adults with HIV who are not on ARVs (Centers for Disease Control and Prevention 2011b). Recently-released data show that the 12-week regimen was better tolerated and had higher treatment completion rates than 9 months of daily IPT among HIV-positive adults and children under 12 years of age not taking ART (Sterling 2012). It is anticipated that the study will be completed by the end of 2013. The TBTC is considering a rifapentine study in children from birth to six months of age but is not able to move the protocol forward until a pediatric formulation of rifapentine is available. Sanofi-Aventis, the maker of rifapentine, has developed a prototype and is aiming to have a child-friendly product ready by 2013.

The potential for a once-weekly regimen with shortened duration may not only improve adherence but also be cost effective by reducing patient visits, staff time, and number of pills. Whether these results can be reproduced as self-administered therapy and whether short-course treatment is appropriate in high-burden countries is unknown until studies are conducted. To increase uptake of this regimen Sanofi-Aventis is developing an FDC of rifapentine and isoniazid that it projects will be ready by the end of 2012.

In a rifapentine study for active TB, the TBTC is comparing rifapentine to rifampicin in the intensive phase of first-line treatment. Both medicines kill active *and* slowly reproducing TB bacteria but data suggest that rifapentine may be more bactericidal than rifampicin at lower doses and better tolerated at higher doses (Heifets 1990). The study is evaluating the microbiological effect and safety of rifapentine taken at varying doses of 10 mg/kg, 15 mg/kg, or 20 mg/kg with food for seven days a week (ClinicalTrials.gov 2011e). Rifapentine is also being tested against rifampicin for treatment of MDR-TB during the intensive phase, at daily doses of 450 and 600 mg, and in combination with moxifloxacin (replacing rifampicin and ethambutol) during the intensive phase of treatment (ClinicalTrials.gov 2011b, 2011d).

As Table 4 indicates, high-dose rifampicin is also being evaluated in treatment-shortening regimens, with the expectation that higher-than-standard doses of rifampicin will result in higher blood concentrations of the medicine and subsequently eliminate TB bacteria more quickly. There are a number of dose-ranging studies underway comparing the safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of varying doses of rifampicin during the intensive phase of first-line treatment to determine the best dose to move forward in treatment-shortening studies. An upcoming phase II trial will test the effect of two higher doses of rifampicin

(900 and 1200 mg) compared to the standard dose (600 mg) over eight weeks in people with DS-TB (ClinicalTrials.gov 2011f).

Fluoroquinolones

Fluoroquinolones are a class of broad-based antibiotics used to treat many bacterial infections, including MDR-TB. WHO recommends the use of fluoroquinolones as part of second-line treatment despite the fact that they are not licensed for TB indication (World Health Organization 2011c). The medicines in this class – levofloxacin, ofloxacin, moxifloxacin, and gatifloxacin – are highly cross-resistant to one another, and resistance to any of them is a precursor to developing XDR-TB.

As indicated in Table 4, studies are evaluating two of the newer fluoroquinolones to shorten treatment for DS-TB from six months to four months. Patient follow-up was completed in April 2011 for the OFLOTUB study evaluating gatifloxacin, but data management problems caused unexpected delays in the analyses. These problems have been addressed, and final safety and efficacy results are expected by the end of 2012 (P. Olliaro, personal communication, 30 April 2012). Enrollment in ReMox – a phase III trial that is evaluating the use of moxifloxacin in place of ethambutol or isoniazid – is ongoing, with final study results expected by 2014 (A. Ginsberg, personal communication, 23 May 2011).

Data from mouse studies have shown that the combination of moxifloxacin and rifapentine has cured TB significantly faster than the standard of cure of HRZE. There are two clinical trials – Rifapentine Plus Moxifloxacin for Treatment of Pulmonary Tuberculosis, and Pharmacokinetic Issues of Moxifloxacin Plus Rifapentine – evaluating this combination to simplify first-line treatment by shortening duration or reducing the number of doses required per week (Clinicaltrials.gov 2011a, 2011b). The studies are sponsored by John Hopkins University and the Federal University of Rio de Janeiro.

It is unlikely that any new first-line regimen will improve upon the 95% cure rate of the current standard of care of HRZE. A new regimen will need to offer a significant improvement in adherence rates and therefore cure rates through easier dosing, shortened treatment duration, fewer medicine interactions, and an improved side-effect profile. Even if a four-month regimen is validated within the next few years, the challenge will be to get national TB programs to adopt the new regimen, train health care workers to implement new treatment guidelines, and build patients' TB treatment literacy to increase demand.

Treatment of DR-TB may take upwards of 24 months, with a high pill burden, many potential side effects, and with some medications requiring twice-daily dosing. WHO recommends that treatment supporters should observe every dose (World Health Organization 2011c). These treatment regimens can be grueling and are resource-intensive for the patient and the health system. A non-randomized, observational study from Bangladesh shows that a nine-month regimen using gatifloxacin, clofazimine, ethambutol, and pyrazinamide throughout, supplemented by prothionamide, kanamycin, and high-dose isoniazid during an intensive phase of at least four months in patients with MDR-TB, had a cure rate of 87% (Van Deun 2010). The Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB (STREAM) trial has begun. This trial uses a variation of the regimen used in Bangladesh while replacing gatifloxacin with moxifloxacin to assess whether this shorter regimen is at least as effective as the lengthier MDR-TB regimens recommended by WHO. The study is examining the efficacy of the shorter regimen especially in settings with high HIV burden.

A study is being developed that would evaluate the efficacy and tolerability of high-dose levofloxacin versus standard-dose levofloxacin or standard-dose moxifloxacin in combination with optimized background regimens for the treatment of MDR-TB. The expectation is that a higher dose of levofloxacin would both improve cure rates and allow for treatment shortening. The interest in levofloxacin is based on data suggesting that prolonged QT intervals (resulting in slower heart rate and risk for ventricular arrhythmia) associated with fluoroquinolones may be less common with levofloxacin (Noel 2003, Rubinstein 2002).

Novel medicines

Several of the novel compounds in the pipeline may present options for treatment shortening upon completion of studies and further research.

