

THE PARADIGM

SHIFT → 2016-2020

Global Plan to End TB

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Stop TB Partnership

a partnership hosted by United Nations at  **UNOPS**

 **END
TB**

Paradigm Shift

noun [c]

"a time when the usual and accepted way of doing or thinking about something changes completely"

[Cambridge Dictionaries]



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www.stoptb.org/global/plan/plan2/annexes.asp



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Global Plan Task Force

Draurio Barreira, Amy Bloom, Paula Fujiwara (Chair), Rein Houben, Michel Kazatchkine, Blessina Kumar, David Lewinsohn, Jon Liden, David Mamefja, Aaron Oxley, Thokozile Phiri-Nkhoma, Mukund Uplekar, Eliud Wandwalo, Richard White.

Alternate Members:

Cherise Scott, Alessandra Varga, Diana Weil, Jennifer Woolley, Mohammed Yassin.

Ad-hoc Group of Economists

Carol D'Souza, Ines Garcia Baena, Andrew Siroka, Shan Soe-Lin, Stephane Verguet.

Stop TB Partnership Coordinating Board members

Timur Abdullaev, Erika Arthun, Patrick Bertrand, Joanne Carter, Mark Dybul, Evan Lee, David Lewinsohn, Susan Maloney, Aaron Motsoaledi, Austin Obiefuna, Anshu Prakash, Miriam Schneidman, Thomas Shinnick, Kitty van Weezenbeek, Cheri Vincent, Deborah von Zinkernagel, Gloria Wiseman.

Secretariat to the Global Plan Task Force

Jennifer Dietrich, Lucica Ditiu, Samuel Nuttall, Catie Rosado, Suvanand Sahu, Anissa Sidibe.

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Sharonann Lynch, Anna Maalsen, Hloniphile Mabuza, Jacques Mader, Rebecca Mahoko-Tadokera, Surya Prakash Makarla, Robert Makombe, Peter Mamacos, Ivan Manhiça, Davide Manissero, Eang Mao, Maphefo Masango, Irina Maslova, Dara Masoud, Benigna Matsinhe, Mea Maura, Thulani Mbatha, Magatte Mboj, Lindsay McKenna, Ruth Mc Nerney, Heather Menzies, Emmanuel Meribole, Philippe Meunier, Ntombi Mhlongo, Evelyn Mhlope, Amit Misra, Naimjon Mizorakhimov, Ntombizodwa Mntambo, Musa Mobolaji, Daria Mogucheva, Fritz Moise, Omphemetse Mokgatlhe, Refilwe Mokgetle, Yvonne Morgan, Svitlana Moroz, Andrei Mosnega, Jose Moya, Mbulawa Mugabe, Sugata Mukhopadhyay, Elchin Mukhtarli, Stephen Mule, Beauty Muringani, Ellen Murray, Seher Musaonbasioğlu, Lindiwe Mvusi, Safar Naimov, Anna Nakanwagi, Angeline Nanni, Alejandro Navarro, Thaddée Ndikumana, Norbert Ndjeka, Luan Quang Nguyen, Vuet Nhung Nguyen, Isabel Nieto, Pierre-Yves Norval, Thomas Novotny, Helena Nygren Krug, Carol Nawina Nyirenda, Oksana Ocheretina, Rafael Olarte, Francisco Olea-Popelka, Cintia Oliveira Dantas, Igor Oliznzk, James Oloya, Christy Omidiji, Viktoriia Osipenko, Oyebanji Oyebola, Seref Oykara, Amindavaa Oyunbileg, Manita Pandey, Basanta Parajuli, Gregory Paton, Kerry Pelzman, Freddy Perez, Luis Perez, Christophe Perrin, Kimsour Phirith, Phyllis Pholoholo, Shiba Phurailatpam, Yogan Pillay, Evgenz Pisemskiy, , Milena Prvulovic, Robert Pukose, John Puvimanasinghe, Pedro Enrique Quinones Figuero, Kirankumar Rade, Stefan Radut, Victor Ramathesele, Oriol Ramis, Bruno Rivalan, Yoir Rayyakov, Alasdair Reid, Stephen Resch, John Ridderhof, Barbara Rijks, Fedora Rodiukova, Florencia Rodriguez, Sandra Roelofs, Mirta Roses Perigo, Gennadz Roshchupkin, Tomas Roubal, Kuldeep Sachdeva, Tsovinar Sakanyan, Margaret Sakatsie, Ataulhaq Sanaie, Babatunde Sanni, Sanjay Sarin, Amy Sarmiento, Irina Schelokova, Khaled Seddiq, Rita Seicas, Ravini Senanayake, Abdulai Abubakarr Sesay, Rita Shah, Amer Irshad Sheikh, Hanna Shevchenko, Viktor Siebert, Dalbir Singh, Pavlo Skala, Anyhela Skopenko, Alena Skrahina, Mandy Slutsker, Caoimhe Smyth, Simeon C. Solomon, Jemberu Soressa, Mel Spigelman, Monica Mira Silvana Spindola, Karen Steingart, David Stevenson, Raminta Stukitze, Todd Summers, Jami Taylor, Miryagaleb Tillyashkhov, Ezio Tavora, David Traynor, Aneta Trgacevska, Alejandro Trossero, Oylen Tumer, Denis Valec, Anke van Dam, Martin van den Boom, Joost van der Meer, Ernesto Varela Villota, Ivan Varentsov, Tonka Verleva, Frank Verreck, Kgomotso Vilakazi-Nhlapo, Andreeva Vladanka, Fanny Voitzwinkler, Gerald Voss, Sergey Votyagov, Shekhar Waikar, Brenda Waning, Peter Warner, Carine Weiss, Charles Wells, Christine Whalen, Ellen Wilcox, David Wilson, Bawa Wuryaningtyas, Phumlani Ximiya, Rajendra Yadav, Mohammad Yassin, Vladimir Yhovtzyk, Merlin Young, Imran Zafar, Maria Zamfirova, Vitaly Zhmazgaliev.



Abbreviations

AIDS

Acquired Immunodeficiency Syndrome

ARV

Antiretroviral

ART

Antiretroviral therapy

BCG

Bacille Calmette–Guérin (vaccine)

BRICS

Brazil, Russia, India, China, South Africa

CPTR

Critical Path to TB Drug Regimens

CSR

Corporate social responsibility

DALY

Disability-adjusted life year

DST

Drug-susceptibility testing

GAVI

The Global Vaccine Alliance

GDF

Global TB Drug Facility

GDP

Gross domestic product

GNI

Gross national income

HBC

High-burden country

HIV

Human Immunodeficiency Virus

IPT

Isoniazid preventive therapy

IUATLD

International Union Against Tuberculosis and Lung Disease

KNCV

Royal Netherlands Tuberculosis Association

MDR-TB

Multidrug-resistant tuberculosis

MSF

Médecins Sans Frontières

NCE

New chemical entity

NDB

New Development Bank

NGO

Nongovernmental organization

NIAID

National Institute of Allergy and Infectious Disease

NIH

National Institutes of Health

NRL

National reference laboratory

NTP

National tuberculosis programme

OECD

Organisation for Economic Co-operation and Development

PLHA

People living with HIV/AIDS

R&D

Research and development

SRL

Supranational reference laboratory

TB

Tuberculosis

TPP

Target product profile

UNAIDS

Joint United Nations Programme on HIV/AIDS

UNICEF

The United Nations Children's Fund

USAID

United States Agency for International Development

VLY

Value of life years

WHO

World Health Organization

XDR-TB

Extensively drug-resistant TB



Glossary

Active TB disease

an illness in which TB bacteria are multiplying in different parts of the body. The symptoms of active TB disease include cough, weakness, weight loss, fever, loss of appetite and night sweats. A person with active TB disease may be infectious and spread TB to others. In the Global Plan, “people with TB” or “people ill with TB” refers to those who have active TB disease.

Antibiotic

a drug used to treat bacterial infections. Anti-TB drugs are also antibiotics. Antibiotics have no effect on viral infections.

Antibiotic resistance

the ability of a microorganism to withstand the effects of antibiotics. Antibiotic resistance typically evolves when a random mutation of the microorganism develops, making it less susceptible to the effects of a particular drug.

Antibiotic-susceptibility test

also known as a drug-susceptibility test (DST), this is a laboratory test to assess whether TB bacteria are sensitive or resistant to certain anti-TB drugs.

Antiretroviral therapy (ART)

the use of a particular class of drugs (antiretrovirals) to treat HIV infection.

BCG

the Bacillus Calmette–Guérin TB vaccine is named after the French scientists who developed it, Calmette and Guérin. BCG provides adolescents and adults with little protection against TB, but it is often given to infants and small children in countries where TB is common, as it can prevent some of the most severe forms of TB in children.

Case detection

when a person’s TB is diagnosed and reported within the national surveillance system. Although the term “case” is used widely in public health to refer to an instance of disease, it should be used with sensitivity in health care settings to avoid dehumanizing people. A person is not a case, but a fellow human being. Individuals seeking or receiving care for TB may find it demeaning if they overhear a health worker describing them as a “case”.

Contact

a person who has spent time with a person with infectious TB.

Close contact

a person who has had prolonged, frequent, or intense contact with a person with infectious TB. This group includes people who live together or spend a great deal of time together in close proximity. Close contacts, or household contacts, are more likely to become infected with *M. tuberculosis* than contacts who see the person with TB less often.

Community systems

community systems are the structures, mechanisms, processes and actors through which communities act on the challenges and needs that they face. They are made up of different types of entities: community members, formal and informal community organizations and networks, and other civil society organizations. Such systems are usually less formalized and less clearly defined than health systems. Entities that make up community systems have close links with communities; therefore, they are in a position to better understand the issues faced by those who are most affected and to find smart solutions.

Community systems strengthening

refers to initiatives that contribute to the development and/or strengthening of community-based organizations in order to increase knowledge of and access to improved health service delivery. It usually includes capacity-building of infrastructure and systems, partnership building, and the development of sustainable financing solutions.

Culture

a test to see whether there are TB bacteria in an individual's sputum/phlegm or other body fluids. This test can take two to four weeks in most laboratories.

Drug-resistant tuberculosis (DR-TB)

disease caused by a strain of TB bacteria that is resistant to the most commonly used anti-tuberculosis drugs.

Extensively drug-resistant tuberculosis (XDR-TB)

disease caused by a strain of TB bacteria that is resistant to isoniazid and rifampicin (the two most commonly used anti-TB drugs), as well as fluoroquinolone and at least one of the three injectable second-line drugs (amikacin, kanamycin, capreomycin).

Extrapulmonary TB

TB disease in any part of the body other than the lungs (for example, the kidney, spine, brain or lymph nodes).

Gender-sensitive

gender-sensitive policies, programmes or training modules recognize that both women and men are actors within a society, that they are constrained in different and often unequal ways, and that consequently they may have divergent and sometimes conflicting perceptions, needs, interests, and priorities.

Gender-specific

refers to any programme or tailored approach that is specific to either women or men, due to the particular challenges faced by that gender.

mHealth

(also written as **m-health**) is an abbreviation for mobile health, a term used for the practice of medicine and public health supported by mobile devices.

Multidrug-resistant tuberculosis (MDR-TB)

disease caused by a strain of TB bacteria that is resistant to at least isoniazid and rifampicin (the two most commonly used anti-TB drugs).

Mycobacterium tuberculosis

bacteria that cause TB infection and TB disease.

Nutritional support

aims at ensuring adequate nutrition and includes assessment of the dietary intake, nutritional status, and food security of the individual or household; offering nutrition education and counselling on how to ensure a balanced diet, mitigate side-effects of treatment and infections, and ensure access to clean water; and providing food supplements or micronutrient supplementation where necessary.

Organisation for Economic Co-operation and Development (OECD)

the OECD brings together 30 member countries sharing a commitment to democratic government and the market economy.

Patient-centred approach to TB care

a patient-centred approach considers the needs, perspectives, and individual experiences of people affected by TB, while respecting their right to be informed and receive the best qual-

ity care based on individual needs. It requires the establishment of mutual trust and partnership in the patient–care provider relationship, and creates opportunities for people to provide input into and participate in the planning and management of their own care. A patient–centred approach improves treatment outcomes, while respecting human dignity.

People affected by TB

this term encompasses people ill with TB and their family members, dependents, communities, and health care workers who may be involved in caregiving or are otherwise affected by the illness.

Person lost to follow-up

someone who does not start or complete TB treatment, generally because of poor quality health services or the lack of a patient–centred approach. Previously, people lost to follow-up were referred to as “defaulters”. The term defaulters should be avoided, however, as it unfairly places all the blame on patients.

Person to be evaluated for TB

in the past, a person who presented with symptoms or signs suggestive of TB used to be referred to as “TB suspect”. The word “suspect” should no longer be used.

People with TB (PWTB)

this term encompasses people who are ill with active TB. The term “people (or person) with TB” recognizes that people with TB should not be defined solely by their condition. The term may be preferable to the word “patient” in certain contexts (e.g. nonmedical and community settings).

Preventive therapy

medicines that prevent TB infection from progressing to active TB disease.

Programme integration

this term refers to joining together different kinds of services or operational programmes in order to maximize outcomes, e.g. by organizing referrals from one service to another or by offering one-stop comprehensive and integrated services. In the context of TB care, integrated programmes may include HIV testing, counselling, and treatment; sexual and reproductive health; primary care; and maternal and child health.

Southern African Development Community (SADC)

is an inter-governmental organization headquartered in Gaborone, Botswana. Its goal is to further socio-economic cooperation and integration as well as political and security cooperation among 15 southern African states. It complements the role of the African Union.

Smear microscopy

a test to see whether there are TB bacteria in sputum. To do this test, lab workers smear sputum on a glass slide, stain the slide with a special dye, and look for any TB bacteria on the slide. This test usually takes one day to produce results.

Sputum

phlegm coughed up from deep inside the lungs. Sputum is examined for TB bacteria using smear microscopy, culture or molecular tests.

Stigma

is derived from the Greek meaning “a mark or a stain”. Stigma can be described as a dynamic process of devaluation that significantly discredits an individual in the eyes of others. Within particular cultures or settings, certain attributes are seized upon and defined by others as discreditable or unworthy. When stigma is acted upon, the result is discrimination that may take the form of actions or omissions.

TB disease

an illness in which TB bacteria multiply and attack a part of the body, usually the lungs. The symptoms of active TB disease include weakness, weight loss, fever, loss of appetite and night sweats. Other symptoms of TB disease depend on where in the body the bacteria are growing. If TB disease is in the lungs (pulmonary TB), the symptoms may include a bad cough, pain in the chest and coughing up blood. A person with pulmonary TB disease may be infectious and spread TB bacteria to others.

TB infection

also called latent tuberculosis infection. It is a condition in which TB bacteria are alive but inactive in the body. People with latent TB infection have no symptoms; they do not feel sick, cannot spread TB bacteria to others, and usually test positive for infection – positive to a tuberculin skin test or a special test called IGRA test. In the Global Plan, people referred to as “infected with TB” are people having such latent TB infection.

TB prevention and care

the efforts of health care workers to provide TB services to the communities they serve. These terms are preferred over “TB control”, which may create the perception that TB experts are in full control of all aspects of prevention, treatment and care of people with TB. It is useful to examine the term “control” critically so as to avoid neglecting community and patient resources and capacities.





Foreword

Many of history's greatest successes in the fight against preventable diseases have been characterized by momentous shifts in people's belief of what is possible. For too long, the world has believed that ending TB is not possible, and that business as usual will suffice. We know that neither is true! We need a paradigm shift now more than ever. The Global Plan to End TB 2016-2020 reflects this paradigm shift and must be implemented with urgency and vigour.

When the world first set out to eradicate smallpox nearly 50 years ago, many felt it was not possible, and some were even strongly against the idea. Visionaries in the early global AIDS response were also met with resistance when they suggested that AIDS medicines could be provided to all who needed them regardless of their income or status in society. As with those who doubted the eradication of smallpox was possible, they were proven wrong.

What shifted and made these successes possible? It was the belief that change was not only possible, but necessary.

While we celebrate the achievement of the Millennium Development Goal target to halt and reverse the spread of TB, we must also ask why TB has now become the leading cause of death from an infectious disease. Even as we focus on the lives that have been saved over the last 20 years, we must also ask why 1.5 million people still die from TB year after year.

These are the questions that The Global Plan to End TB 2016-2020: The Paradigm Shift seeks

to answer. It is an ambitious plan of action that provides a blueprint for the TB community to drive bold action and ambitious change. A Task Force of world renowned experts and a wide community of dedicated people working on TB came together to contribute to the development of this plan.

The Global Plan 2016–2020 sets out the actions and resources needed over the next five years to set the world on a course to end the global TB epidemic by 2030, as endorsed by world leaders in the newly adopted Sustainable Development Goals.