Addressing drug-drug interactions

Repurposed/existing medicines: rifabutin

There is concern that coadministration of rifampicin-containing TB treatment regimens with certain ARVs and OST could lead to insufficient medicine levels, treatment failure, and the emergence of drug-resistant HIV and/or increased risk of opiate drug relapse. As a result WHO recommends the use of rifabutin in place of rifampicin for people on ARVs or OST. But there is insufficient evidence to guide dosing recommendations of rifabutin and how to use it in the current regimen for DS-TB (World Health Organization 2010f). Studies are underway evaluating the safety, efficacy, and drug-drug interactions of rifabutin.

There have been little to no drug-drug interaction studies of SLMs with medicines used for other common conditions, especially in people with HIV.

Novel medicines

Both Otsuka and Janssen have initiated drug-drug interaction studies with ARVs and their compounds, and a phase I trial has been opened that will study the interactions of PA-824 and two common ARVs.

Otsuka's delamanid (OPC-67683) neither induces nor suppresses the cytochrome p450, and this bodes well for people on ART and/or OST. Indeed, data released in July 2012 from a 14-day study administering delamanid with tenofovir or lopinavir/ritonavir showed no clinically relevant changes in drug exposure occurring with combined administration of delamanid and these ARVs (Paccaly 2012). Otsuka will include people on ART in its just-started phase III study of delamanid, which suggests that there is also not a significant drug-drug interaction with efavirenz (ClinicalTrials.gov 2011c); data on studies of the coadministration of delamanid and efavirenz should be available by the end of 2012.

Drug-drug interaction studies have confirmed the role of cytochrome p450 in the metabolism of Janssen's bedaquiline (TMC-207), which leads to potential for interactions with some ARVs. The company, in collaboration with the U.S. National Institutes of Health (NIH), is conducting studies with ARVs and has found that coadministration with the boosted PI lopinavir/ritonavir increased exposure to bedaquiline by approximately 20% (Van Heeswijk 2010). No change in exposures was found with coadministration of bedaquiline and the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (Van Heeswijk 2011). A drug-drug interaction (DDI) study of TMC207 and efavirenz demonstrates that there is unlikely to be a clinically significant interaction. However, a DDI with repeated dosing of TMC207 has not been conducted. Further data will be presented by the ACTG at the International Workshop on Clinical Pharmacology of Tuberculosis Drugs in September 2012 (M. Haxaire-Theeuwes, personal communication, 19 April 2012).

Bedaquiline is also being studied with other TB medicines. A study with rifampicin showed that the exposure to bedaquiline was significantly reduced (Lounis 2008), and a study examining the differences between bedaquiline in combination with rifabutin versus rifampicin recently completed enrollment and results are anticipated in late 2012 (ClinicalTrials.gov 2012k, S. Murray, personal communication, 8 May 2012). Until more data are available, Janssen has stopped coadministration of moxifloxacin and bedaquiline because of increased risk for prolonged QT intervals.

There is a critical need for research into whether delamanid and bedaquiline can be safely and effectively coadministered, as they are the two novel TB medicines furthest in development. When they receive approval, they will likely be used together, particularly in people with MDR- or XDR-TB who have few other viable options. The approval of both medicines is anticipated in the coming year, and so it is urgent that the safety and efficacy of these compounds used in combination is determined as soon as possible (Harrington 2011).

Improving cure rates for MDR-TB and XDR-TB

New molecules with novel ways of inhibiting or killing the TB bacteria, and second-generation compounds with better activity and better safety profiles than their predecessors, are being developed to improve cure rates for DR-TB.

Alternatives to IPT for persons exposed to MDR- and XDR-TB

There are no standard recommendations for what to offer the contacts of individuals with DR-TB because MDR-TB patients are, by definition, resistant to isoniazid, the medicine otherwise given to contacts of people

with tuberculosis. In fact, WHO 2006 guidelines recommend no preventive treatment for the contacts of MDR-TB patients (World Health Organization 2006b). So if treatment occurs, it is based on anecdotal evidence and medicine availability. The AIDS ACTG – a research network funded by the NIH – were developing a study to evaluate the efficacy and tolerability of bedaquiline compared with IPT for persons who have household contact with persons with confirmed DR-TB. Participation was planned to be open to children once appropriate dosing has been established and formulations developed. However, the entire study was put on hold as Janssen has not yet made bedaquiline available for this indication.

Novel medicines and regimens

Several of the novel compounds in the pipeline, including PNU-100480, SQ 109, PA-824, delamanid, and bedaquiline, are being developed to treat DR-TB. Gatifloxacin is being studied as a repurposed medicine for this use. With the exception of PA-824, all these medicines are currently being tested with optimized background regimens, indicating that they will likely be added to existing regimens. PA-824, the only exception, is currently being studied as part of a novel regimen with moxifloxacin and pyrazinamide. Plans exist to evaluate it in several combinations with bedaquiline, pyrazimamide, and clofazimine, as well (Mendel 2012)

Pediatric medicine development

More than half of the ARVs approved to treat HIV have established simple weight-band tables with pediatric dosing ranges and child-friendly formulations (U.S. Food and Drug Administration 2011a). Meanwhile, there is a dearth of evidence guiding TB treatment for children (Burman 2008). In recent years there has been greater advocacy for inclusion of children in treatment research but no plan or clarity on how to do so. A consensus statement is being developed by experts in the childhood TB and TB medicine development fields that outlines the priorities for childhood TB treatment research. The consensus statement identifies the development of pediatric medicine formulations for children of all ages as a priority research need. Once toxicity, safety, and efficacy data have been established from young animal and adult studies, further efficacy studies in children will not be necessary. If a medicine is able to kill TB in adults it will be able to kill TB in children, who require less TB bacteria to cause disease. Because young children cannot swallow tablets or capsules, the development of child-friendly formulations is critical so that PK studies of new compounds and SLMs can be initiated. Pediatric PK studies would identify the therapeutic dose needed based on the absorption, metabolism, distribution, and excretion of the medicine based on age and stage of development. Some TB medicines have been studied in children – the PK of rifapentine, for example, has been evaluated in children 2 years of age and older – but not as child-friendly formulations. Regulatory authorities have not clarified their position on the age groups of children that will need to be included in PK studies.

Novel medicines

Otsuka and Janssen have produced pediatric investigational plans (PIPs) that will guide future clinical studies of delamanid and bedaquiline in children to establish safe and effective dosing based on age and development. The PIPs have been approved by the EMA per the agency's guidelines and the bedaquiline PIP has been shared with the FDA (European Medicines Agency 2011a, 2011b). The NIH-funded International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network is planning a PK study of bedaquiline in children of all ages in collaboration with Janssen. The trial would start with adolescents and work down to infants from birth to six months of age. Once data from HIV-positive adults become available, children with HIV will also be included (A. Hessling, personal communication, 21 May 2011). Janssen is working on a pediatric formulation and is planning to have a product ready for use in studies in 2013. Bedaquiline is also working on its pediatric formulation and will conduct pediatric studies of delamanid in-house.

1.4 Research challenges

TB medicines research suffers from a number of challenges that hinder the development of the new compounds. The most prominent of these include:

- Lack of reliable TB biomarkers;
- Low research capacity;
- Regulatory requirements; and
- Research Funding.

1.4.1 Biomarkers that can predict cure, treatment failure, and relapse

Starting in the early 1990s, the FDA began to approve HIV medicines based on their effect on biomarkers – biological measures that might indicate a treatment effect and predict clinical outcomes – such as changes in CD4 cell levels and then in HIV viral load. These changes allowed for an unprecedented acceleration of clinical trials, paving the way for the combination ART revolution of 1996. However, most approved TB medicines came to market in an era when such techniques did not exist. The measures used in the streptomycin trial for monotherapy of TB in the 1940s – including chest X-ray and solid bacterial culture, as well as clinical improvement and relapse – are the same tools used to measure TB medicine activity in 2011. Unfortunately for TB patients and researchers, at this time the TB field lacks a biomarker that measures medicine activity in real time or can predict whether a medicine or regimen will result in a stable cure for a patient.

Biomarker discovery requires well-characterized samples from people with and without TB and at various stages of disease and cure so that potential biomarkers can be validated in specimens from a wide variety of patients. With funding from the FDA, the TB Alliance has partnered with the TBTC and the ACTG to form the Consortium for TB Biomarkers (CTB^2). The consortium is banking samples collected from volunteers enrolled in their TB treatment trials, and will be able to provide well-characterized samples from different phases of TB disease and cure. This knowledge could lead to the development of better biomarkers to predict the efficacy of TB medicines in individual patients or in clinical trials. Even though the CTB^2 has only just begun to bank samples, the demand from researchers is exceeding the supply.

1.4.2 Research capacity

Over the past several years there has been a level of activity in TB medicine research that has not been witnessed since the 1950s and ’60s, when the introduction of combination therapy and the regulatory approval of rifampicin revolutionized TB treatment. Since that time no new compounds from novel medicine classes have been granted regulatory approval, and this has contributed to reduced research capacity in TB treatment. But recent partnerships and investments by developers are increasing TB treatment research capacity.

The U.S. National Institute of Allergies and Infectious Diseases (NIAID) – the largest public funder of TB research in the world – is reconfiguring its HIV clinical trials network system, including the ACTG and IMPAACT, to include TB as one of the focal areas. By broadening the scope of the NIAID-supported clinical trials infrastructure to include studies evaluating TB medicines for both monoinfection and HIV coinfection, the TB treatment research field will almost double its capacity to conduct clinical trials in high- and medium-TB-burden settings among geographically and demographically diverse groups. All interventional clinical trials supported by NIAID have to meet the standards of WHO’s good clinical practice (GCP) and international ethical standards (C. Sizemore, personal communication, NIAID response to UNITAID survey, 2011). Therefore NIAID offers GCP training in international settings for all of its infectious disease research.

The newly configured network’s TB research will be focused on the treatment and prevention of TB through therapeutics. The priorities are the development of treatment-shortening regimens for LTBI and active disease, strengthening laboratory infrastructure, mentoring new investigators, and collaborating with other research institutions.

One potential partner of the NIH research network is the Critical Path to TB Drug Regimens (CPTR) Initiative, which was launched to accelerate the evaluation and regulatory approval of novel TB treatment regimens. The initiative is a collaborative effort of public- and private-sector stakeholders to identify more efficient ways to study TB medicines in combination to expedite regimen change rather than introducing the medicines sequen-

tially. As has been mentioned, the move to regimen development is a paradigm shift for the field and will require regulatory agencies, research institutions, funders, policy makers, and advocates to work more collaboratively to ensure that the efficient testing and approval of new regimens is safe and maximizes resources. The CPTR Initiative is coordinating efforts to increase the capacity of the TB research field to conduct large-scale phase III trial capacity because no one group can conduct all of the studies required.

Another key player in strengthening research capacity is the European and Developing Countries Clinical Trials Partnership (EDCTP), which aims to accelerate the development of new tools to prevent, diagnose and treat HIV, TB, and malaria in sub-Saharan Africa. The EDCTP collaborates with public and private research and development partners to provide technical and operational support to African research institutions in all aspects of clinical studies – from ethics reviews to site capacity – to conduct trials that will meet international standards required by stringent regulatory authorities. The EDCTP has partnered with WHO to create a common regulatory framework and the establishment of an African Regulators Forum (Mathewson 2011).

Otsuka and Janssen have invested significant resources into building and sustaining local research infrastructure. Because in many high-TB-burden countries there is limited (or no) experience conducting studies in compliance with the regulatory standards of the International Conference on Harmonisation and WHO's GCP guidelines, sponsors of studies need to commit sizable resources to strengthen the research infrastructure. For instance, Otsuka addressed the issue of weak laboratory capacity by developing detailed manuals translated into local languages, training, and standardization exercises to qualify the laboratories in accordance with international guidelines, and then had an outside vendor conduct proficiency testing and frequent monitoring and oversight (P. Carlevaro, personal communication, 29 September 2011). These investments can add significant costs but are necessary to assure quality data. Capacity development is needed for regulatory authorities to ensure that they are able to respond to trial sponsors and provide timely feedback on protocols and medicine applications. The Regulatory Pathways group of the CPTR Initiative was created to specifically address this challenge and is focusing on clarifying the regulatory pathways for approval of new TB medicines and regimens and streamlining the process for submitting dossiers to health authorities.