This Plan makes it clear that what is needed to end TB is a paradigm shift – a change in the way we fight TB at every level, in every community, in every health facility, in every country.

TB has persisted throughout history because its roots are deeply intertwined with economic and social inequalities. TB has always been a disease of poverty, and a litmus test for our commitment to social equality and health for all. Unfortunately, its longevity has created a sense of acceptance that it is here to stay and a sense of complacency.

The Global Plan sets out to smash this status quo, and provides a way to address these challenges

though scaling up and integrating TB care into a wider health and community system approach, to eliminate poverty, and build healthy, sustainable societies.

This Global Plan has the potential of reaching the milestones and targets of the End TB Strategy if fully resourced and implemented. By establishing the 90–90–90 targets for TB, it demands that the global community focuses and implements programmes that put people at the center of all efforts. It brings key populations, the most vulnerable, and communities to the centre of our efforts, and positions the private sector as an essential partner.

In concrete terms, the Global Plan will ensure that 29 million people are treated, that 10 million lives are saved and that 45 million people are prevented from getting TB. The Plan will drive the development of much-needed new tools against TB, diagnostics, vaccines and new shorter acting medicines to accelerate progress towards a world free of TB.

We support the Global Plan and call on colleagues, partners and all stakeholders to work together to commit to and fully fund the Global Plan, and to achieve its targets.

Working together we will end TB in our lifetime!

Dr. Aaron Motsoaledi

Chair of the Stop TB Partnership
Coordinating Board

and

Minister of Health of the
Republic of South Africa

Dr. Joanne Carter

Vice-Chair of the Stop TB Partnership
Coordinating Board

and

Executive Director, RESULTS and
RESULTS Educational Fund



Preface

The scale of the response to today's global tuberculosis (TB) epidemic demands urgent and effective action now.

This curable disease known to humanity for thousands of years is now the top infectious disease killer on the planet, with 4,400 victims every single day. TB and HIV/AIDS are "partners in crime", often affecting the same persons, and reducing their hope for life, especially when they have resistant forms of TB. The current very limited investments in TB research and development have left the TB community to fight the disease with old and completely inadequate tools. The rate of decline of TB incidence is so slow that if the current situation continues, it will take up to 2182 to reach the World Health Organization's End TB targets.

The Stop TB Partnership was established in 2000 as a global movement to accelerate social and political action to stop the spread of TB. Fifteen years since its establishment, we have the pleasure to introduce the fourth edition - the Global Plan to End TB 2016-2020: the Paradigm Shift.

Developed over 18 months under the leadership of a Task Force comprised of world renowned TB experts and partners, and having benefited from inputs from global, regional and country TB and HIV experts through four regional and one global online consultations, the Plan should be owned by every single partner and country programme.

It provides a coherent roadmap for the next five years to rally all partners, implement and scale up proven interventions, accelerate research and development, and push country-level implementation to move towards ending the TB epidemic.

A fully funded Global Plan will allow the world to move at the greatest possible speed to reach the End TB targets endorsed by the world's Ministers of Health in 2014. Only in this way we will be able to have a world without TB. **We can do it.**

Dr. Paula Fujiwara
Chair
Task Force of the Global Plan to End TB
and
Scientific Director, International Union
Against Tuberculosis and Lung Disease

Dr. Lucica Ditiu
Executive Director
Stop TB Partnership Secretariat



INTRODUCTION



Ending tuberculosis: Challenges and opportunities

Measured by the numbers of people who die each year, tuberculosis (TB) is the world's deadliest infectious disease. Transmitted through the air and primarily targeting the lungs, this disease caused by a bacterial infection claims three lives every minute.^{1,2} In 2014, more than 9 million people became ill with TB and 1.5 million died, making it the world's leading infectious killer.³ Worldwide over 2 billion people are infected with *Mycobacterium tuberculosis*, the bacterium that causes TB, comprising a source of the illness that must be addressed if we are to be successful in ending the disease.

In 2000, to drive progress against TB, the UN Millennium Development Goals committed to halting and beginning to reverse the global TB epidemic by 2015. The world met that goal, and TB programmes saved some 43 million lives worldwide between 2000 and 2014.

However, the Stop TB Partnership's targets of halving TB prevalence and death rates by 2015 have not been met in all regions of the world. Between 2000 and 2014, TB incidence fell by an average of only 1.5% a year⁴ – an unacceptably slow rate of decline for a preventable and cur-

able disease. Recent prevalence surveys show that TB levels in several high-burden countries are even greater than previously estimated.

Of the more than 9 million people who become ill with TB each year, more than 3 million are not diagnosed, treated, or officially registered by national TB programmes. Collectively, these "missed" millions are a global public health failure. This is especially the case considering that TB is airborne and that each undiagnosed and untreated person can infect as many as 15 individuals per year.

Progress against HIV has far outstripped global efforts to tackle TB. In 2014, for the first time in decades, TB killed more people than any other infectious disease in the world. Moreover, TB continues to be the leading cause of death among people living with HIV, accounting for nearly one in three HIV-related deaths. Despite increased collaboration between TB and HIV programmes and significant progress, especially in the African region, less than half of TB patients are tested for HIV and only half of the estimated number of people who become ill with HIV-related TB receive treatment.

A number of middle-income countries have seen high and steady economic growth over the past 15 years. Yet, in many of these countries, reductions in TB incidence and deaths have remained disappointingly small. Economic growth has not always been accompanied by the domestic investments needed to adequately fund TB programmes. Compounded by decreasing inter-

1 The top 10 causes of death. Geneva: World Health Organization (<http://www.who.int/mediacentre/factsheets/fs310/en/>).

2 Leading the fight against TB. Geneva: The Stop TB Partnership (<http://www.stoptb.org/assets/documents/resources/publications/acsm/NEW%20STOP%20TB%20BROCHURE.pdf>).

3 Global tuberculosis report 2015. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1http://www.who.int/tb/publications/global_report/indicators_global_and_regional_summaries.pdf).

4 Ibid.

national financial support for TB, the result is a chronic shortage of funding for the global fight against TB. Even with current efforts there is a shortage of about 2 billion USD per annum globally, excluding research.

Drug-resistant TB poses a grave and overarching challenge. More than half a million people develop multidrug-resistant TB (MDR-TB) each year. Extensively drug-resistant TB (XDR-TB), an even more severe form of the disease, has been reported in 105 countries. In spite of all the efforts made, three out of four people with drug-resistant TB are not accurately diagnosed, and less than a quarter of those estimated to have the disease start treatment each year. While two promising new MDR-TB drugs are making their way to the field, the prevailing full course of treatment for MDR-TB is expensive and extremely toxic, and requires two years. Moreover, the treatment success rate among

individuals who start treatment for drug-resistant TB is only 50%.

Unless we address this challenge now, decades of progress will be undone and the billions of dollars invested in fighting TB will be wasted. According to the Antimicrobial Resistance (AMR) Review, an initiative that UK Prime Minister David Cameron commissioned in 2014, by 2050 drug-resistant TB could kill as many as 2.5 million people per year and cost the global economy as much as US\$ 16.7 trillion – the equivalent of the annual economic output of the European Union.¹ In addition to the human and economic costs posed by drug-resistant TB, its airborne nature makes it a threat to global health security.

¹ All Party Parliamentary Group on Global TB. The price of a pandemic: counting the cost of MDR-TB; 2015 (<http://www.appg-tb.org.uk/#!/publications/cghg>).

The End TB Strategy

In 2014, the World Health Assembly unanimously approved the End TB Strategy, a 20-year strategy to “end the global TB epidemic”², with the vision of a world with “zero deaths, disease and suffering due to TB”.

The End TB Strategy identifies four barriers to achieving progress in the fight against TB³:

1.WEAK HEALTH SYSTEMS, including those with large, unregulated nonstate sectors

2.UNDERLYING DETERMINANTS of TB such as poverty, undernutrition, migration and aging populations; and risk factors such as diabetes, silicosis and smoking

3.LACK OF EFFECTIVE TOOLS

4.CONTINUOUS UNMET FUNDING NEEDS

As shown in Fig.1, the Strategy rests on four principles and three pillars of action.

The End TB Strategy aims to address these barriers by eliciting a strong, systemic response to end the TB epidemic, drawing on the opportunities provided by the Sustainable Development Goals, especially those goals aimed at achieving universal health coverage and social protection from disease (see Box 1: The Sustainable Development Goals). As more than half of the global TB burden and two thirds of the global MDR-TB burden are borne by Brazil, Russia, India, China, and South

² “Ending the TB epidemic” is defined as an average global TB incidence of 10/100 000. The phrase “end TB” is used throughout this document with reference to this operative definition.

³ Uplekar M, Weil D, Lonnroth K, et al. WHO’s new End TB Strategy. *Lancet*. 2015;385(9979):1799–801. doi:10.1016/S0140-6736(15)60570-0.

FIGURE 1: END TB STRATEGY



VISION | A world free of tuberculosis—zero deaths, disease and suffering due to tuberculosis

GOAL | End the global tuberculosis epidemic

INDICATORS

MILESTONES

TARGETS

	2020	2025	SDG 2030	End TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	zero	zero	zero	zero

PRINCIPLES

1. Government stewardship and accountability, with monitoring and evaluation
2. Strong coalition with civil society organizations and communities
3. Protection and promotion of human rights, ethics and equity
4. Adaptation of the strategy and targets at country level, with global collaboration

PILLARS AND COMPONENTS

1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION

- A. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
- B. Treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support
- C. Collaborative tuberculosis/HIV activities, and management of co-morbidities
- D. Preventive treatment of persons at high risk, and vaccination against tuberculosis

2. BOLD POLICIES AND SUPPORTIVE SYSTEMS

- A. Political commitment with adequate resources for tuberculosis care and prevention
- B. Engagement of communities, civil society organizations, and public and private care providers
- C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
- D. Social protection, poverty alleviation and actions on other determinants of tuberculosis

3. INTENSIFIED RESEARCH AND INNOVATION

- A. Discovery, development and rapid uptake of new tools, interventions and strategies
- B. Research to optimize implementation and impact, and promote innovations

Africa (BRICS) and other emerging economies, increased and sustained commitment by the BRICS countries will play a central role in meeting the global milestones set by the Strategy.

By 2020, the End TB Strategy aims to eliminate catastrophic costs associated with TB, i.e. those related to treatment or loss of income that drive

individuals and families into poverty. To achieve this, TB diagnosis and treatment should be free or affordable in all countries (eventually through universal health coverage systems), combined with access to social welfare systems in most countries.

BOX 1:

The Sustainable Development Goals

In September 2015, the General Assembly of the United Nations approved the Sustainable Development Goals (SDGs). These goals will be the focus of global priorities for development cooperation and will also guide national priorities in most countries for the coming 15 years.

Ending the TB epidemic by 2030 is one of the targets under Goal 3, which is to “ensure healthy lives and promote well-being for all at all ages”.

The SDGs will be achieved only if addressed together, understanding the clear links between the goals and how progressing towards one goal will aid in the achievement of others. Not only is ending the TB epidemic closely linked to achieving a number of SDGs, but incorporating appropriate TB responses into efforts to meet some of the other SDGs will accelerate the end of TB.

There are multiple links between TB and poverty and food security (Goals 1 & 2). Preventing lost work hours due to TB globally will add US\$ 12 billion to achieving sustainable economic growth, and full and productive employment (Goal 8). Goal 17 calls for strengthening domestic resource mobilization and finding additional financial resources from multiple

sources, as well as for developed countries to fully implement their commitments to provide official development assistance, including the commitment to devote 0.7% of gross national income (GNI) to official development assistance. As economies grow, associated improvements in both living conditions (Goal 11) and equal rights to health care treatment (Goal 16) will contribute to slowing the spread of TB. When the world strengthens enforceable legislation for the promotion of gender equality (Goal 5) and reduces inequalities by eliminating discriminatory practices (Goal 10), people will be able to access TB diagnosis and care more easily in cases where financial inequity, family responsibilities and cultural barriers may have prevented them from receiving care in the past.



The Global Plan to End TB 2016–2020

The Global Plan to End TB 2016–2020 (hereafter, the “Global Plan”) is the costed plan for implementing the first five years of the End TB Strategy. It takes the End TB Strategy as its foundation and pro-

vides countries and policy makers with a path towards achieving the Strategy’s milestones.

The Global Plan presents a means for how the world can break out of the current trend of slow decline and “bend the curves” of incidence and mortality towards ending TB. It provides a set of people-centred targets that countries can use to guide their planning and an overview of the funding needed to end TB.

The development of the Global Plan has involved extensive inputs and contributions from research and development stakeholders, communities and civil society, and national TB programmes in a number of countries. These contributions have significantly informed the modelling work and composition of the investment packages included in the Global Plan.

To develop the Global Plan, the Stop TB Partnership Coordinating Board established a Task Force of 15 people, each representing an area of expertise or group of stakeholders within the TB community. The Global Plan development process was led by the Task Force, and informed by a two-month online web-based consultation and four regional consultation meetings in Addis Ababa, Bangkok, Buenos Aires, and Istanbul. Through these consultations, the task force gathered input from governments, TB programmes, donors, technical partners, other implementers, private sector providers, the corporate sector, civil society, and affected communities.

To end TB, all stakeholders should commit to and fully fund the Global Plan, and work together to achieve its targets.



1.

A PARADIGM SHIFT IN THE FIGHT AGAINST TB

KEY MESSAGES

- ✦ For the first time in history, we have an ambitious strategy that aims to end TB, defined as achieving an incidence rate of 10 new people with TB per 100 000 population per year.
 - ✦ To end TB, we need to bring about a paradigm shift in TB care and prevention. The current 1.5% annual decline in global TB incidence is unacceptable, and it is feasible to accelerate that decline to 10% per year.
 - ✦ The Global Plan introduces three people-centred targets called the 90-(90)-90 targets: reach 90% of all people who need TB treatment, including 90% of people in key populations, and achieve at least 90% treatment success.
 - ✦ The Global Plan proposes a paradigm shift in the way that we fight TB globally, regionally and nationally. This shift is needed under eight broad areas and includes securing bold political leadership at the highest level; implementing an approach to TB that is grounded in human rights and gender equity; and maintaining a central focus on patients and communities affected by TB.
 - ✦ To help countries reach the 90-(90)-90 targets, the Global Plan provides a set of illustrative investment packages, tailored for different country settings and designed for maximum impact and return on investment.
-

The global decline in TB has slowed over the past decade to a 1.5% annual reduction in global incidence. So, how do we achieve a 10% annual decline in TB by 2025? TB programmes in many countries are constrained at the outset leading to modest impact. Today, programmes typically limit their delivery of TB treatment and care to people with TB who present themselves at health facilities, by

which time they have likely exposed others to TB infection. If programmes proactively reached out to people who might have been exposed to TB, they would provide care and treatment early, thereby stopping transmission.

The End TB Strategy and the Global Plan, therefore, shift the emphasis from controlling and reversing the advance of the TB pandemic to a much more aggressive goal: ending TB. This goal means driving the pandemic back to a point where TB is no longer a drag on eco-

nomics and human development. To achieve this paradigm shift, the Global Plan calls for a change in mindset, a change in ambition, an aggressive focus on achieving people-centred targets, and full investment in the pillars of the End TB Strategy.

The Global Plan's analysis and modelling show that if countries expand health interventions to end – not merely contain – TB, it will be possible to achieve the Strategy's 2020 and 2025 milestones.



People-centred global targets: 90-(90)-90

There is huge potential to improve the reach and quality of current medical interventions for TB. Of the more than 9 million people estimated to fall ill with TB each year, more than 3 million are not reached through national TB programmes and may not receive proper diagnosis or treatment. Of those who do receive quality treatment, 86% have a successful recovery. Of the 9 million who fall ill, at least 480 000 people develop drug-resistant TB each year and less than 20% of them receive proper treatment. As a result, only around half of those who become ill with TB have the opportunity to be cured.

The Global Plan’s targets are designed to address an unacceptable gap in the provision of TB care. Its targets are inspired by both the UNAIDS 90-90-90 treatment targets and the Communiqué of the 4th Meeting of BRICS Health Ministers in December 2014, which urges the BRICS nations to aspire to three 90% targets for their countries’ TB activities by 2020.¹

¹ Communiqué of the IV Meeting of BRICS Health Ministers; 2014 (<http://brics.itamaraty.gov.br/category-english/21-documents/242-ivhealth>).

THE GLOBAL PLAN ARTICULATES THESE AS THE 90-(90)-90 TARGETS:

Reach at least

90%
OF ALL PEOPLE WITH TB

and place all of them on appropriate therapy—first-line, second-line and preventive therapy as required

As a part of this approach, reach at least

(90)%
OF THE KEY POPULATIONS

the most vulnerable, underserved, at-risk populations

Achieve at least

90%
TREATMENT SUCCESS

for all people diagnosed with TB through affordable treatment services, adherence to complete and correct treatment, and social support.