1.4.3 Regulatory requirements

Regulatory rules and requirements vary from country to country and among regions. Approval from stringent regulatory authorities like the FDA or the EMA has traditionally been sufficient for countries with limited regulatory capacity to grant approval for new treatments, particularly for life-threatening conditions. However, there is limited regulatory experience in the TB field because no new medicine class has been approved since the 1960s and regulatory science is much more demanding now than it was then. Requirements for regulatory approval for TB treatments are not harmonized across agencies; for instance, the EMA requires that medicine developers submit a pediatric investigational plan and timeline for evaluating a new TB compound in children while the FDA does not because TB qualifies under the Orphan Drug Act. Efficacy endpoints for late-stage clinical trials remain controversial, as do the durations of the follow-up periods. The EMA, for example, encourages a 24-month follow-up period after treatment is completed in clinical trials to assess relapse (European Medicines Agency 2008), whereas the FDA does not appear to have established specific guidelines for the duration of follow-up, though a 2009 draft concept paper, *Pulmonary Tuberculosis: Developing Drugs for Treatment*, had recommended 24 months, as well (U.S. Food and Drug Administration 2009). These lengthy follow-up periods slow the development of new medicines, and the lack of regulatory harmonization means that medicine developers are faced with sequential and/or parallel regulatory filings in high- and low-burden countries along with long review timelines and individual application requirements. An application to conduct a clinical trial in a country may take up to one year to get approved. These administrative delays hinder implementation, raise the cost of studies, and may deter companies from investing in developing treatments for TB.

It appears that the FDA may be willing to consider basing future approvals of TB medicines on a combined microbiologic endpoint plus a combined symptomatic endpoint, and then using clinical follow-up to assess relapse rates, based on the division's acceptance of symptomatic endpoints in trials of community-acquired bacterial pneumonia (United States Food and Drug Administration Division of Anti-Infective Products/Office of Antimicrobial Products 2011). In this case, efficacy analyses of the primary endpoint would include all enrolled patients, and would not have to account for patient drop-outs during a lengthy follow-up. Analyses also would not be required to show a statistically significant effect on relapse rates, provided that improvements in relapse rate paralleled those in symptomatic and microbiological endpoints. This is encouraging, as it could signifi-

cantly reduce the sample sizes and costs of trials evaluating new TB medicines. However, identifying appropriate symptomatic endpoints could prove challenging: even patients cured of TB may continue to exhibit cough or other clinical symptoms due to lung damage and the increased susceptibility to bronchial infections brought about by the lengthy nature of TB infection.

The CPTR Initiative and other medicine developers are engaging regulatory agencies to clarify the pathway to develop a medicine regimen as opposed to taking each new medicine through regulatory approval by adding a new medicine to a regimen. The data and regulatory pathway on how best to combine more than one new compound to come up with a new regimen in a clinical trial need to be clarified.

The EMA and FDA have regulations that will accelerate approval for medicines being studied for patients that have very limited treatment options, such as pre-XDR or XDR-TB patients. Both Otsuka and Janssen are anticipating getting accelerated approval for their new medicines for use in such patients with highly resistant forms of TB. The FDA Code of Federal Regulations 21, Title 21 subpart H, which covers the topic of accelerated approval, states that the FDA could grant marketing approval based on the effect the medicine has on surrogate endpoints or other evidence that is likely to predict clinical benefit if the medicine is being studied for safety and efficacy in treating serious or life-threatening illnesses and it is able to provide benefit over existing treatments (U.S. Food and Drug Administration 2011b). This conditional approval will require that the developer further study the medicine to confirm its clinical utility. The EMA has similar regulations for accelerated assessment of marketing authorization applications for medicinal products that are expected to be of major public health interest as they address a great unmet need that can maintain or improve the health of the community (European Medicines Agency 2006).

1.4.4 TB research funding

The *Global Plan to Stop TB 2011-2015* estimates that US$2 billion per year is needed to adequately fund research efforts (Stop TB Partnership 2010). To reach this target, funding must increase more than threefold from 2011 levels, but with the current global financial crisis and budget cuts looming for public-sector funders like the NIH and CDC, it seems unlikely that this will happen. In fact, the TBTC's 2011-2012 budget saw a 10% reduction. Despite the fact that the discovery of reliable biomarkers is critical to accelerating TB treatment research, funding for the CTB^2 is uncertain. The FDA gave a three-year grant to the CTB^2 but has already had to reduce funding levels for the second year of the grant, and future commitments are in jeopardy. On the other hand, as new compounds move through the pipeline, private-sector investment is increasing. Just by continuing a phase II study of its new compound, Otsuka Pharmaceuticals became the leading funder of TB treatment research in 2009 (Jiménez 2011). While public sector funding for TB research fell 5% between 2009 and 2010, private sector investments increased 24% (Jiménez-Levi 2012).

TB medicine development consistently receives the most funding of any area within TB research, yet it is still wholly insufficient to address the gaps to support even current efforts. The Global Plan called for US$1.96 billion to be spent across all fields of TB research in 2010, 38% of which was to be spent on new TB medicines research. However, total TB R&D funding in 2010 only surpassed US$0.5 billion dollars. While TB medicines research accounted for 42% of this amount (Jiménez-Levi 2012) the US$230.5 million spent is far below the US$740 million per-year target called for by the *Global Plan*. Despite being the most robust TB medicine pipeline in years, it is still not enough to meet global demand. The *Global Plan* also estimates that 21 new medicine candidates will need to be in preclinical studies by 2015 in order to keep the pipeline adequately filled to make any significant improvement on TB. Without adequate investment the products in the pipeline will get stalled, and no new products will move into clinical trials.

Current treatment strategies cannot eliminate TB as a public health threat by 2050. Better medicines are needed, as are more data on how best to use current treatments in people with HIV and in children – those who are at greater risk for disease progression and more severe disease. A key challenge is funding and research capacity. Expertise and facilities exist to conduct quality clinical trials, but more investment is necessary to grow and sustain these efforts. It is critical that potential collaborations be identified to maximize resources, avoid redundancy, standardize processes, and improve communication among all stakeholders engaged in improving TB treatment.

Section 2:
Market challenges in promoting access to quality-assured TB medicines

With 1.4 million deaths from TB – a curable disease – and only 16% of MDR-TB patients receiving adequate treatment in 2010, access to safe and effective existing medicines to prevent and cure TB is clearly insufficient (World Health Organization 2011b). Given the limitations of current treatment and the paucity of research into improved medicines, the inadequacy of investment in research on new TB medicines is obvious.

Inadequate access to quality-assured existing medicines and inadequate investment in developing new medicines are among the most critical market shortcomings in the TB medicines landscape. While by no means an exhaustive analysis, this report examines three important factors that underlie these market shortcomings:

- Poor market forecasting, leading to an inaccurate projection of demand;
- Unclear regulatory environment, leading to delays in approval and access; and
- Ineffective medicines procurement and challenges in the distribution of medicines in the public and private sectors.

2.1 Obstacles in market forecasting

The two key market shortcomings identified in this report – inadequate access to existing QA medicines and inadequate investment in novel medicines – are driven in part by inaccurate estimates of the need for these medicines.

The market for TB medicines, especially for SLMs, is perceived to be smaller than it really is, which (i) contributes to inadequate procurement of existing treatments by treatment programs, (ii) deters producers from becoming involved in QA manufacturing, and (iii) dissuades developers from investing in new treatments. At the national level, accurate demand forecasting could drive better procurement – preventing stockouts and ensuring availability of the robust variety of SLMs required to properly treat DR-TB and prevent the amplification of resistance. Regionally and globally, precise assessments of the demand for existing first- and second-line medicines could potentially create incentives for new QA suppliers to enter the field and encourage more robust competition. Additionally, projections of demand in areas of unmet need could encourage increased investment in novel compounds. Market sizing for both existing and novel medicines is currently challenging, however. As a result, the returns are uncertain for developers and manufacturers, resulting in weak incentives to invest in TB medicines.

The biggest obstacles in market forecasting are (i) the poor performance of available diagnostic tools, (ii) limited access to more effective diagnostics, (iii) inadequate efforts to actively find cases at the program level, (iv) inadequate consolidation of demand among fragmented public sector procurers, and (v) lack of data on private sector purchases. The following sections expand upon these challenges.

2.1.1 Diagnostic challenges

In 2010, of the estimated 8.8 million incident cases of TB disease, 6.2 million were reported to NTPs, leaving nearly 30% of TB cases unreported. Of the estimated 650,000 MDR-TB prevalent cases, only 50,000 were reported to NTPs in 2010, meaning that less than 8% of MDR-TB cases were reported to the WHO (World Health Organization 2011b).

The lack of a cheap, accurate point-of-care (POC) diagnostic test to detect TB and diagnose resistance at the health post level – where most people with TB disease access services – results in poor detection rates (Batz 2011). The inexpensive POC tests that are commonly used have poor sensitivity and specificity, and more accurate tests are currently unsuitable for widespread implementation at the POC sites where most TB cases could be identified. Accordingly, the actual burden of TB is not well documented. Without the ability to accurately assess the prevalence of TB and identify the population in need of treatment, it is difficult to stimulate development in the pipeline. Accurate and rapid profiling of drug susceptibility in particular is lacking, and contributes to a vague picture of the market for current SLMs and for new medicines to fight DR-TB.

2.1.2 Inadequate case finding

Accurate market forecasting is also impeded by a lack of emphasis on finding people with TB infection and disease. Reliance on passive case finding – that is, people who are sick enough to present to a health care setting – does not give a clear picture of the burden of TB. As the symptoms of TB can wax and wane, and because the disease tends to affect people of low socioeconomic status, many people with TB do not seek care. People with LTBI do not present to health care settings as they are, by definition, asymptomatic. Thus, both to prevent and treat TB, and to determine a clear market for TB medicines, TB programs need to actively work to identify cases of TB and LTBI.

Given the difficulties, delays and expense associated with diagnosing TB, it is unsurprising that there is not more emphasis on active case finding at the programmatic level. Yet the reliance on passive methods of case identification is also a top-down problem: scarce resources are allotted to TB programs, and the WHO's widely promoted Directly Observed Therapy, Short-course (DOTS) strategy omits active case finding, thereby ingraining passive identification into global and national policies. Indeed, an analysis of DOTS' impact revealed that its technical package improved overall treatment success, but that DOTS expansion had no effect on case detection (Obermeyer 2008).

Recent data point to the importance of active case finding. The ZAMSTAR study showed that evaluating household contacts of TB patients, with counseling, HIV testing, TB testing, and referral to services, can reduce the prevalence of culture-positive TB in communities with high TB and HIV burdens (CREATE 2012). This approach also makes it possible to identify more cases and better determine the need for TB medicines in a given setting. Targeted interventions to screen for TB at the household level, at HIV and maternal/child health clinics and other health care facilities could provide data that in aggregate could impact efforts to better estimate the true market size for TB medicines.