Impact modelling shows that achieving the above targets by 2025 at the latest will ensure that the goal to end TB will be met.

The Global Plan therefore proposes that the 90–(90)–90 targets should be reached as soon as possible, ideally by 2020 and at the latest by 2025.

TARGET 1 focuses on reaching people who require treatment and providing them with effective therapy. This requires early detection and the prompt treatment of 90% of people with TB (including both drug-susceptible and drug-resistant TB) and 90% of people who require preventive therapy (e.g. people living with HIV/AIDS and those in contact with TB patients). Countries should also provide preventive therapy (therapy that treats TB infection before it progresses to TB disease) to additional groups of people based on international guidelines. By improving the rates at which people are diagnosed and treated, countries can reduce the spread of the disease and drive down incidence.

TARGET 2 is a subset of Target 1 (hence the parentheses). Vulnerable, underserved, at-risk populations vary depending on country context, but in all cases these key populations are more frequently missed by health systems, often unable to access health services, or suffer particularly detrimental consequences as a result of TB. Equity and human rights demand a special effort to reach these populations. Targeting the most vulnerable populations constitutes good public health and economic policy. The purpose of Target 2 is also to provide treatment and care through affordable programmes that protect patients and their families from the often catastrophic costs associated with having TB. Chapter 3 describes key population groups. The Global Plan recommends that each national TB programme work with communities affected by TB to define its key populations, to plan and implement appropriate services, and to measure progress towards reaching these populations.

TARGET 3 aims at ensuring the quality treatment, support and follow-up needed to achieve at least a 90% treatment success rate among people identified as needing treatment – including treatment for drug-susceptible TB, drug-resistant TB, or preventive TB therapy. This target is more ambitious than previously established targets for treatment success, as it covers 90% of all people diagnosed with TB – not just those who start treatment. Currently, in many settings, a large number of people who are diagnosed with TB do not initiate treatment and might not even be notified of their status. The Global Plan urges TB programmes to adopt this new approach of notifying all people diagnosed with TB of their status, ensuring full and proper treatment for all in need, being accountable for the outcomes of treatment, and reporting all outcomes nationally.

Measuring progress in terms of the Global Plan targets

The Stop TB Partnership will measure progress towards the 90–(90)–90 targets, along with the milestones for research, development and funding goals set out in the Global Plan.

Detailed indicators and targets for the End TB Strategy are provided in Annex 1.¹ Data should be disaggregated to allow for monitoring progress among adults, children, males, females and key populations. The Plan recommends that additional process-oriented targets be developed to track progress against elements related to the paradigm shift described in the next section, including the number of people tested for TB, community systems, key populations and private sector care.

¹ www.stoptb.org/global/plan/plan2/annexes.asp

The paradigm shift

It is important to understand the challenges countries will face in reaching the targets. The Global Plan, therefore, identifies eight fundamental changes that must be implemented as part of the paradigm shift needed to end TB.

1. A CHANGE IN MINDSET



To end TB, governments of countries with high burden will need to be ambitious, declaring that TB has no place in the future of their societies and that the current paradigm – controlling the disease with modest incremental gains – will be replaced by an energized and sustained effort to end TB. Progress as dramatic as that envisioned in the End TB Strategy can only be achieved

once a country's leadership announces to its people – and its health services – that TB will be fought on a long-term campaign basis, similar to HIV or even polio, and that it will dedicate the resources needed to end TB in the country. All stakeholders need to adopt a mindset of responding to TB in a manner that will end the disease.

2. A HUMAN-RIGHTS AND GENDER-BASED APPROACH TO TB



A human-rights-based approach to TB is grounded in international, regional and domestic law. These laws establish rights to health, nondiscrimination, privacy, freedom of movement, and enjoyment of the benefits of scientific progress, among others. Human rights law also establishes the legal obligations of governments and private actors.

In order to implement a human-rights-based approach to TB, countries should:

- ✦ **PROHIBIT DISCRIMINATION AGAINST PEOPLE WITH TB**
- ✦ **EMPOWER PEOPLE TO KNOW THEIR TB STATUS** and establish legal rights to access TB testing and treatment, including the elimination of financial and physical barriers to treatment and care
- ✦ **ENSURE THE PARTICIPATION OF PEOPLE WITH TB IN HEALTH POLICY DECISION-MAKING PROCESSES**

✦ **ESTABLISH MECHANISMS TO ADDRESS RIGHTS OF PEOPLE WITH TB** and ensure their implementation

✦ **PROTECT THE PRIVACY OF PEOPLE WITH TB.**

A gender-based approach to TB aims at addressing the social, legal, cultural and biological issues that underpin gender inequality and contribute to poor health outcomes. It encourages activities that are gender-responsive investments to prevent new cases of TB, and strengthen the response to fulfil the right to health of women and girls, men and boys in all their diversity.

Wherever applicable, these protections should be included in constitutional law or legislation. If this is not possible, they should be incorporated as legal rights in national and local TB policies.

3. CHANGED AND MORE INCLUSIVE LEADERSHIP

Ending TB will require the mobilization of a broad spectrum of government officials – presidents and prime ministers, members of parliament, mayors, and community administrators – to work with civil society organizations and individual citizens in a long-term effort to diagnose, treat and prevent TB. This effort will demand political commitment and coordination at the highest levels that tie together govern-

ment ministries – especially ministries of finance and labour – and will require effective alliances between government, civil society, affected communities, and the private sector for action on poverty, social protection, justice and labour reform. Furthermore, this will require greater South-South collaboration on capacity-building in countries, as well as strategic regional initiatives.

4. COMMUNITY- AND PATIENT-DRIVEN APPROACH

People with TB and the groups that represent them must be at the heart of the paradigm shift. Affected communities must be included in every area of decision-making, serving on boards of organizations and institutions that provide care, and sharing their experience and knowledge as equal and valuable partners in all TB forums. The community must also be resourced and empowered to form caucuses, to choose its own representatives, and to interact with the media.

People with TB and their communities must be partners in the design and planning of strategies to end TB, and given a key role in monitoring and evaluation, especially at the point of need. New tools, including social media, social auditing and social observatories, have the potential to be used alongside traditional tools to make progress in this area.

5. INNOVATIVE TB PROGRAMMES EQUIPPED TO END TB

The paradigm shift requires that TB programmes be equipped to end TB as an epidemic. National authorities responsible for the fight against TB need to be empowered to undertake necessary policy changes, to allocate resources, and to implement activities that will have an impact. These programmes need to respond to the needs of local settings, identifying TB hot spots and areas that will require more intensive efforts, such as areas with high levels of poverty.

TB programmes must focus not only on saving lives, but also on stopping transmission through early case detection and stronger prevention, with a targeted approach to serve communities at high risk. TB programmes should be equipped to leave behind the past approach of slowly scaling up pilot projects in order to

more rapidly scale up treatment and care for drug-sensitive and drug-resistant TB. This will require programmes to look for innovative approaches in service delivery, embracing the use of social media and m-health. Local programmes need to be empowered to find innovative solutions to identify and treat vulnerable groups. It will require the collection of high-quality data, real-time monitoring, and private-sector expertise. Programmes must also be equipped to rapidly and efficiently roll out any new medicines, diagnostics and vaccines that reach the market before 2025.

6. INTEGRATED HEALTH SYSTEMS FIT FOR PURPOSE



Integrated health systems are essential for ending TB. The fragmentation and isolation of TB programmes within country health systems must end, as must the separation of programmes aimed at tackling different forms of TB and coinfections with specific diseases. Instead, TB interventions should be integrated to the greatest extent possible with HIV/AIDS and maternal and child health programmes, and made part of the efforts to deliver primary health care in the context of universal health coverage.

Efforts to tackle TB should also include zoonotic TB, embracing the One Health approach that recognizes that the health of humans is connected to the health of animals and the environment. There is an urgent need to increase the human resources available to end TB, and to improve the collection and analysis of data to better inform and correct programming.

7. NEW, INNOVATIVE AND OPTIMIZED APPROACH TO FUNDING TB CARE



A sustained increase in funding for TB programmes and TB R&D, with significant front-loaded investments in the period of the Global Plan, will be required to end TB (see Chapter 7 on resource needs). Significant changes should also be made to the way that funds are raised and deployed.

TB programmes must make a compelling business case for increased and frontloaded budgets and then make efficient use of resources – prioritizing investments and pooling resources with other programmes. Innovative financing approaches, including better use of incentives, present an opportunity to increase TB resources. Results-based financing approaches are being

rolled out in numerous countries, and is beginning to generate positive results by providing financial incentives to providers and facilities for specific results attained – TB programmes must be part of such initiatives.

Furthermore, TB programmes must engage the business sector and private-sector health providers as partners, harnessing companies' consumer-led approaches and embracing their ability to generate revenue through social business models. As social health insurance initiatives and innovative, blended finance mechanisms scale up, TB programmes need to proactively align and integrate with these initiatives.

8. INVESTMENT IN SOCIOECONOMIC ACTIONS



Medical interventions alone will not be enough to end TB. Nonmedical actions and investments, such as in improved housing and sanitation, poverty reduction, and strengthened social safety nets, will drive down the numbers of peo-

ple becoming ill and dying from TB. Planning for and investing in such nonmedical activities cannot wait, as they normally take several years to implement and to affect TB incidence.

Country settings

The Global Plan provides sets of recommended actions – “investment packages” – designed to achieve the 90–(90)–90 targets. These investment packages are tailored to the local characteristics of the TB epidemic, as well as to the health system constraints and socioeconomic situations in various country settings.

Similarities exist between countries within a particular region or between countries with similar histories, socioeconomic conditions or health system constraints. As a result, countries can be grouped into different “settings”¹. Countries

can be associated with the characteristics of more than one setting, and provinces within a single country can fit into different settings. The method for defining each setting is explained in Annex 2.²

¹ Country settings are not meant to form any alternative to existing formal groupings in public health, such as WHO regions, etc. They are also not meant to form classifications for funding allocations or any other operational decisions.

² www.stoptb.org/global/plan/plan2/annexes.asp

THE COUNTRY SETTINGS (DESCRIBED IN MORE DETAIL IN CHAPTER 2) ARE DEFINED BELOW:

- 1 EASTERN EUROPEAN AND CENTRAL ASIAN SETTINGS** that have a high proportion of drug-resistant TB and a hospital-based care delivery system
- 2 SOUTHERN AND CENTRAL AFRICAN SETTINGS** where HIV and mining are key drivers of the epidemic
- 3 AFRICAN SETTINGS** with moderate to high HIV where mining is not a significant issue
- 4 SETTINGS WITH SEVERELY UNDER-RESOURCED HEALTH SYSTEMS** or country settings with challenging operating environments (COE)
- 5 SETTINGS WITH A HIGH TO MODERATE BURDEN OF TB** with a large proportion in private sector care
- 6 MIDDLE-INCOME COUNTRY SETTINGS** with a moderate TB burden
- 7 INDIA SETTING**
- 8 CHINA SETTING**
- 9 LOW-BURDEN SETTINGS** and country settings on the verge of eliminating TB



Investment packages

The economic case for ending TB is compelling. Treatment is low-cost and highly effective. On average, effective treatment may give an individual in the middle of his or her productive life about 20 additional years of life, resulting in substantial economic and health returns.¹ The High-Level Panel for the UN's Sustainable Development Goals has estimated that an investment of US\$ 1 in TB care yields a return of US\$ 30.² Other studies put the return as high as US\$ 115 for each dollar invested.³ Donors and funders of health increasingly favour an investment approach focused on results and returns over a simple funding approach focused on inputs.

The Global Plan's investment packages propose interventions tailored to have the greatest impact and to provide the maximum return on investment for the particular setting. The investment packages selected for the different settings are described in detail in Chapter 2 and provided as Annex 3.⁴

1 Vassal A. Tuberculosis perspective paper. Benefits and costs of the education targets for the post-2015 development agenda. Copenhagen Consensus Center; 2014 (<http://www.copenhagenconsensus.com/publication/post-2015-consensus-health-perspective-tuberculosis-vassal>).

2 The Report of the High-Level Panel of Eminent Persons on the Post-2015 Development Agenda; 2015 (http://www.un.org/sg/management/pdf/HLP_P2015_Report.pdf).

3 Goodchild M, Sahu S, Wares F, et al. A cost-benefit analysis of scaling up tuberculosis control in India. *Int J Tuberc Lung Dis*. 2011;15:358–62.

4 www.stoptb.org/global/plan/plan2/annexes.asp

BOX 1.1:

South Africa: The paradigm shift in practice

Some countries are already showing that a paradigm shift is possible. South Africa, the country with the world's highest TB rates, has embarked on a broad, four-year campaign to dramatically drive down TB rates in the country. The country has already largely integrated its HIV and TB care, seeking to ensure that every individual diagnosed with HIV is also tested and if necessary treated for TB, using modern tools.

The campaign now focuses on those most vulnerable – going house-to-house in six mining districts where TB disease rates are the highest – to reach 5 million people. In the coming years, the campaign will expand to additional cities and provinces with high burdens. It will test at least 90% of the country's 150 000 prisoners.

This initiative is the result of a joint push from South Africa's President and Health Minister, with strong support from the country's parliament. Their efforts have provided strong signals to all local leaders to engage in the fight.

South Africa, with its infrastructure and research capacity, is also playing a critical role in the research and development of new, more effective tools to prevent, diagnose and treat TB. South African researchers are making major contributions to global efforts to develop these new tools, from early-stage research through to large-scale clinical trials.





2. IMPACT MODELLING AND A DIFFERENTIATED APPROACH



KEY MESSAGES

- ✦ The 2020 milestones of the End TB Strategy for reductions in people falling ill with TB and deaths due to TB can be met if countries aggressively scale up interventions in line with the 90-(90)-90 targets.
- ✦ The Global Plan’s standard investment scenario calls for countries to take action to meet these targets by 2025, preventing 38 million people from getting ill with TB and saving 8.4 million lives.
- ✦ The Global Plan’s accelerated investment scenario calls for meeting these targets earlier by 2020, preventing 45 million people from getting ill with TB and saving 9.5 million lives. In either scenario, achieving the 90-(90)-90 targets would generate massive economic and social benefits for TB-affected countries.
- ✦ Given the tremendous gains to be had by reaching the 90-(90)-90 targets earlier, it is imperative that all countries reach these targets as early as possible.
- ✦ A differentiated approach with investment packages tailored to the needs of different settings is important to ensure scale up and to maximize impact.

The Global Plan has modelled the impact of achieving the 90-(90)-90 targets to demonstrate the effects of an accelerated global response to the TB epidemic.

Projections are made by applying the TB Impact Model and Estimates (TIME) model¹ to nine countries, one from each of the settings identified in Chapter 1, and then extrapolating the results to produce global estimates. Further information on the methodology is available in Annex 2.²

scriptive, but rather shows how an ambitious scale-up of existing interventions can enable countries to achieve the Global Plan targets and End TB Strategy milestones.

The impact modelling is not designed to be pre-

¹ The TIME modelling framework has been developed by The London School of Hygiene and Tropical Medicine and Avenir Health.. It estimates current trends in key epidemiological indicators using cubic-splines (penalized B-splines in particular) – a technique widely used for projecting trends forward in time. The model’s application to TB estimates is described in Pretorius C, Glaziou P, Dodd P, et al. Using the TIME model in Spectrum to estimate TB/HIV incidence and mortality. AIDS. 2014;28(4):S477–87.

² www.stoptb.org/global/plan/plan2/annexes.asp



The global impact of reaching the 90-(90)-90 targets

The Global Plan focuses on two investment scenarios: a standard scenario and an accelerated scenario.

The standard investment scenario aims to achieve the 90-(90)-90 targets globally by 2025. This scenario would hit the End TB milestone for a 20% decline in TB incidence by 2020. When compared to current efforts, it would avert an additional 4 million TB cases and save an additional 830 000 lives. Compared to a counterfactual scenario of no TB-related care, the Global Plan standard investment scenario would save 8.4 million lives and prevent 38 million people from getting ill with TB..

The accelerated investment scenario aims to achieve the 90-(90)-90 targets globally by 2020. In this scenario, the projected impact would reach – and exceed – the End TB Strategy milestones. This would prevent an additional 7 million people getting ill with TB and will save an additional 1.1 million lives beyond the standard investment

scenario. The total impact of the accelerated investment scenario when compared to no TB-related care is 45 million people prevented from getting ill with TB and 9.5 million deaths averted.

The accelerated scenario takes into consideration the fact that high TB-burden countries have national strategic plans that aim to achieve universal access with 90% coverage levels by 2020. It is also inspired by the 2014 BRICS goal of reaching 90% coverage levels by 2020.