2.1.3 Fragmented public sector market

The fragmentation of the public sector market makes it challenging to quantify the use of TB medicines in this sector, and therefore create accurate projections of need. Although the public sector is more tightly linked to international medicine procurement agencies than is the private sector, publicly purchased medicines are not all obtained from prequalified (PQ) organizations. Not all funders or country governments require that a country procure only PQ and QA medicines; some countries prefer to use their public funds to purchase medicines from manufacturers based in country, even if a global institution or stringent regulatory authority has not prequalified these medicines. Thus, the GDF – the global institution responsible for procuring QA TB medicines – supplies only between 14% and 20% of the market of the public sector (Kimerling 2011, Matiru 2007). One study suggests that up to 73% of public-sector funding for FLMs is spent on medicines that are not up to WHO standards (Stop TB Partnership 2010). Given that many high-burden countries will purchase non-PQ medicines, manufacturers may lack sufficient market incentive to submit to a stringent prequalification process. The purchasing of non-PQ medicines, in addition to increasing the risk that patients will not receive appropriate treatment and will develop and transmit DR-TB, undermines the ability of the GDF to leverage its pooled procurement mechanism to cover a greater proportion of the TB medicines market (Bogren 2011).

2.1.4 Lack of data on private sector

Private sector markets are largely unregulated and not served by the public procurement agencies. While the private sector for TB procurement is huge, related data are scarce. It is therefore challenging to assess and forecast the state of the total global market.

In 10 of the countries with 60% of TB cases globally, 67% of new TB cases are treated in the private sector at some point during the course of illness. The proportion of those patients who eventually come to the public sector to continue or complete treatment is not known. Though the size of the private sector among these 10 countries varies, in total their private sectors used medicines sufficient to treat 66% of these countries' incident TB cases, or 39% of worldwide TB cases. The prescription of irrational regimens described later in this document makes it even more difficult to evaluate demand in the private sector market, as the use of specific medicines cannot be estimated simply based on number of patients treated. Though the private-sector market remains significant in many of the high-TB-burden countries studied, it is not very well characterized (Wells 2011).

An analysis of 10 countries with high burdens of TB has demonstrated that four manufacturers supplied approximately 70% of the FDCs used in the private sector. This suggests that working with the leading manufacturers of FDCs as well as with procurement agencies could improve market projections for FLMs in the private sector, as well as increase access to QA medicines and reduce the irrational use of medicines (Stop TB Partnership 2010).

Currently, the GDF only serves the public sector and therefore is unable to harness the full market demand that combines the purchasing power of the public and private sectors to reduce costs and provide incentives for QA medicine manufacturers to enter into and stay in the field of TB medicines.

2.2 Unclear regulatory environment

The two key market shortcomings – inadequate access to existing medicines and inadequate investment in novel medicines – are further fueled by an unclear and outdated regulatory environment. Vague or conflicting guidance affects the uptake of new formulations of existing medicines – for example, pediatric FDCs – and the development of novel medicines. This creates further challenges for manufacturers and developers, who may not be willing to invest in a product if they cannot be sure that there is a clear process for its eventual approval and rollout.

The main areas in which unclear or outdated guidance may prevent manufacturers from entering the market are in (i) WHO guidelines for the development of pediatric FDCs, (ii) FDA and EMA guidelines for both traditional and expedited conditional approval programs, and (iii) national regulatory guidelines for access to medicines both pre- and post-approval by a stringent regulatory authority such as the FDA or EMA.

2.2.1 Guidelines for pediatric FDC development

The 2010 updated guidelines for pediatric first-line FDCs – and the lack of appropriate medicines formulated to meet those guidelines – has become a barrier to the availability of appropriate pediatric medications (please refer to Section 1.2.5 for more information). The current pediatric formulations and FDCs of FLMs are based on previous WHO dosing recommendations, which have now been shown to be underdosing children. Until more guidance is available on the formulations for the updated FDCs, it is difficult to encourage research and development of these products.

As a result of these challenges, the WHO's Department of Essential Medicines and Pharmaceutical Policies convened an informal consultation to determine a way forward in the development of child-friendly products that adhere to the revised dosing guidelines. Recognizing that countries will continue to use their current stock of TB medicines, WHO has issued interim guidelines on using the existing FDCs to achieve the new dosages; but these are complicated with potential for error, and therefore few countries are implementing these guidelines. Consequently, manufacturers may be dissuaded from producing pediatric FDCs, as the outdated FDCs are challenging to fit into the new guidelines, but formulations for the new FDCs have not yet been established.

A number of challenges need to be addressed to encourage manufacturers to invest in the development of new formulations, such as identification of ideal product specifications (i.e., the number of medicines and which ones should be included in any FDC), and addressing the formulation challenges of the FDC.

2.2.2 Guidelines for full and expedited conditional approval

The FDA and EMA can provide expedited conditional approval for medicines currently being studied for TB after completion of phase II studies. Once these medicines are approved, guideline developers will then examine the data to incorporate the new medicines into a recommended treatment regimen. Some medicine developers are concerned that the data requirements are unclear.

These issues were discussed at the Expert Meeting on WHO Policy for Introduction of New TB Drugs held in Geneva, 8-10 June 2011, including the compassionate use of medicines under investigation for MDR-TB. Further work is required to ensure that these processes are clear as medicine developers are preparing new compound dossiers to be submitted for expedited approval.

2.2.3 Lack of regulatory infrastructure at national level

In addition to the above-described challenges to access and development that stem from unclear guidance from stringent regulatory authorities and global policy-setting institutions, a lack of regulatory guidelines at the national level also threatens the market for TB medicines. As new TB medicines have not been approved for decades, there is a lack of capacity in regulatory approval for new TB medicines in many high-burden settings. Many local regulatory authorities do not have specific committees of TB experts in place. As a result, guidance on the process for local registration of a product is often unavailable, or at best outdated. This in turn deters developers and producers from investing in TB medicines, as they are uncertain of the process and timeline for having new products actually enter their intended markets.

In the instance of accelerated or conditional approval from the FDA or EMA, for example, the process for how new medicines can be incorporated into country-level treatment guidelines while phase III studies are ongoing is yet to be determined. Even pre-approval access to compounds in development via compassionate use, which has been long-established in other disease areas such as HIV, is proving difficult with TB medicines. XDR-TB patients in South Africa with life-threatening limitations to their treatment options must wait months for pre-approval access to bedaquiline (which is available already in several other countries) while the South African Medicines Control Council determines how to best allow for its administration. In addition to limiting access to potentially helpful treatment, these regulatory delays threaten future investment in TB medicines by demonstrating to potential developers and producers the lack of infrastructure in place to approve and adopt the use of new TB medicines in an efficient and timely manner.

2.3 Strategic procurement and distribution challenges at the country-level

The inability of global public sector procurement groups to harness the majority of the TB medicines market described in Section 2.1.3 is one of the factors that contribute to inaccurate market forecasting. Procurement and distribution problems at the country-level are also a unique problem. Issues include poor planning for procurement, irrational private sector medicine use, and lack of coordination between the private and public sectors. As a result of these issues, people with TB and LTBI lack consistent access to quality existing medicines, and developers and manufacturers lack confidence in the existence of a stable, sizeable market for novel products.

2.3.1 Inadequate planning for medicine procurement at the national level

For treatment programs, both stockouts of TB medicines and expired medicines are dangerous. Individual patients risk relapse, the development of resistance, and even death if they go without effective treatment. If resistant strains – which are much more difficult and expensive to treat – are transmitted, this creates further challenges for treatment programs. A number of factors at the national level contribute to poor medicines management, which in turn can lead to stockouts or expired medicine stocks. These include:

- Lack of staff capacity to manage the procurement system;
- Lack of basic infrastructure to store, distribute, and track level of supplies;
- Increased donor dependence (contributing to the exclusion of medicines costs in national budgets, impacting country capacity to buy needed medicines following changes in disbursements of donor funds); and
- Lack of accurate information needed to facilitate procurement and supply management (Bogren 2011).

In addition to causing stockouts that jeopardize the treatment of individuals and threaten the broader population with resistance, these factors make the TB treatment market a high-risk one for developers and manufacturers to enter. Developers of new medicines are hesitant to invest in a product that, because of poor administration, could quickly face resistance and become obsolete. Similarly, manufacturers are reluctant to enter an unpredictable market.

2.3.2 Irrational medicines use in the private sector

As mentioned in Section 2.1.4, irrational medicines use is rampant in the private sector. In the absence of adequate mechanisms for obtaining QA medicines that match the regimens recommended by regulatory agencies, inappropriate medicines and regimens are prescribed using available medicines.

The number of medicines sold in the private sector is disproportionate to the number of cases known to be detected in a given country. A 2011 analysis of global TB medicines usage showed that some countries, such as India and Indonesia, use enough medicines to treat over 100% of their incident TB cases with a full-length, daily regimen (Wells 2011). The absence of a similar amount of necessary companion medicines also indicates that the medicines are not being prescribed in the recommended regimens in countries that were studied.

The patterns of TB medicine use in the private sector in 10 countries that make up 60% of the global TB burden were studied. In these 10 countries, the private sector sold the four FLMs for TB in a wide variety of nonstandard strengths that were not aligned with WHO guidelines or country treatment recommendations. Thirty-five percent of the medicines sold in the private sector in these countries were not aligned with WHO recommended dosages. In India, 100 private doctors prescribed 80 different regimens. Among private doctors surveyed in the Philippines, inappropriate regimens were prescribed 89% of the time.

Estimates based on limited data in the 10-country study suggest that a much smaller proportion of MDR-TB patients (around 10%) are treated in the private sector. The medicine regimens used in the private sector are not aligned with WHO-recommended treatment guidelines and often involve the addition of a fluoroquinolone to a failing first-line regimen without adding any other SLMs. This increases the potential for the emergence of XDR-TB. Each of the 10 countries studied has access to only five of the 17 potentially useful SLMs. Certain medicines for MDR-TB were likely overprescribed. Assuming daily dosages for an 18-month regimen, the amount of fluoroquinolones used in India, Indonesia, and Pakistan was sufficient for 54%, 15%, and 11% of the estimated total incident MDR-TB cases, respectively. India, Indonesia, and Pakistan reported that in 2010 they treated less than 5% of their estimated MDR-TB cases (Wells 2011, World Health Organization 2011b).

Limited data from these 10 countries show that the use of medicines in the private sector does not adhere to global or national treatment guidelines for DR- and DS-TB. These practices of the private sector contribute greatly to poor treatment outcomes and the emergence of DR-TB (Global Alliance for TB Drug Development/ World Health Organization 2011; Wells 2011).

2.3.3 Lack of coordination of public and private sectors

Public-private mix (PPM) programs that promote coordination among public and private sector entities represent an opportunity to maximize the effectiveness of medicines procurement groups. These programs may harness the private and public sectors' ability to reach patients, and support the rational use and purchase of QA medicines in line with global and national treatment guidelines.

The PPM collaboration in Ghana illustrates the benefits of rational use of TB medicines achieved through linking the two sectors. In the late 1990s, the NTP began working with Ghanaian public, private, and governmental bodies to restrict the sale and importation of non-PQ TB medicines. The Ghanaian Food and Drugs Board stopped importing non-QA medications, public education was conducted on the risks presented by unregulated TB medicines, and the NTP offered to provide free TB medicines to the private and public sectors (World Health Organization 2010d). The NTP is currently the only provider of TB medicines, and collaborates with pharmacies and hospitals. Treatment success rose from 31.9% in 1996, before the implementation of this program, to 84.5% in 2008. Treatment default rates concurrently fell from 11.6% to 2.4% (Bonsu 2010).

Though there is an urgent need to scale up PPM programs, the Global Fund portfolio analysis for 2003-2008 showed that out of the 93 countries with TB grants, only 58 had PPM programs. These grants allocated a median of only 5% of funds for PPM activities (Lal 2011).

Additional strategies to reduce the divide between the private and public sectors could include a public insurance system that reimburses private providers when they follow recommended guidelines and use QA medicines provided by the public sector, or a cohesive organizing of the private sector to facilitate public-private partnerships and provide incentives to the private sector to purchase QA medicines and prescribe them in line with WHO and country guidelines.

2.4 Civil Engagement and Advocacy Obstacles

Current TB advocacy and regulatory processes do not benefit from the same type of vibrant civil society engagement that exists around HIV research and treatment. This cross-cutting issue leads to a lack of community-based advocacy for the uptake and development of TB medicines.