As shown in Fig. 2.1 and 2.2, implementing the standard investment scenario would achieve the End TB Strategy milestones of 20% incidence reduction and 35% mortality reduction by 2020.

FIGURE 2.1. GLOBAL TB INCIDENCE

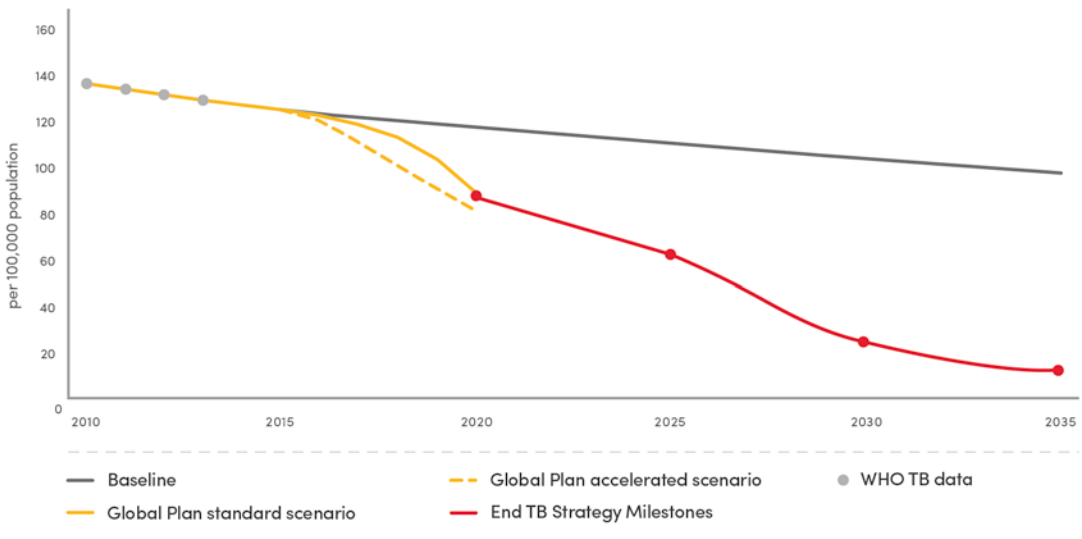
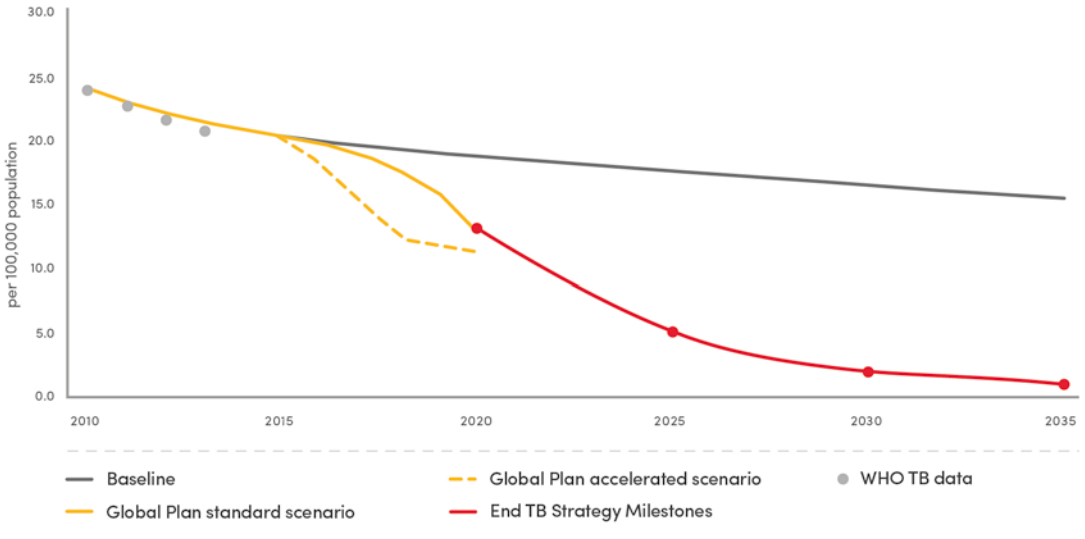


FIGURE 2.2. GLOBAL TB MORTALITY



Given the tremendous gains to be had by reaching the 90–(90)–90 targets by 2020, the Global Plan urges all countries to strive to implement the accelerated investment plan.

Impact modelling at the country level

Detailed impact modelling has been carried out for nine countries, which together account for over half of all TB deaths worldwide. Although these countries are not explicitly named in the Global Plan, each of them represents a typical set of characteristics for a particular country setting.

As shown in Fig. 2.3–2.11, the impact of achieving the 90–(90)–90 targets is significant for all countries.

The graphs show the decrease in incidence and mortality that can be achieved through the Global Plan’s standard and accelerated investment plans, as well as the combined impact

of the Global Plan’s standard investment plan together with the UNAIDS plan for 90–90–90 treatment scale-up (in green).

For each of the country settings, the Global Plan outlines a package of investments that could be implemented in order to reach the 90–(90)–90 targets (see Annex 3¹). A summary of current national plans for the different country settings is provided in Annex 4.¹

¹ www.stoptb.org/global/plan/plan2/annexes.asp



Setting 1:

Eastern European and central Asian settings that have a high proportion of drug-resistant TB and a hospital-based care delivery system

FIGURE 2.3a. SETTING1-TB INCIDENCE

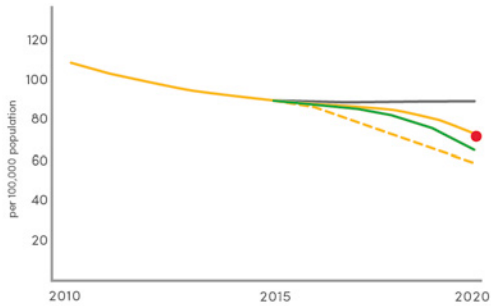
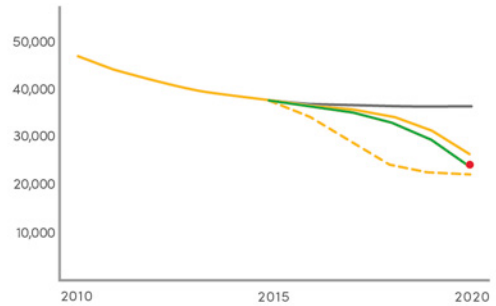


FIGURE 2.3b. SETTING1-TB MORTALITY



- Global Plan accelerated scenario Global Plan standard scenario • End TB Strategy Milestone
- Baseline Standard scenario & UNAIDS Plan

How can countries in Setting 1 achieve the targets?

The epidemic in these countries involves a very high proportion of drug-resistant TB. Traditionally, centralized TB care is delivered through specialized TB hospitals, relying heavily on in-patient care. This model is expensive and does not ensure the best outcomes for people with TB. Furthermore, key populations, such as prisoners, people who use drugs, and migrants, are the most vulnerable in this setting and often face barriers to accessing TB care.

THE INVESTMENT PACKAGE FOR SETTING 1 FOCUSES ON:

- 1** Reforming and decentralizing the health system
- 2** Using rapid molecular diagnostics to ensure early diagnosis of TB and drug-resistant TB
- 3** Improving treatment adherence and outcomes
- 4** Improving access to care for prisoners, migrants, and people who use drugs
- 5** Screening of contacts and social protection measures.

The health system reform and decentralization process is expected to promote patient-centred models of care, including ambulatory treatment, and substantially reduce the cost of treatment. This will free up resources to prioritize early diag-

nosis and better treatment. Social protection measures, including nutritional support, could further improve treatment outcomes. Peripheral health and community systems will require attention as critical functions are decentralized.



Setting 2:

Southern and central African settings where HIV and mining are key drivers of the epidemic

FIGURE 2.4a. SETTING2-TB INCIDENCE

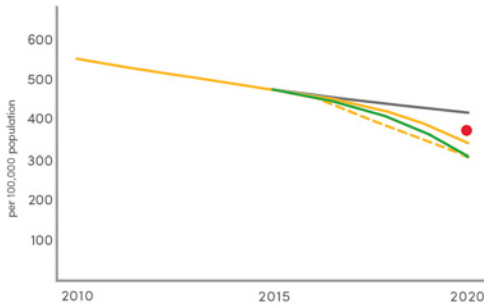
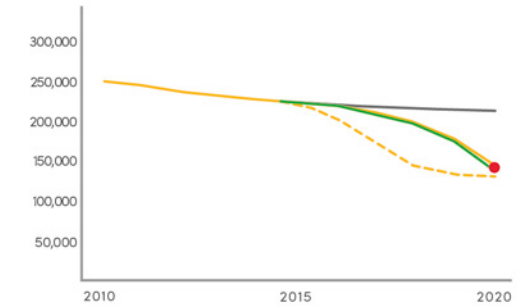


FIGURE 2.4b. SETTING2-TB MORTALITY



--- Global Plan accelerated scenario

--- Global Plan standard scenario

• End TB Strategy Milestone

--- Baseline

--- Standard scenario & UNAIDS Plan

How can countries in Setting 2 achieve the targets?

The TB epidemic in these countries is fueled by the HIV epidemic, with 50–80% of people with TB also living with HIV. The mining industry also poses significant challenges. Mining-related silicosis is a risk factor for TB, and labour migration across international borders complicates the provision of proper TB treatment and care. There is already strong political commitment at the highest level of the Southern African Development Community (SADC) countries to address mining-related TB. Meanwhile, multilateral agencies have started to commit additional resources to a regional response in order to supplement individual country efforts.

THE INVESTMENT PACKAGE FOR SETTING 2 FOCUSES ON:

- 1 Providing screening among people living with HIV/AIDS and mining communities
- 2 Implementing interventions in the mining sector to reduce dust and address silicosis
- 3 Increasing access to care for prisoners, children and other key populations
- 4 Scaling up rapid molecular tests for universal access
- 5 Strengthening the laboratory network and specimen shipment system
- 6 Improving treatment outcomes
- 7 Providing ART for all HIV-positive people with TB and preventive therapy for all HIV-positive people who do not have active TB disease
- 8 Strengthening the health and community systems
- 9 Establishing uniform treatment regimens and electronic patient information systems across countries in the region.



Setting 3: African settings with moderate to high HIV where mining is not a significant issue

FIGURE 2.5a. SETTING3-TB INCIDENCE

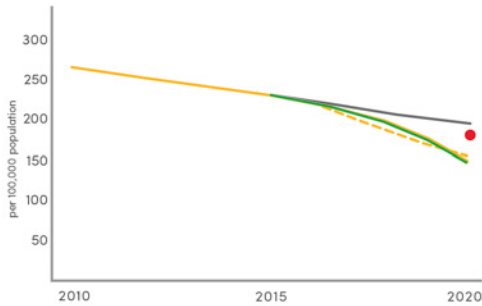
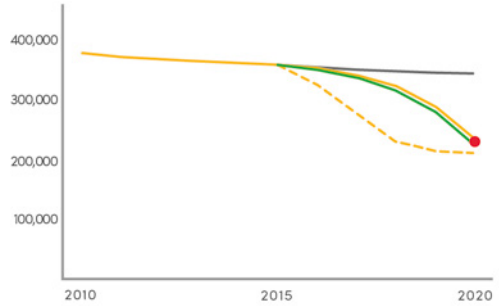


FIGURE 2.5b. SETTING3-TB MORTALITY



- Global Plan accelerated scenario Global Plan standard scenario • End TB Strategy Milestone
- Baseline Standard scenario & UNAIDS Plan

How can countries in Setting 3 achieve the targets?

While, similar to Setting 2, HIV fuels the TB epidemic in these countries, mining activities have a comparatively smaller impact on the TB situation.

THE INVESTMENT PACKAGE FOR SETTING 3 FOCUSES ON:

- 1** Providing integrated care delivery for TB and HIV
- 2** Scaling up intensified TB case finding among people living with HIV/AIDS using rapid molecular diagnostics
- 3** Scaling up capacity for DST, ART, and preventive therapy coverage
- 4** Supporting community systems for TB and HIV care
- 5** Improving access to care for key populations in remote areas
- 6** Establishing specimen transportation systems and innovative care delivery models to reach underserved groups.



Setting 4: Settings with severely under-resourced health systems or country settings with challenging operating environments (COE)

FIGURE 2.6a. SETTING4-TB INCIDENCE

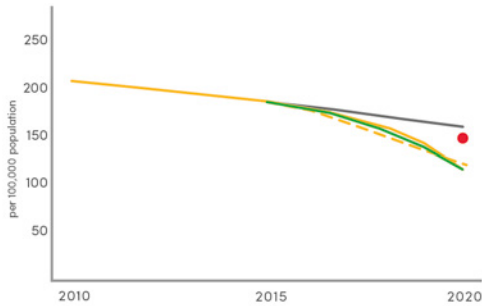
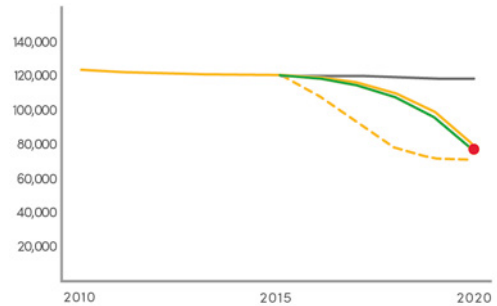


FIGURE 2.6b. SETTING4-TB MORTALITY



- Global Plan accelerated scenario
- Global Plan standard scenario
- Baseline
- Standard scenario & UNAIDS Plan
- End TB Strategy Milestone

How can countries in Setting 4 achieve the targets?

These countries face ongoing conflicts that have severely weakened the health care system and pose significant security-related barriers to the provision of TB care. While it may not be feasible to expect rapid scale up in these countries over the next few years, it is possible to make an impact with targeted actions.

THE INVESTMENT PACKAGE FOR SETTING 4 FOCUSES ON:

- 1 Strengthening existing care delivery pathways
- 2 Improving access to refugees, internally displaced populations, and people in detention
- 3 Providing innovative and flexible care delivery models to reach population groups without access to the health system.



Setting 5:

Settings with a high to moderate burden of TB with a large proportion in private sector care

FIGURE 2.7a. SETTING5-TB INCIDENCE

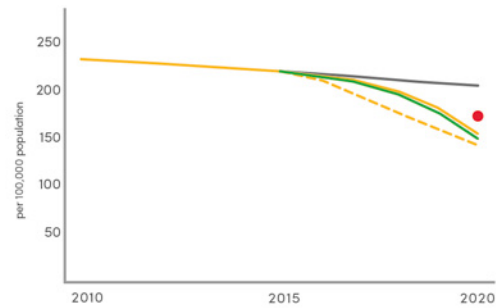
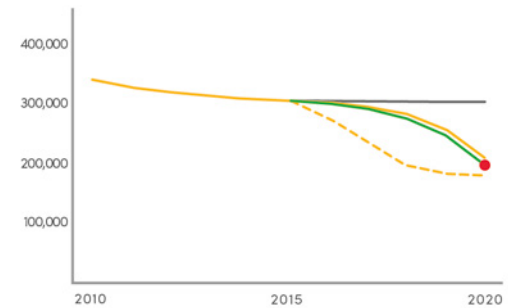


FIGURE 2.7b. SETTING5-TB MORTALITY



- Global Plan accelerated scenario
- Global Plan standard scenario
- Baseline
- Standard scenario & UNAIDS Plan
- End TB Strategy Milestone

How can countries in Setting 5 achieve the targets?

These are primarily high TB-burden countries in Asia where people with TB tend to be seen by private providers. These countries also have public hospitals that in most situations are not linked to the national TB programme or notification system. As a result, many people seeking care are diagnosed and treated in the private health care system where it is difficult to assess the quality of care. Some people end up in the public health system where they encounter limited treatment options (e.g. no opportunity to treat based on early detection) and substantial out-of-pocket expenses.

THE INVESTMENT PACKAGE FOR SETTING 5 FOCUSES ON:

- 1** Addressing the private health system and hospitals, including mapping of care providers; improving the quality of care in the private health sector; implementing business models that aim to improve quality of care, notification, and public health responsibilities; and addressing out-of-pocket expenses through insurance, vouchers or cash transfers
- 2** Scaling up laboratory capacity, particularly for rapid molecular tests, X-rays and DST, which will facilitate private health system engagement
- 3** Improving access for the urban poor as well as other key populations that have a high burden of TB and face barriers to accessing care
- 4** Scaling up health insurance under universal health coverage in order to facilitate the provision of universal TB care and eliminate catastrophic costs for people with TB.



While referrals from private sector to public sector are working to some extent, greater progress can be made by establishing business models that improve private health sector care, develop user-friendly systems for universal TB notification, and address out-of-pocket expenses.

Setting 6: Middle-income country settings with a moderate TB-burden

FIGURE 2.8a. SETTING6-TB INCIDENCE

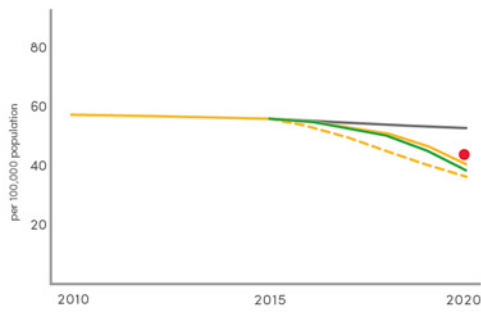
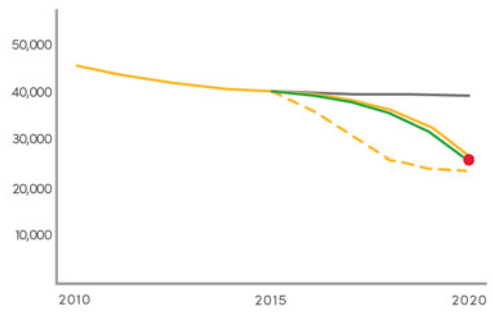


FIGURE 2.8b. SETTING6-TB MORTALITY



- Global Plan accelerated scenario
- Global Plan standard scenario
- Baseline
- Standard scenario & UNAIDS Plan
- End TB Strategy Milestone

How can countries in Setting 6 achieve the targets?

These predominantly Asian and Latin American countries have moderate levels of TB and the resources to address most of the investment needs for scale-up. Although these countries have social support schemes focused on poor and marginalized groups, these key populations continue to face barriers to health care access, which can lead to delayed diagnosis and result in catastrophic expenses for individuals and families. These countries usually have social schemes focused on the poor and marginalized groups that need to be tapped into.

THE INVESTMENT PACKAGE FOR SETTING 6 FOCUSES ON:

- 1** Rapid scale up of TB diagnosis and treatment in order to achieve universal access
- 2** Focusing on key population groups, including targeted outreach to detect TB early and provide effective treatment
- 3** Investing in social supports and coordination with the social sector in order to connect people with TB and their families to social protection schemes.



Setting 7: India setting

FIGURE 2.9a. SETTING7-TB INCIDENCE

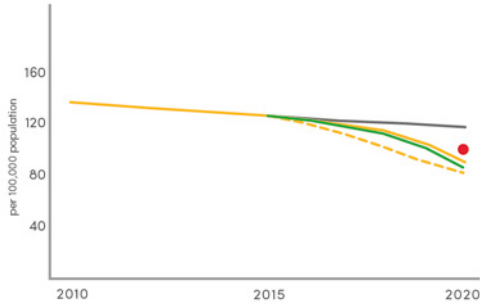
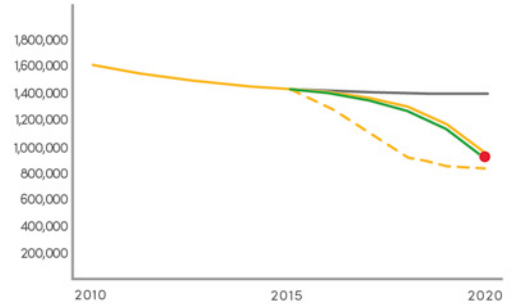


FIGURE 2.9b. SETTING7-TB MORTALITY



- Global Plan accelerated scenario
- Global Plan standard scenario
- Baseline
- Standard scenario & UNAIDS Plan
- End TB Strategy Milestone

How can India achieve the targets?

As India is home to one in four people living with TB and has the largest TB control programme in the world, the country must be considered as a separate setting. To a great extent, the progress made in India will determine global progress. The private sector is usually the first point of contact for people seeking health care. However, patients frequently change between public and private sector. Accordingly, India needs to further invest in the public health infrastructure and improve the quality of services across public and private sectors for the greater public good.

Several groundbreaking innovations and research studies conducted in India have shaped the global response to TB. However, given its strong economic growth, the country should consider investing more resources in its public health sector. According to World Bank data, in 2013 India spent 1.3% of its GDP on the public health sector; by contrast, Brazil spent 4.7%, China 3.1%, and South Africa 4.3%.¹

TB's impact varies greatly within the country, severely and disproportionately impacting the urban poor and certain population groups, such

as indigenous/tribal peoples. This demands a differentiated approach across states, urban and rural hot spots, and key populations.

Even though the country has achieved the MDGs, the rate of decline of incidence remains very low, and the country is unlikely to make strides towards TB elimination unless there is a significant increase in the investment package for TB care.

¹ World Development Index online database. Washington, DC: The World Bank; 2013 (<http://data.worldbank.org/indicator/SH.XPD.PUBL.ZS>).



THE INVESTMENT PACKAGE FOR SETTING 7 FOCUSES ON:

- 1** Increasing domestic funding for TB
- 2** Taking advantage of modern technology for improving public-sector-funded programmes.
- 3** Reforming and modernizing TB care in the public sector
- 4** Improving the quality of care in the private sector
- 5** Scaling up special models of care for the poor residing in large cities
- 6** Increasing access to care for remote and tribal populations
- 7** Reaching PLHA, indigenous/tribal peoples and other vulnerable groups
- 8** Strengthening existing community systems to improve access and implement screening campaigns
- 9** Scaling up rapid molecular tests and DST towards universal access
- 10** Improving the use of X-ray as a screening tool
- 11** Establishing electronic web-based, mobile-based, and call-centre-based models for notification, and incorporating information technology in key programme functions
- 12** Eliminating catastrophic costs for people by using cash transfers, insurance and social protection
- 13** Addressing risk factors, such as HIV, malnutrition, smoking and diabetes.

Setting 8: China setting

FIGURE 2.10a. SETTING8-TB INCIDENCE

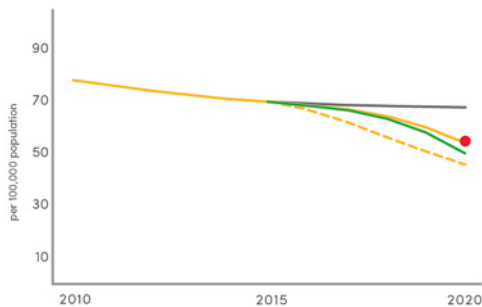


FIGURE 2.10b. SETTING8-TB MORTALITY



- Global Plan accelerated scenario
- Global Plan standard scenario
- End TB Strategy Milestone
- Baseline
- Standard scenario & UNAIDS Plan



How can China achieve the targets?

As a high TB-burden country with the domestic resources and capacity to address the epidemic, China must also be considered separately. Nearly all TB funding in China is domestic. The country has conducted several prevalence surveys that demonstrate declining levels of TB. This decline has been mainly attributed to high levels of case detection and treatment success, as well as rapid socioeconomic development. Linking hospitals to the public health system via electronic notification systems, coupled with good governance, has massively increased the proportion of TB that is notified.

In short, while China appears to have high levels of health coverage, diagnosis and quality care is sometimes out of reach for the poor and other marginalized populations due to user fees and other costs for accessing care.

THE INVESTMENT PACKAGE FOR SETTING 8 FOCUSES ON:

- 1** Further improving TB case detection and treatment success to rapidly reach universal coverage
- 2** Ensuring faster scale up of care for drug-resistant TB
- 3** Rapidly scaling up automated molecular tests
- 4** Ensuring inclusive socioeconomic development.

Setting 9:

Low-burden settings and country settings on the verge of eliminating TB

FIGURE 2.11a. SETTING9-TB INCIDENCE

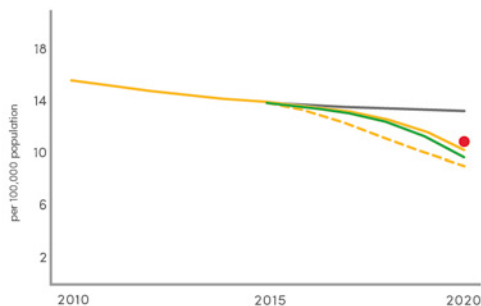
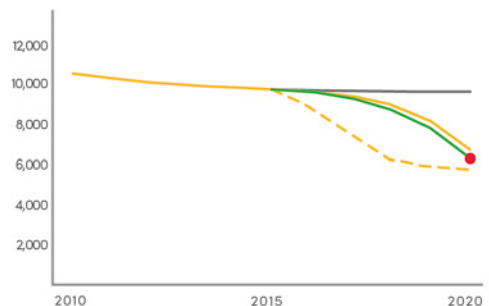


FIGURE 2.11b. SETTING9-TB MORTALITY



- Global Plan accelerated scenario
- Global Plan standard scenario
- Standard scenario & UNAIDS Plan
- Baseline
- End TB Strategy Milestone



How can countries in Setting 9 achieve the targets?

These are low-burden, high-income countries that have already reached or are close to reaching an incidence of 10 per 100 000 population – the goal of the End TB Strategy. In these countries, TB is concentrated among the most vulnerable populations, such as migrants, the poor and other marginalized groups. The unit cost of managing TB in these countries is high, but they have the capacity to adequately fund TB care.

THE INVESTMENT PACKAGE FOR SETTING 9 FOCUSES ON:

- 1 Targeting hot spots – places where there are high concentrations of TB
- 2 Establishing screening programmes for key populations
- 3 Providing treatment for latent TB infection.

From impact modelling to country plans

The Global Plan aims to inspire countries to develop and scale up their own set of interventions to achieve the 90-(90)-90 targets and End TB milestones.

Countries are therefore encouraged to update or develop their national strategic plans using the impact models and technical support available from domestic and international sources. As part of this planning, it is recommended that, in addition to plans at national level, countries differentiate plans to address targeted populations and hot spots, especially in large countries.

As the modelling in the Plan demonstrates, **early investment will lead to faster achievement of the 90-(90)-90 targets, resulting in more lives saved and cost savings in the long term (see Chapter 7 on return on investments). Therefore, countries that have the requisite capacity are encouraged to front-load their investments in order to reach the 90-(90)-90 targets by 2020.**

Limitations of the modelling

While the impact modelling used for the Global Plan shows the epidemiological impact of improving TB case detection and treatment outcomes, it does not model the impact of specific interventions. Furthermore, the modelling methodology is focused on the impact during the Global Plan period and therefore has limited capacity to project longer term impact.

The Plan recommends that the global TB community invest in data collection and suitable modelling methods so that the areas not covered by the Plan can be explored as countries develop their strategies.

Locally collected data, for example, on the size and TB prevalence of local key populations will enable country-specific modelling on the



priority interventions needed to improve case detection and treatment outcomes to reach the 90–(90)–90 targets. This will assist countries in choosing high-impact interventions with optimized resource allocation. Large countries are also encouraged to undertake sub-national quantitative analyses to identify the different interventions that need to be scaled up in different parts of the country and among specific subpopulations – both for impact as well as for equity.

Operational research

Operational research and data collection play an essential role in the effective implementation of new and existing tools, adapting international guidelines into practical country-level policies, and monitoring progress against targets. Operational research is also needed to fine-tune the ways in which tools and interventions are used in different settings and among different population groups.

Partners in the fight against TB should strive for continuous improvement in the tools used to fight TB. Constraints and barriers to effective implementation need to be converted into research questions that can be answered through operational research. Given the need for rapid progress, it is important that operational research be carried out swiftly in a way that does not hinder scale-up or policy changes.

Operational research does not usually need substantial resources compared to other types of research (e.g. for new tools), but its results are important because they create the evidence base for policy improvements and the optimal allocation of resources. While specific quantitative and qualitative research is required in TB, the Global Plan strongly encourages countries and partners to consider opportunities for integrated research along with other disease programmes, and within the context of wider health systems and institutional research on health and

other social determinants. Countries are encouraged to invest in relevant operational research, build staff capacity, and actively partner with in-country academic and research institutions. South–South collaboration between high-burden countries also has great potential for such research, an example being the BRICS initiative on research. The cost of operational research is addressed in Chapter 7.





3. REACHING KEY POPULATIONS



KEY MESSAGES

- ✦ Reaching key populations will be essential for ending TB. Beyond epidemiology, it is imperative from an equity and human rights perspective that we strive to protect people in key populations, provide them with care, and involve them as key stakeholders in the fight against the disease.
 - ✦ The Global Plan defines “key populations” as people who are vulnerable, underserved or at-risk of TB infection and illness.
 - ✦ Key populations vary by country and include people with increased exposure to TB due to where they live or work, people with limited access to quality TB services, and people at greater risk due to biological or behavioural factors.
 - ✦ The Global Plan recommends that countries set an operational target of reaching at least 90% of people in key populations—through improved access to services, systematic screening where required, and new case-finding methods – and providing all people in need with effective and affordable treatment.
 - ✦ Countries are encouraged to identify key populations at the national and subnational level according to estimates of the risks faced, population size, particular barriers to accessing TB care, and gender-related challenges. Countries are also encouraged to report on progress in TB with data that are disaggregated by key population.
 - ✦ Reaching key populations will require increased support for patients, active partnership with key populations in the delivery of services, and the provision of TB care in safe environments.
-

Whether someone gets infected and becomes ill with TB depends on a variety of factors, including living and housing conditions; contact with someone who has TB; income; nutrition; and pre-existing health conditions. Furthermore, the development and progression of TB is closely linked to several other risk factors; diseases such as diabetes and HIV increase the risk of people becoming ill with TB. There are similar associations with silica dust, indoor smoke,

tobacco and alcohol use, and, perhaps the most widespread risk factor, malnutrition or undernutrition.

Many individuals are vulnerable due to where they live and what they do for a living. They

may also be vulnerable due to the stigmatization, discrimination, and criminalization of certain groups of people, for example, people living with HIV, people who are lesbian, gay, bisexual, or transgender, or people who inject drugs.



Together, people who are vulnerable, underserved or at-risk are referred to in the Global Plan as “key populations”.

Countries are encouraged to report on progress in TB with data that are disaggregated by key population. Technical partners are encouraged to provide countries with frameworks for prioritization, action and monitoring progress in improving access to TB services for key population groups.

In a number of countries, reaching key populations will be essential for ending TB. However, the importance of reaching these groups goes beyond epidemiological reasons; it is an equity and human rights imperative.

It is unacceptable that nearly half of the world’s 7 billion people are still unable to afford or access quality health care, live in unhealthy environments, or are malnourished. We have a collective responsibility to protect these people from TB, to provide them with a cure, and to involve them as key stakeholders in the fight against the disease.

Reaching key populations will require better access to services, extended support for patients,

quality information, and the provision of TB care in safe environments that are free from stigma and discrimination. The key population groups themselves can provide many of these services. For this to happen, the right policy and legislative frameworks must be in place, backed by adequate funding.

The Global Plan recommends that countries set a separate operational target of reaching at least 90% of those they would define as key populations – through improving access to services, systematic screening¹ where required, and active, new, and innovative case-finding methods – and providing all people who require it with effective and affordable treatment.

Examples of successful interventions that have been implemented to reach key populations can be found in a compendium of case studies from the Stop TB Partnership’s TB Reach programme.²

1 For guidance, see WHO’s guidelines on systematic screening for active tuberculosis at: <http://www.who.int/tb/tbscreening/en/>

2 Stop TB Partnership. Improving tuberculosis case detection: A compendium of TB REACH case studies, lessons learnt and a monitoring and evaluation framework; 2014.

Key population groups

For the purpose of the Global Plan, three key population groups are further expanded in Table 3.1 below, along with examples of populations within these groups. This is not an exhaustive list and does not represent a prioritization of these populations at the global level. To prevent stigma and discrimination it is important that key populations be described as such without reference to their behaviour or characteristics. It is important to note that people who are likely to fall into one of these categories are also likely to be part of one or both of the other groups. A miner, for example, may live in a community with little access to health care and may be living with HIV. He may also smoke and/or have diabetes. He may also pass TB to his children.

Gender disparities in TB present huge challenges in providing access to services. Globally, more men than women have TB. In addition, men are likely to be over-represented in some of the key populations due to a variety of cul-

tural, religious, and economic factors. Improving access to services for both men and women in some contexts demands a gender-sensitive approach.