Since the 1960s there has been limited experience in putting a TB medicine through the process of regulatory approval. Unlike for HIV, the data safety monitoring boards and ethics committees that review TB medicines often do not have community participation. In the absence of requirements for TB medicine developers to explicitly engage and build the capacity of TB patient activists, there is no clear incentive for product developers to proactively engage with activists in TB medicine development and invest in community advisory boards (CABs). This lack of community participation is a symptom of the broader field of TB research, which lacks patient-driven and community activist-driven demand for new TB tools and their uptake.

In 2011, the international TB Community Advisory Board (TB CAB) was created and convened for the first time, including participants representing five continents. Participants met with members of TB Alliance, Janssen, and Otsuka, and discussed issues ranging from communication with regulatory authorities to the need for development of novel regimens, and recently convened again at the South African TB Conference in June 2012. The TB CAB may present an opportunity to initiate and strengthen the engagement of TB activists and researchers in the drug development and regulatory processes (Harrington 2011).

Still, there is limited funding or capacity-building support to develop a cadre of science- and research-literate activists for TB who not only are engaged in the research process for a specific medicine but are advocates for TB program implementation and funding overall. This prevents robust advocacy for addressing the factors described in this section that lead to the shortcomings in the TB medicines market.

Section 3:
Key findings

Despite unprecedented activity in diagnostics that can identify TB cases and R&D for treatments that can shorten and simplify TB treatment, the TB medicines market still suffers from a number of challenges that hinder development of new TB medicines and prevent access to existing QA medicines. Primarily, these challenges include poor market forecasting, an unclear regulatory environment for the development and uptake of novel medicines or formulations, problematic procurement and distribution of TB medicines, and a lack of civil engagement.

3.1 Market forecasting

In order to improve market forecasting, there is a need for new, accurate diagnostics that can be effectively used at POC sites to appropriately identify all those in need of TB treatment. Additionally, the fragmented public-sector market must be consolidated. Currently, the Global Drug Facility purchases medicines for less than 20% of the public-sector market. The absence of coordination between the leading funders of TB medicine procurement contributes to this problem, as does the fact that countries that purchase medicines with their own funds often favor in-country medicine manufacturers even if they charge higher prices for non-QA medicines. This lack of consistent and coordinated procurement practices needs to be addressed to achieve the lowest sustainable price for QA TB medicines.

Furthermore, there is little information about the quality of medicines and their appropriate use in the private sector. Better data on the private sector will allow a more accurate assessment of the total global market. Accurate documentation will aid in forecasting of a stable and predictable market demand, which could act as an incentive to bring in more manufacturers to the field of TB medicines and encourage the development of novel medicines.

3.2 Regulatory requirements

Regulatory requirements and pathways for the approval of new treatment regimens, expedited approval programs, compassionate use programs, and the formulation of pediatric FDCs need to be clarified. Key players like the CPTR, NIAID, the TB Alliance, the EDCTP, the TBTC, and WHO – as well as private-sector medicine developers – are collaborating to address these challenges. Increased resources are urgently needed to expedite progress in this area of work. Though there are new medicines that are likely to come to market in the next three years, they are being studied with the goal of being added to current treatment regimens and are not likely to radically replace existing first- or second-line treatments. Until there is a clear guidance from leading stringent and other national regulatory authorities for the approval of new regimens, it will be risky for developers and manufacturers to invest in novel regimens that are critically needed, and people with TB and LTBI will have to wait lengthy periods to access those products that are in development.

3.3 Procurement and distribution

Although stakeholders like GDF, CHAI, TB Alliance, WHO, and MSF are working to address issues related to insufficient uptake of QA medications, more must be done. Increasing the effectiveness of procurement mechanisms may significantly improve this. In the public sector, this requires better national planning for medicines stockouts. In the private sector, available data reveal irrational use of medicines in inappropriate dosages and regimens. Strategies such as the public-private mix need to be fully rolled out to ensure rational use of medicines in line with global treatment standards and to harness the private-sector demand to further strengthen the market for QA TB medicines.

Further efforts to accurately anticipate demand, increase purchasing power through pooled procurement to reduce prices, or provide incentives to increase robust competition to ensure accessibility of quality treatment are required.

3.4 Civil engagement

In addition to the clear ethical and human rights reasons to engage members of TB-affected communities in TB medicines research and uptake processes, civil society advocacy has the potential to positively impact forecasting efforts, the regulatory environment and procurement and distribution. However, there is a significant lack of civil society engagement in and advocacy around TB medicines. The recently created TB CAB and Good Participatory Practice guidelines in development may begin to address these issues, but other interventions will be needed to create the type of advocacy that can spur further improvement in development and access for TB medicines.

This report documents that:

- There is an urgent need for new diagnostics and medicines to get patients on appropriate treatment to prevent and cure TB infection and disease and to accurately size the market for TB medicines.
- Investment in the TB medicine market is high-risk because it is characterized by unclear demand and forecasting, imprecise guidance for the integration and uptake of novel medicines, and fragmented and underutilized QA procurement mechanisms.
- There are a small number of key players working on strengthening the TB treatment research infrastructure and clarifying the regulatory pathway for new TB medicines and regimens.
- The area of charting global strategies to facilitate rational and speedy uptake of new TB treatment regimens – especially those focused on high-TB-burden countries – is relatively underdeveloped. These strategies, such as the public-private mix, focus mostly on improving rational use of medicines but have not documented their effect on improving forecasting for QA medicines and pooled procurement. These strategies can improve market dynamics, attract more manufacturers, and ultimately increase access to quality and accessible TB treatment.
- External donor funding and country-based public-sector funding must be coordinated to demonstrate actual demand and strengthen market forecasting of QA products.

Concerted and coordinated leadership of the public and private sectors is essential to improving research processes, increasing research capacity, and clarifying regulatory guidance. The harnessing of public- and private-sector markets and procurement processes are critical to ensuring that the full potential of the global TB market is exploited to increase access to appropriate and effective medicines vital to reduce the burden of TB disease and to prevent the loss of the 1.45 million lives that TB claimed in 2010 (World Health Organization 2011b).

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