TABLE 3.1. KEY POPULATIONS FOR TB



<p>People who have INCREASED EXPOSURE to TB due to where they live or work</p>	<p>Prisoners, sex workers, miners, hospital visitors, health care workers and community health workers</p> <p>PEOPLE WHO:</p> <ul style="list-style-type: none"> ✦ live in urban slums ✦ live in poorly ventilated or dusty conditions ✦ are contacts of TB patients, including children ✦ work in environments that are overcrowded ✦ work in hospitals or are health care professionals
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<p>People who have LIMITED ACCESS TO QUALITY TB SERVICES</p>	<p>Migrant workers, women in settings with gender disparity, children, refugees or internally displaced people, illegal miners, and undocumented migrants</p> <p>PEOPLE WHO:</p> <ul style="list-style-type: none"> ✦ are from tribal populations or indigenous groups ✦ are homeless ✦ live in hard-to-reach areas ✦ live in homes for the elderly ✦ have mental or physical disabilities ✦ face legal barriers to access care ✦ are lesbian, gay, bisexual or transgender
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<p>People at INCREASED RISK of TB because of biological or behavioural factors that compromise immune function</p>	<p>PEOPLE WHO:</p> <ul style="list-style-type: none"> ✦ live with HIV ✦ have diabetes or silicosis ✦ undergo immunosuppressive therapy ✦ are undernourished ✦ use tobacco ✦ suffer from alcohol-use disorders ✦ inject drugs
--	---

Increased exposure to TB due to where people live or work

Children

An estimated 74 000 children die from TB each year and account for around half a million new cases annually. The actual burden among children is likely higher, given the challenges of diagnosing childhood TB. Children with TB often come from families that are poor, lack knowledge about the disease, and live in communities with limited access to health services.



Children from impoverished communities also face a much higher risk of malnutrition and wasting, both in utero when their mothers are malnourished and after birth.¹ Infants and children under 5 years of age are the most challenging to diagnose and are the most likely to die from TB.

Childhood TB must be a cross-cutting national health priority and not the sole responsibility of national TB programmes. It should be addressed in collaboration with child health services, as care for sick children is primarily sought through pediatric services, and should be part of overall efforts to scale up maternal and child health services. Health care workers and pediatricians in both public and private sectors should report all children diagnosed with TB to national TB programmes. In turn, national TB control programmes must report treatment

outcomes for these children.

Tackling TB in children will require a focus on mothers, too. Women living with HIV – who are more likely to have TB – need assistance and care from the health system in order to reduce the possibility of passing infections to their children.² Thus, TB should be integrated at the primary-care level in maternal and child health programmes through antenatal and postnatal clinics.

The Roadmap for Childhood TB (see Fig. 3.1) sets up the goal of reaching zero TB deaths among children worldwide. It describes key actions and an urgent need for enhanced investments in order to ensure that the goal is met.³

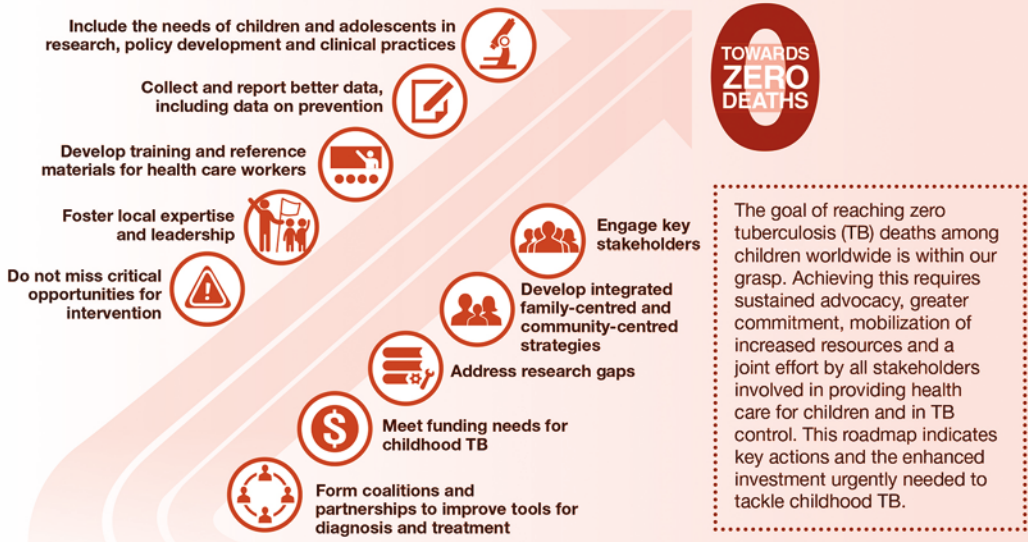
1 Odone A, Houben RMG, White RG, Lonnroth K. The effect of diabetes and undernutrition trends on reaching 2035 global tuberculosis targets. *Lancet Diabetes Endocrinol.* 2014;2:754–64.

2 Gupta, A, Bhosale, R, Kinikar, A, et al. Maternal tuberculosis: a risk factor for mother-to-child transmission of human immunodeficiency virus. *J Infect Dis.* 2011;203:358–63.

3 A roadmap for childhood tuberculosis: towards zero deaths. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/89506/1/9789241506137_eng.pdf).

FIGURE 3.1. ROADMAP FOR CHILDHOOD TUBERCULOSIS

ROADMAP FOR CHILDHOOD TUBERCULOSIS





HEALTH WORKERS

TB remains a significant occupational risk for health workers in low-income and lower middle-income countries, and in some institutions in high-income countries. The risk is particularly high in situations where there is increased exposure to TB and inadequate infection control measures.⁴

Health care workers are at risk of acquiring TB from patients that they care for (in the case of nurses and physicians) or from exposure to infected specimens (in the case of laboratory workers). The risk is not limited to health care workers and visitors in hospitals. Health care workers in primary health care facilities and community health workers also have an increased risk of getting TB.⁵

Health care workers who are in contact with people having TB or clinical material need to be offered TB testing and, if necessary, preventive therapy. Appropriate infection control methods need to be more widely applied in low-resource settings.

Miners

In countries in southern Africa, mining, along with HIV, is a major driver of TB. Leading risk factors include high prevalence of silicosis (a severe pulmonary disease caused by exposure to silica dust), high temperatures and humidity in mine shafts, crowded working and living conditions, high rates of HIV infection, and tobacco and alcohol use.⁶ Furthermore, miners in southern and central Africa are often migratory, which complicates access to health care. Migration

also spreads TB to miners' home communities in other parts of the country or across national borders.

Comprehensive TB strategies must explicitly address the role of mining activities in the epidemic.⁷ South Africa has taken the lead by introducing mandatory TB screening for miners. Fifteen southern African countries have recently pledged to improve treatment and care for current and former miners with TB and their families.⁸ Other methods to tackle TB among miners⁹ should include reducing silica dust, providing better housing, improving cross-border care, tracing contacts, and screening for HIV.

Prisoners

The conditions in many prisons fuel the spread of TB. In sub-Saharan Africa, for example, some prisons have rates of TB that are up to 1000 times higher than that of the general population.¹⁰ In Brazil, a population-based study showed that over half of TB strains circulating in the population could be traced back to prisons.¹¹ Prisons are also a breeding ground for drug-resistant TB, as incoming and outgoing prisoners are unlikely to complete a full treatment course.

Addressing TB in prisons will require significant collaboration among the health and judicial sectors and the research community for mapping the scale of drug resistance within prisons and devising innovative ways to prevent transmission.

4 Menzies, D, Joshi, R, Pai, M. Risk of tuberculosis infection and disease associated with work in health care settings. *The International Journal of Tuberculosis and Lung Disease*. 2007;11(6):593–605(13).

5 Claassens MM, van Schalkwyk C, du Toit E, et al. Tuberculosis in health care workers and infection control measures at primary health care facilities in South Africa. *Pai M, ed. PLoS ONE*. 2013;8(10):e76272. doi:10.1371/journal.pone.0076272.

6 Stuckler D, Steele S, Lurie M, Basu S. Dying for gold: the effects of mineral mining on HIV, tuberculosis, silicosis, and occupational diseases in southern Africa. *Int J Health Serv*. 2013;43:639–49.

7 Stuckler D, Basu S, McKee M, Lurie M. Mining and risk of tuberculosis in sub-Saharan Africa. *Am J Public Health*. 2011;101(3):524–30.

8 Baleta A. Southern African declaration targets TB in mining sector. *Lancet*. 2012;380(9849):1217–8.

9 Fitzpatrick S, Jakens F, Kuehne J, Mabote L. Tuberculosis in South Africa's gold mines: a united call to action (<http://results.org.uk/sites/default/files/TB%20in%20South%20Africa's%20Mines%20-%20A%20call%20to%20action.pdf>).

10 Biadlegne F, Rodloff AC, Sack U. Review of the prevalence and drug resistance of tuberculosis in prisons: a hidden epidemic. *Epidemiol Infect*. 2015;143:887–900.

11 Sacchi FP, Praca RM, Tatar MB. Prisons as reservoir for community transmission of tuberculosis, Brazil. *Emerg Infect Dis*. 2015;21:452–5.



Linking the health care provided inside and outside prisons will be vital to ensuring continuous TB care.

People affected by zoonotic TB

Zoonotic TB in humans, caused by *Mycobacterium bovis* (the causal agent of bovine TB), is mostly acquired from domestic animals and their products. The general public that consumes unpasteurized milk or untreated animal products from infected animals, people living in rural communities in which bovine TB is endemic, cattle herders, dairy workers, and workers that come in contact with infected animals or animal products are all at a higher risk of contracting zoonotic TB.

The scale of zoonotic TB cases is unknown (due to the lack of adequate diagnostic tests for *M. bovis*) and its measurement complicated by a

lack of routine surveillance. This is especially concerning in developing regions in which bovine TB is endemic and sociocultural practices increase the risk of transmission of *M. bovis* to humans.

Zoonotic TB deserves further attention,^{1,2} and is included in the Global Plan. However, the issue goes beyond the need to reach key affected populations. Efforts to prevent and control zoonotic TB must be cross-sectoral and multidisciplinary, including both human health and veterinary sectors in controlling the disease in its animal reservoir, developing diagnostic tools for diagnosing *M. bovis*, strengthening surveillance systems and data quality, and assessing economic impact.

1 Muller B, Dürr S, Alonso S., et al. Zoonotic *Mycobacterium bovis*-induced tuberculosis in humans. *Emerging Infect Dis.* 2013;19:899–908. doi:10.3201/eid1906.120543.

2 Cosivi O, Grange JM, Daborn CJ, et al. Zoonotic tuberculosis due to *Mycobacterium bovis* in developing countries. *Emerging Infect Dis.* 1998;4:59–70.

Limited access to quality TB services

Migrants

An increasing proportion of the world's population – about 1 billion people – is now comprised of migrants. As a group, migrants are particularly vulnerable to TB.³ As with miners, workers who have migrated nationally or internationally often live and work in overcrowded and poorly ventilated environments; are malnourished or use drugs; and are at increased risk of HIV infection and becoming ill with TB. These populations often have poor access to health services, possibly because they are living in an area illegally, because of differences in language or ethnicity and/or because of a lack of awareness of entitlement to services. Undocumented migrants face particular difficulties in accessing care.

Even when migrants can access treatment, the need to move for employment or the threat of forced displacement (either because of illegal immigrant status or political conflict) often results in disrupted TB treatment.

Especially in these settings, health service provision must be sensitive and operate from a human-rights perspective, allowing people to access TB diagnosis and treatment regardless of immigration status.⁴ Similarly, immigration or

3 Tuberculosis prevention and care for migrants. Geneva: World Health Organization, International Organization for Migration; 2014.

4 Plan to Stop TB in 18 high-priority countries in the WHO European Region, 2007–2015. Geneva: World Health Organization; 2007.



labour policies should ensure that a person is not excluded from consideration for recruitment or retention based on his or her TB status.

Health care workers must also be sensitized to the needs of migrants, especially the potential for TB and HIV coinfection and drug-resistant TB. Continuity of care is particularly important in migrant populations, and the development of cross-border referral systems with contact tracing and information sharing will be important to harmonize treatment protocols across borders along migration corridors. This will require not only collaboration between health actors, but also collaboration between government ministries on migration policy.

People who inject drugs

Drug use has been linked to a higher incidence of both latent TB and active TB disease.⁵ The increased risk of infection is due in part to the physiological effects of drug use, especially opiates, in terms of compromised immunity. In addition, people who use drugs are at risk for a variety of environmental and behavioural factors that tend to coexist with drug use, such as homelessness, tobacco and alcohol use, imprisonment, and risk of HIV and hepatitis C from infected needles.⁶

The effects of drug use can also mean that people do not access health services at critical junctures, such as for TB diagnosis and treatment immediately after HIV diagnosis. Even when people who use drugs do have access to TB care, they may have difficulty complying with a complicated or lengthy TB drug regimen. Moreover, opiates may suppress telltale TB symptoms such as persistent cough.

Integrating TB treatment with drug addiction

5 Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update. *Clin Infect Dis*. 2009;48:72–82.

6 Grenfell P, Baptista Leite R, Garfein R, et al. Tuberculosis, injecting drug use and integrated HIV–TB care: a review of the literature. *Drug Alcohol Depend*. 2013;129:180–209.

therapy can help reach the most vulnerable, so long as TB treatment continues after drug rehabilitation. Psychosocial support and day hospitals could greatly increase the rate of treatment adherence.⁷ Because close contacts are at higher risk, TB infection can often spread among groups of people using drugs together. Therefore, interventions targeted at these populations must include TB preventive therapy.

The elderly

This population comprises the largest reservoir of TB infection, particularly in developed nations. Those 65 years and older are more vulnerable to TB, partly because immunity diminishes with age. Studies have found a higher frequency of underlying illnesses, more adverse reactions to drugs, and higher mortality in elderly TB patients.⁸

Clinical features may be atypical, and older adults with pulmonary TB are more likely to have non-specific symptoms.⁹ Special attention to this population is also needed because treatment outcomes are usually poor in older people with TB. Diagnosis in this population is difficult and frequently overlooked; this treatable disease may unfortunately be recognized only at autopsy.¹⁰

7 Figueroa–Munoz JJ, Ramon–Pardo P. Tuberculosis control in vulnerable groups. *Bull World Health Organ*. 2008;86:733–5.

8 Rajagopalan S. Tuberculosis and aging: a global health problem. *Clinical Infectious Diseases*. 2001;33(7):1034–9.

9 Lee JH, Han DH, Song JW, Chung HS. Diagnostic and therapeutic problems of pulmonary tuberculosis in elderly patients. *J Korean Med Sci*. 2005;20(5):784–9.

10 Rajagopalan S, Yoshikawa TT. Tuberkulose im Alter. *Zeitschrift für Gerontologie und Geriatrie*. 2000;33(5):374–80.

Increased risk due to biological or behavioural factors



HIV and AIDS

TB is the most common cause of death in people with HIV/AIDS.¹ High rates of TB and HIV coinfection are a major challenge to driving down TB incidence in many countries. An estimated 1.1 million people worldwide living with HIV fall ill with TB every year. Among people with latent TB infection, people living with HIV are up to 30 times more likely to develop TB disease.² People living with HIV are often subject to stigma and discrimination, which can prevent them from accessing services.

TB and HIV coinfection is particularly acute in Africa, where 80% of people who have active TB are also living with HIV.³ There is also an urgent need to tackle both diseases in an integrated manner in countries outside of Africa. Data show that eastern Europe is seeing rising rates of both HIV prevalence and drug-resistant TB.

The Global Plan provides an opportunity for greater alignment between efforts to fight both diseases. Taking inspiration from the UNAIDS target of providing treatment to 90% of people who know their HIV-positive status, the Global Plan calls for countries to find at least 90% of all people with TB in the population that require treatment (including those living with HIV) and place them on appropriate therapy (including TB treatment and preventive therapy for people living with HIV).

Reaching these targets will require an accelerated integration of TB and HIV services, as well as strong leadership and political commitment. There also needs to be separate but interconnected approaches to addressing HIV infection in people with TB and to reducing the risk of TB in people living with HIV, in line with the interventions recommended by WHO and UNAIDS for jointly addressing HIV and TB.⁴

Diabetes

By weakening the immune system, diabetes raises the risk of developing TB by two to three times.⁵ The association between these diseases is of great concern, since diabetes rates are rising sharply in many low- and middle-income countries with a high TB burden.

There are a number of ways to jointly tackle TB and diabetes, including improved nutrition and exercise for people with diabetes. Lessons can be learned from the successes and challenges of integrating TB and HIV programmes in different countries.

Furthermore, people diagnosed with diabetes should be considered for systematic screening in high TB-burden settings.⁶ People with TB diagnosed with diabetes could be managed under the TB programme in order to ensure coherent disease management. They could then be referred to diabetes programmes after completing their treatment for TB.⁷ Community health workers whose role is to reach out to TB patients can be trained in blood glucose testing to ensure dual care. Information on TB should also be provided to diabetes treatment centres so that health care workers are able

1 Pawlowski A, Jansson M, Skold M, et al. Tuberculosis and HIV co-infection. *PLoS Pathog.* 2012;8:e1002464.

2 WHO. TB/HIV coinfection (<http://www.who.int/tcdr/diseases-topics/TB-HIV/en/>).

3 Co-infection: new battlegrounds in HIV/AIDS. *Lancet Infect Dis.* 2013;13:559.

4 WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012 (http://www.who.int/tb/publications/2012/tb_hiv_policy_9789241503006/en/).

5 Marais BJ, Lonnroth K, Lawn SD. Tuberculosis comorbidity with communicable and non-communicable diseases: integrating health services and control efforts. *Lancet Infect Dis.* 2013;13:436–48.

6 WHO and International Union Against Tuberculosis and Lung Disease. Collaborative framework for care and control of diabetes; 2011 (http://whqlibdoc.who.int/publications/2011/9789241502252_eng.pdf).

7 Sullivan T, Ben Amor Y. The co-management of tuberculosis and diabetes: challenges and opportunities in the developing world. *PLoS Med.* 2012;9:e1001269. doi:10.1371/journal.pmed.1001269.



to identify when to refer people for TB investigation. Systems set up to ensure procurement and delivery of TB drugs could be used for the provision of insulin, which can be unreliable in low- and middle-income countries.

There are opportunities for the prevention of both diseases, since levels of hyperglycemia associated with pre-diabetes appear to correlate with a higher risk for TB.⁸ In addition, efforts to integrate diabetes and TB care should not remain separate from those to address HIV and TB jointly, but rather all the risk factors for TB should be approached holistically in order to maximize resources.

Tobacco and indoor air pollution

Tobacco smoking (and passive smoking) and indoor air pollution from burning biomass fuels in poorly ventilated kitchens and homes are major risk factors for TB.⁹ According to some estimates, up to 20% of TB cases worldwide are linked to tobacco smoking.¹⁰ This is especially concerning, since smoking and burning fuels indoors are highly prevalent practices in countries where TB is common. These practices increase the risk of not only becoming infected with TB, but also developing active TB disease, experiencing poor treatment outcomes, and relapsing.¹¹

Reducing the number of people who smoke and reducing indoor air pollution are therefore key interventions for ending TB. Despite the fact that tobacco smoking is such a high risk factor for

TB, smoking cessation efforts are not routinely integrated into TB programmes. Advice and support for giving up smoking could form part of TB-related counselling and care on initial diagnosis.

Malnutrition

Malnutrition and TB are strongly linked, with undernutrition reducing immune defenses against TB and encouraging the transition from latent to active disease. TB can lead to the impaired absorption of nutrients and micro-nutrients, which in turn leads to malnutrition and wasting.

Many of the people who are already at high risk for TB infection, such as impoverished people living in crowded, unsanitary housing, are also likely to be undernourished. So strong is the association between undernutrition and TB that people who are overweight have even lower incidence of TB than people of a healthy weight (although obesity of course increases risk factors for diabetes and other metabolic diseases).

Ensuring food security for the general population is an important component of preventing TB. There is also some evidence that tailored nutritional support during TB care can help patients adhere to treatment, especially those with drug-resistant TB.¹² WHO has provided relevant guidance.¹³ To make nutritional support a reality, interdepartmental efforts from other ministries, including those responsible for social welfare, finance, food and agriculture, will be vital.

8 Viswanathan V, Kumpatla S, Aravindalochanan V, et al. Prevalence of diabetes and pre-diabetes and associated risk factors among tuberculosis patients in India. *PLoS One*. 2012;7:e41367.

9 Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLoS Med*. 2007;4:e20.

10 Zellweger J-P, Cattamanchi A, Sotgiu G. Tobacco and tuberculosis: could we improve tuberculosis outcomes by helping patients to stop smoking? *Eur Resp J*. 2015;3:583–5. doi:10.1183/09031936.00221814.

11 Stop TB Partnership. Improving tuberculosis case detection: A compendium of TB REACH case studies, lessons learnt and a monitoring and evaluation framework; 2014.

12 Sinclair D, Abba K, Grobler L, Sudarsanam TD. Nutritional supplements for people being treated for active tuberculosis. *Cochrane Database Syst Rev*. 2011;9(11):CD006086.

13 Guideline: nutritional care and support for patients with tuberculosis. Geneva: World

Health Organization; 2013 (http://apps.who.int/iris/bitstream/handle/10665/94836/1/9789241506410_eng.pdf).



4.

KEY COLLABORATING PARTNERS: CIVIL SOCIETY, COMMUNITIES, AND THE PRIVATE SECTOR



KEY MESSAGES

- ✦ To find and treat all people with TB and achieve the End TB Strategy milestones, countries must abandon the passive, top-down disease programmes of the past. A radical new approach is required – one that engages civil society, community organizations and the private sector as partners at all stages of planning and implementing the response to TB.
 - ✦ Civil society and community-based organizations must play a key role in the planning and provision of TB care by increasing awareness; active case finding; improving access to care; encouraging adherence; providing psychosocial support and reducing stigma; monitoring programmes; and facilitating community engagement in research and development.
 - ✦ Private health care providers and businesses have an important role to play in providing, developing and partnering to deliver quality and affordable TB care, new tools, resources and expertise.
 - ✦ Investments are required to strengthen health and community systems and public–private partnerships. A change in mindset along with an enabling environment is needed in order to meaningfully engage with communities and unlock the full potential of the private sector.
 - ✦ TB is a problem that affects us all. We will not beat the disease unless those currently involved in the fight against TB are prepared to actively encourage new actors to join the fight.
-

Civil society and communities as partners in the response to TB

The current approach to TB detection, diagnosis and treatment is largely based on a strategy to control TB, with national, public TB programmes working in isolation to respond to the TB burden. In order for countries and TB programmes to move away from this passive approach to one in which they actively seek to find and treat all people with TB, a radical shift in mindset and approach is needed – one that recognizes and empowers patients and communities as valuable partners.

Civil society and community-based organizations have a critical role to play in this shift. These stakeholders – including patient-based

organizations, nongovernmental organizations, faith-based organizations, youth groups and community volunteers – are fundamental



partners in the drive towards better access to health and universal health coverage.¹

Community health workers provide vital support to health systems in many resource-poor countries. Furthermore, civil society organizations act as a voice for the most vulnerable, advocating for the needs of TB patients and advising on interventions that are feasible in their specific setting.

Yet, despite the wealth of evidence pointing to the critical role played by community and civil society actors,² these stakeholders remain at the fringe of the planning, implementation and monitoring of TB programmes. The result is often top-down disease programmes that may be aligned with global and national strategies, but that lack an understanding of the local context, community dynamics, and ownership.

Countries need to strengthen community health systems in a way that is linked to the overall health systems and a national response to TB. Civil society and community organizations must be engaged from the start in planning TB programmes, and involved as active partners in the implementation and monitoring of TB services. For example, WHO's Engage-TB guidance, developed in 2012, offers some guidance to NTPs on how they can effectively work with nongovernmental organizations and civil society organizations that are not already working on TB.³ Social media and social audit mechanisms need to be used to enable patients, civil society organizations and community members to contribute to improving services and monitoring progress.

A key challenge in engaging communities and civil society is that, compared with the HIV/

AIDS community, there are far fewer individuals and networks committed to ending TB. This under-representation also has an impact on national and global planning, where the voices of civil society and communities are not always heard.

The HIV/AIDS community has long been seen as an inspiration for TB activism. However, TB advocacy has yet to achieve the scale and impact of HIV advocacy. Since an HIV infection is lifelong, the diagnosis becomes a part of the patient's identity. This automatically draws people into communities fighting for access to treatment. By contrast, TB is a disease that people often deal with in isolation. It also needs to be acknowledged that unlike HIV the TB response has not prioritized and systematically invested on empowering people that had TB. There is a need to encourage and build the capacity of people that had TB to engage in advocacy and other elements of the TB response. This would help to strengthen the community response to TB.

HIV and TB communities have much to offer each other by pooling resources. High rates of TB and HIV coinfection necessitate integrated approaches; this is crucial at the community level. People living with HIV should be an integral part of TB advocacy efforts.

The TB advocacy community must better engage organizations involved in HIV response and other action-oriented advocacy constituencies that offer the potential for collaboration. This includes faith-based organizations, legal clinics, human rights organizations, microcredit networks and women's networks. We must also find ways to increase the number of active TB networks, forums, and groups both nationally and internationally.

All of these endeavours will require significant increases in funding, and above all a surge of political will. Ending TB can only happen if the disease itself becomes part of the national agenda, and all barriers to treatment and civil society engagement are removed.

1 The Global Health Workforce Alliance Strategy 2013-2016. Geneva: Global Health Workforce Alliance; 2012.

2 Sinanovic E, Floyd K, Dudley L, et al. Cost and cost-effectiveness of community-based care for tuberculosis in Cape Town, South Africa. *Int J Tuberc Lung Dis*. 2003;7:S56-62.

3 Engage-TB: integrating community-based tuberculosis activities into the work of non-governmental and other civil society organizations: operational guidance. Geneva: World Health Organization; 2012.



Awareness and active case finding

Community health workers play an important role in reaching people who are missed by case-finding efforts. Through community outreach and educational programmes, community workers encourage people who have TB symptoms to contact a health care worker or visit a health facility. When people are not able to travel, community workers can also help to transport sputum samples to the nearest health facility for diagnosis. The participation of existing community health workers in such active case-finding initiatives has improved case detection and treatment outcomes.⁴ However, this role has yet to be fully maximized.

Integrating TB case finding with other programmes, such as those for HIV and maternal and child health – for example, by encouraging people living with HIV or pregnant women to be tested for TB – will be critical to detecting a larger proportion of TB cases. Community health workers can also facilitate behavioural change by educating people about the causes and spread of TB.

Access to care

A major challenge in TB care is that many people in high-burden countries who have symptoms first seek care from traditional healers or pharmacists, rather than from public health clinics or hospitals. TB programmes need to reach out to these traditional healers to ensure that people with TB get access to good quality care at an affordable price. Community systems can play a transformative role in securing this link between informal providers and the formal health system.

Unless all providers ensure good quality care, the

4 Yassin MA, Datiko DG, Tulloch O, et al. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in southern Ethiopia. PLoS ONE. 2013;8:5 (<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0063174>).

diagnosis of people with TB will be delayed as they shop around for diagnosis and treatment, leading to unnecessary out-of-pocket expenses. Such pre-diagnosis outlays are a major factor causing the catastrophic costs associated with TB. Encouraging people with TB symptoms to seek appropriate medical care relies on the trust and peer-to-peer relationship that a community representative can bring (see Box 4.1 on Ethiopia: Community Health Workers⁵).

Treatment adherence, psychosocial support and reducing stigma

Ensuring adherence to TB treatment is complex and challenging. The treatment itself is lengthy and inevitably has side effects, making counselling an important resource. Community members, who may have had TB themselves, are a vital provider of this psychosocial support.

5 Yassin MA, Datiko DG, Tulloch O, et al. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in southern Ethiopia. PLoS ONE. 2013;8:5 (<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0063174>).

BOX 4.1:

ETHIOPIA: Community health workers

In Ethiopia's rural Sidama Zone, health extension workers (HEW) were trained to work in their communities to identify people with TB symptoms, collect sputum samples, and prepare slides in the field for testing before being transported to the laboratory for staining and reading. More than 1000 HEWs collected sputum samples from more than 200 000 people with TB symptoms and identified more than 17 500 people with smear-positive TB. This intervention doubled the number of people put on treatment in a zone of more than 3 million people. In addition, the HEWs provided treatment support, with treatment success rates improving from 77% to 95%.



Travelling to clinics to access treatment can be expensive, especially for people living in remote areas. It can also mean that people with TB lose income in the process of seeking treatment. Civil society members could ensure that people with TB are linked with social protection schemes, such as food vouchers or conditional cash vouchers for treatment adherence.

Faith-based groups of all religions are an untapped resource for community care in many countries. These groups, along with other community workers, can help to provide palliative care to people with TB at home – a service that is beyond the capacity of most health systems.

There is considerable stigma surrounding TB. Many people with symptoms of TB do not seek diagnosis or treatment for fear of losing their jobs or being evicted from their homes if their disease is confirmed and becomes known. In countries with high rates of TB and HIV coinfection, many people do not admit to having TB because they may be suspected of having HIV.

Eradicating the stigma surrounding TB is a crucial component of encouraging people to seek diagnosis and treatment, along with psychosocial support or social protection benefits after diagnosis. Since stigma is rooted in social and cultural perceptions, and sometimes in existing laws and policies, education campaigns in communities will be important for helping to break down misconceptions and bias. Advocacy for law reform is also crucial for eradicating stigma. Social media can play an important role in eliminating stigma and overcoming other social barriers.

Community engagement in research

Engaging TB-affected communities in all aspects of research – from early-stage research to the design of clinical trials and the delivery and large-scale uptake of successful innovations – will help to make communities equal

partners in the fight against TB. Studies have shown that this approach can have remarkable results in terms of TB research – boosting study outcomes, generating public visibility and stimulating demand – similar to the effects seen in HIV and AIDS research. Community engagement leads to greater ownership of research in communities and integrates the perspective of those who will ultimately benefit from the incorporation of new technologies.

All researchers and sponsors should therefore develop community engagement plans and take steps to include affected communities, patient groups and civil society in TB R&D. Community

BOX 4.2:

The Global Tuberculosis Community Advisory Board (TB CAB)

The Global Tuberculosis Community Advisory Board (TB CAB) is a group of research-literate community activists from HIV and TB networks in Asia, Europe, Africa, and North and South America. Founded in 2011, the TB CAB acts in an advisory capacity to:

- ✦ advise product developers and institutions conducting clinical trials of new TB drugs, regimens, diagnostics and vaccines
- ✦ provide input on study design, early access, regulatory approval, post marketing and implementation strategies

The TB CAB is dedicated to mobilizing political will and increasing community involvement in TB research and access to the tools to fight TB.

More information is available at:
www.tbonline.info/tbcab



advisory boards (see Box 4.2 below) offer one platform for achieving meaningful community engagement.¹

1 Critical Path to New TB Drug Regimens. Good participatory practice guidelines for TB drug trials; 2012.

Action needed to partner with civil society and communities

Community system strengthening is a useful approach to planning engagement with civil society and affected communities.² By considering communities and their role as part of a system, it allows for an analysis of the different facets of that system, how they are interconnected, and what aspects need to be strengthened.

Community strengthening

Community strengthening is a necessary precursor to effective engagement with affected communities. Without the necessary skills and resources, communities cannot determine the needs of people with TB, nor advocate for better services or hold donors and governments accountable. While civil society and community representatives have abundant grassroots expertise, they may need training and support in order to meaningfully participate at high-level meetings and engage with international organizations and governments.

Human-rights-based advocacy has an important role to play in removing barriers to TB care and ensuring the rights of people with and affected by TB. Therefore, capacity-building should include training in the use of human rights impact assessment tools. Such tools can enable communities to anticipate and respond to the potential human rights impacts of government, trade, and corporate policies related to TB.

2 Community systems strengthening framework. Geneva: The Global Fund To Fight AIDS, Tuberculosis and Malaria; 2014.

In order for community organizations to function effectively, they need sufficient and sustained funding. Communities hold critical knowledge about the health needs of and feasible interventions for their TB-affected communities. All stakeholders, including donors, should consider ensuring sustainable funding for civil society and community organizations. Consistent, sustained investment in **community system strengthening** is vital to realizing the full potential of communities in the fight against TB.

Active engagement with civil society and community workers

Although the role of these stakeholders has been recognized for some time, there has been insufficient engagement both nationally and internationally.³

Civil society and especially communities should be core partners in international and national

3 Getahun H, Raviglione M. Transforming the global tuberculosis response through effective engagement of civil society organizations: the role of the World Health Organization. Bull World Health Organ. 2011;89:616–8.



TB activities. They need to be brought on board at the start of the planning process, rather than asked for feedback at the end. TB programmes should look to include civil society organizations (CSOs) in core activities, inviting them to attend key meetings, such as those for strategy setting and programme reviews, and to sit on scientific boards. The ultimate aim should be well-designed TB services that are owned and sustained by communities, working in close

collaboration with the government and other stakeholders.

Monitoring and evaluation: Impact assessment and effectiveness

It can be challenging to assess the impact of civil society organizations and community workers. Therefore, reliable indicators are needed to

BOX 4.3:

SPOTLIGHT: The Global Coalition of TB Activists (GCTA)

The GCTA is a coalition of TB-affected communities and their representatives. Its aim is to bring together activists from diverse backgrounds and regions in order to ensure that TB-affected communities are at the centre of all processes on TB.

The coalition's mission is to provide an advocacy platform and to effectively represent TB-affected communities in order to influence the global TB agenda through patient empowerment, strategic advocacy, and community mobilization. The GCTA aims to develop regional, national and local alliances for collaboration with all stakeholders. The GCTA's objectives are to:

- ✦ Improve community engagement and networking and to strengthen partnership with all TB stakeholders
- ✦ Strengthen the capacity of activists and representatives of affected communities for effective engagement at all levels
- ✦ Promote the effective communication of TB issues at all levels
- ✦ Advocate for increased resources for addressing TB

Since December 2013, the GCTA network has grown to 130 members, both individuals and organizations, in over 30 different countries. Among other activities, the GCTA has worked

closely with the Stop TB Partnership to facilitate the participation of civil society and TB-affected communities in all of the Global Fund processes, including its Funding Model. The GCTA has organized regional workshops to build the capacity of local activists to understand and implement the Global Fund NFM in countries. It also ensures the inclusion of key populations, human rights and gender in country dialogues and the development of concept notes.

Members of the GCTA serve on many global, regional and national committees and boards, ensuring that affected community perspectives inform policy and are reflected in all decisions.

The GCTA is governed at the global level by a steering committee comprised of a chair, vice chair, six regional focal points, and six alternates. The two community representatives and the representatives of the developing country NGOs and developed country NGOs on the Stop TB Partnership Coordinating Board serve as advisors to the steering committee.

www.gctacommunity.org



effectively assess progress and impact on the fight against TB, and to direct resources where they will be most effective.

Umbrella networks

An NGO-coordinating body could represent the different civil society and community organizations, allowing individual organizations to share experience and knowledge from the grassroots level.

BOX 4.4: SPOTLIGHT: TB Europe Coalition

The TB Europe Coalition (TBEC) is a network that brings together civil society representatives and community actors and advocates from across the WHO European Region.

It seeks to strengthen the role of affected communities and civil society in the response to TB, and to increase the political and financial commitment to fighting the epidemic. TBEC was formed by a group of TB advocates in 2009 in order to address two major concerns: the high rates of drug resistance in Europe and the low level of awareness among the general public and policy makers.

Part of the lack of awareness was due to a scarcity of civil society stakeholders working on TB in the region. Civil society plays a particularly important role in the TB response for several reasons: it has an in-depth knowledge of local contexts and has the ability to reach out to some of the most inaccessible communities and groups; it can ensure that TB programmes address the social dimension of TB; it can effectively influence policy and programming and act as a watchdog to ensure the supply of affordable, accessible, and efficient health care for all populations; and it can play a leading role in reducing the stigma associated with TB.

TBEC has built the capacity of CSOs so that they are able to carry out the above activities

effectively. The network has facilitated national and regional advocacy training, and regularly invites CSOs and community advocates to participate in regional and international TB conferences. TBEC members also participate in direct advocacy with key decision-makers both at the national and EU level. As one TBEC member, who previously had MDR-TB, says, "I was lucky enough to meet activists from other countries and see what they made possible. I was inspired and started calling my ward-mates and people who had TB, to form a support group, to build community systems that can help those who suffer from the disease".

This same member has formed a national Stop TB Partnership in his own country in central Asia. TBEC seeks to inspire similar coalitions elsewhere and has been working with groups such as the Global Coalition of TB Activists to share learning and best practices. Several national coalitions have now been built throughout the WHO European region with the support of TBEC. These coalitions are based on the TBEC model and are driving change in their respective countries.



Partnering with the private and business sector

To make progress in the fight against TB, it is essential to look at how the growth of the private sector is transforming health care delivery around the world. The private sector has contributed immensely to economic development around the world, providing innovation, diversity of choice, and new approaches to meeting market demand and overcoming barriers.

The private sector makes an enormous contribution to health through research into new tools, the manufacturing of health commodities, corporate social responsibility (CSR) initiatives, and the provision of health care. Public-private partnerships among government agencies and private organizations (both non-profit and for-profit entities), independent and corporate foundations, faith-based organizations, and start-up entrepreneurs have improved the health of billions of people over the last few decades.

In the context of the fight against TB, partnering with the private sector encompasses the following stakeholders:

PRIVATE SECTOR TB COMMODITY SUPPLIERS.

Pharmaceutical companies, as well as manufacturers of laboratory equipment and vaccines, contribute directly to the research and development of new tools, and the production and supply of diagnostics and drugs to meet the needs of TB programmes and people with and affected by TB worldwide.

Public-private partnerships with such companies are essential for fast-tracking the development of new tools, as well as for making drugs, diagnostics and vaccines affordable and accessible to people with TB. The significant price reduction for the purchase of GeneXpert test cartridges made possible through the joint partnership of USAID, OGAC, the Bill & Melinda Gates Foundation, and UNITAID with Cepheid is an example of the great potential of such collaborations.

There is a role for private sector in technology transfer approaches should that be considered

as an approach to improve access – an example is the technology transfer done by Lilly for two medicines used to treat MDR-TB.

More recently, the new drug bedaquiline was made available free of cost to high-burden countries through a donation programme set up by a partnership between USAID and Janssen, the drug's manufacturer. As new diagnostics, drugs and vaccines are developed for TB, such partnerships are expected to play a key role in providing access for people with TB. Partnering with private sector manufacturers of TB diagnostics and drugs is also important to ensure a steady supply to match demand, especially during the rapid scale-up of services.

PRIVATE INDUSTRY AND BUSINESSES. These organizations contribute to the fight against TB in two ways: by taking care of their own staff and their families, and by undertaking CSR activities in wider society. Businesses and industries, especially those that are labour-intensive, need to adopt non-discriminatory recruitment and retention policies, promote infection-free and safe workplaces, and provide their staff and families with good-quality and affordable TB diagnostic, treatment and notification services. It is important for TB programmes to proactively partner with such businesses.

Efforts to tackle TB have yet to fully take advantage of the CSR initiatives of businesses, which provide important resources and opportunities for collaboration. This is therefore an important area for further engagement between TB programmes, their stakeholders, and businesses. Financial and in-kind contributions from the private sector are critical to progress in many areas, particularly in innovation, the use of infor-



mation technology, and logistics management. Additionally, businesses with products and services that reach large populations may provide opportunities for education and outreach.

THE PRIVATE HEALTH CARE SYSTEM. Public and private health care systems coexist worldwide. People in many countries prefer private sector care because of its ease of access and the perception of higher quality. In a number of countries in Asia, a substantial proportion of people with symptoms of TB, including the poor, seek care first at private clinics. A large proportion of TB drugs are also sold on the private market, sometimes exceeding the value and volume of transactions in the public sector market.¹ In sub-Saharan Africa, private informal providers – traditional healers and drug shops – are the first point of contact for a significant proportion of people with common symptoms such as cough.

The public–private mix (PPM) initiative formed an essential component of the earlier Stop TB Strategy. PPM has helped to engage care providers, both public and private, in TB care and control. As a result, many countries now work with different types of care providers that are outside of the national TB programme. In countries as diverse as India, Kenya, Malawi, Myanmar, and Pakistan, about 10–30% of the people with TB who are registered by public health systems are referred from private care providers. However, in most country settings, only a small proportion of private providers refer or notify people diagnosed with and treated for TB. There is therefore much greater potential for making the private health system a true partner in TB care and prevention and addressing case notification gaps.

NTPs face major constraints in their efforts to engage with the private sector to scale up TB care, chiefly a lack of funding or capac-

ity. Successful projects have addressed these challenges by investing in private intermediary agencies and creating social business models for the provision of quality TB care. Such models have not derailed the business models of private health care providers, but worked with them synergistically to improve quality, affordability, and public health responsibilities. The use of digital health tools and innovative voucher-based reimbursement systems has also contributed greatly to the success of these projects. Such projects have now been implemented in a few cities, including Mumbai, Karachi, Mehsana, and Dhaka.

¹ Wells WA, Fan Ge C, Patel N, et al. Size and usage patterns of private TB drug markets in the high burden countries. PLoS ONE. 2011;6:e18964.



COUNTRIES SHOULD WORK TO SECURE ADEQUATE RESOURCES TO IMPLEMENT AND SCALE UP AN APPROPRIATE MIX OF THE FOLLOWING PRIVATE HEALTH SECTOR ENGAGEMENT STRATEGIES:

- a** Sharing the burden of engaging numerous independent private practitioners with private “intermediary organizations” that can establish and scale up social franchising and social business models; NGOs with the capacity and skills to work with private practitioners; and professional societies and associations
- b** Optimizing and expanding engagement with large hospitals, academic institutions and NGOs
- c** Mobilizing and supporting corporate and business-sector health services in order to initiate and expand workplace TB programmes to serve workers, their families and communities
- d** Engaging communities and civil society to seek care from and promote private providers offering high-quality TB care
- e** Enforcing mandatory TB case notification through simplified and user-friendly digital tools, the rational use of TB medicines, and certification and accreditation systems to identify and incentivize collaborating providers.

It is also important for national authorities and international donors to recognize that, in a number of settings, people have more confidence in the private health sector. Investments should therefore be made to strengthen both public and private sectors in order to help scale up good-quality, affordable TB care in both sectors.

Investment in public-private partnership approaches to strengthening private sector TB care is important for all countries. The Global Plan highlights this need particularly in two

of the nine settings: Setting 6 (middle-income country settings with a moderate TB burden) and Setting 7 (India). Even in countries where most TB treatment is handled by the public sector, engagement with the private sector is still required for referrals and early TB diagnosis and treatment. The resultant reduction in diagnostic delay could have a major impact on reducing TB transmission.





5. UNIVERSAL HEALTH COVERAGE AND SOCIOECONOMIC ACTIONS IN TB



KEY MESSAGES

- ✦ The traditional model of tackling TB through diagnosing and administering observed treatment in the public sector is not sufficient to end the disease. New strategies focusing on socioeconomic actions are required to achieve the 90–(90)–90 targets and end TB. Ministries and agencies across government, beyond the ministries of health and the public health sector, must collaborate in order to have maximum impact on the TB epidemic.
 - ✦ Universal health coverage (UHC) must be at the heart of such strategies, with the goal of making TB programmes high-quality, accessible and affordable. People affected by TB need the support of social protection schemes to help them beat the disease.
-

Bold new strategies to tackle TB must move beyond the traditional model of administering observed treatment through the public health sector. Instead, ending TB will require a holistic approach that incorporates a broad range of medical and nonmedical interventions delivered through multiple points in the public system.

The nonmedical interventions that must be implemented in parallel to medical services include social protection, poverty alleviation and urban regeneration. Each of these interventions has the potential to enhance prevention, improve access to care, and mitigate TB-related catastrophic costs.

Social protection and UHC are core components of the End TB Strategy, pillar two of which seeks to ensure that health and social sector policies work jointly to address the social determinants of TB.

Implementing these measures will require greater involvement with the private sector,

civil society and community health workers. However, the need for nonmedical interventions means that a greater range of nonmedical actors must also be engaged. Planning and investing to end TB is not solely the task of health ministries, but also of other ministries and government agencies, including those responsible for social welfare, finance, labour, housing and urban regeneration, and agriculture.

Investing in and planning such nonmedical actions cannot wait, as they normally take several years to implement and start making an impact on health outcomes. Committing to and initiating investments in socioeconomic actions must therefore be an integral part of the 2016–2020 Plan.



Improving medical services: Universal health coverage

The global push towards achieving UHC provides an opportunity for TB services to scale up, become more affordable and accessible, and improve in quality. It is imperative that TB programmes recognize the opportunity and actively engage in efforts to secure greater access to TB care through UHC. Depending on the country context, in order to be part of the UHC and health insurance initiative, TB programmes may need to restructure their budgets, service delivery mechanisms and data collection methods.

Health care financing has become a prominent aspect of global efforts towards UHC, and health insurance schemes are increasingly being rolled out in many low-income countries. However, many people at risk for TB still lack coverage. UHC must therefore not be limited to health care financing, but must also include the expansion of critical health services. As discussed in Chapter 4, community health workers can help reach the “missed” millions of cases by reaching out to communities, tracing contact with people impacted by TB, and educating family members.

Countries are encouraged to undertake an assessment of barriers to accessing TB services and to address them in their UHC agenda. In addition, TB services should be prioritized within the social benefit packages that exist within countries.

BOX 5.1:

What Is Universal Health Coverage?

Universal health coverage (UHC) is defined as ensuring that all people can use the health services they need, that these services are of sufficient quality to be effective, and that the use of these services does not expose the user to financial hardship.¹ Sustainable Development Goal 3 ensures healthy lives and promotes well-being for all at all ages. This goal focuses on achieving UHC, which includes financial risk protection, access to quality essential health care services, and access to safe, effective, quality, and affordable essential medicines and vaccines for all.

¹ WHO. What is universal coverage? (http://www.who.int/health_financing/universal_coverage_definition/en/).

Integrating TB into poverty alleviation and social justice programmes

There is a strong correlation between TB and poverty. A 2012 study in India showed that the very poorest people are more than five times as likely to have TB compared to the richest. TB prevalence in this group is 1105 per 100 000 people, which is higher than the 782 per 100 000 reported in South Africa, where high levels of

HIV drive the TB burden.¹

One of the reasons for this disparity is that, in many emerging economies, an increase in national wealth has not translated into poverty

¹ Oxlade O, Murray M. Tuberculosis and poverty: why are the poor at greater risk in India? PLoS ONE. 2012;7(11):e47533. doi:10.1371/journal.pone.0047533.



reduction at the individual level,² nor have these countries always invested more money in services. A number of middle-income countries have seen steady economic growth over the past 15 years, yet few efforts have been made to ensure the more equitable distribution of wealth or to invest in improving living conditions and access to water and sanitation. In addition,

many poor people in middle-income countries still face unaffordable out-of-pocket costs in accessing health care.

As a result, progress in the fight against TB will require countries to identify pockets of poverty and implement targeted interventions to ensure that the poorest have access to care.

2 OECD. Focus on inequality and growth – December 2014; 2014.

Social protection programmes

In addition to the direct health costs of seeking TB care, many households also incur significant related expenses, including costs for travel, food, and childcare, and loss of income. These costs can be catastrophic for families, as their spending on health care can exceed 40% of their disposable income.³ Income loss accounts for, on average, 60% of the costs incurred by people with TB, with 25% attributed to direct costs such as tests, medicines, and hospitalization.⁴ Addressing these costs is especially relevant in the fight against TB, since the disease disproportionately affects families who are impoverished and malnourished.

Countries provide different levels of social protection. Most high-income countries have near universal coverage, whereas the lowest income countries have almost no coverage. Many low- and middle-income countries are now moving toward broader coverage. Evidence is emerging that shows how social protections, particularly those focused on treatment adherence, can improve TB outcomes and operational results (see Box 5.3: Peru).⁵ Many social protection programmes have used conditional cash transfers to incentivize participation. This model has been employed to improve public health in many low- and middle-income countries, notably Brazil (see Box 5.3: Social Protection in Brazil).

BOX 5.2: What Is Social Protection?

Social protection can be understood as a set of public actions that address not only income poverty and economic shocks, but also social vulnerability. It thus takes into account the interrelationship between exclusion and poverty. Through income or in-kind support and programmes designed to increase access to services (such as health, education and nutrition), social protection helps to realize the human rights of children and families.²

2 UNICEF. Social protection (http://www.unicef.org/socialpolicy/index_socialprotection.html).

3 Xu K, Evans DB, Kawabata K. Household catastrophic health expenditure: a multicountry analysis. *Lancet*. 2003;362:111–7.

4 Eliminating the financial hardship of TB. Geneva: World Health Organization; 2013 (http://www.who.int/tb/publications/UHC_SP_factsheet.pdf).

5 Boccia D, Hargreaves J, Lonnroth K. Cash transfer and microfinance interventions for tuberculosis control: review of the impact evidence and policy implications. *Int J Tuberc Lung Dis*. 2011;15:S37–49.

Social protection efforts will require support from health systems and other sectors. Nutritional programmes should collaborate with the World Food Programme and national agencies responsible for food and nutrition. Cash transfer programmes for the poor that often



exist under social welfare ministries need to be made accessible to people with TB. Additional operational research can demonstrate impact and identify effective means of delivering social protection schemes.¹

Furthermore, in order to ensure the systematic implementation of social protection programmes, a clear analysis that identifies the socioeconomic factors contributing to vulnerability in specific settings is needed. For instance, in some regions, catastrophic costs may be primarily due to travel costs and loss of income. In others, food security plays a major role in poor treatment outcomes.²

NTBs can undertake elements of this analysis in order to see how best to intervene with their expertise and knowledge. In addition, health care staff treating people with TB should be aware of social protection schemes, such as disability grants, for which people with TB are eligible.

Improving the urban environment

The majority of the world's population growth is set to occur in urban areas over the coming decades. In many low-income countries, and even in many middle-income ones, urban areas have grown rapidly, but without much planning or resources. This has left the poorest to live in slums. For an airborne disease such as TB that is fueled by overcrowding, poor ventilation, inadequate sanitation, and undernutrition, this development trend has significant implications.

Urban development strategies that improve the physical environment and reduce overcrowding

therefore have the potential to make a significant impact in the fight against TB³. Well-located health care facilities with respect to housing could enable better links to health services. Improving urban living conditions would also greatly benefit efforts to tackle other diseases such as diarrhoea and pneumonia, which are caused by overcrowding and poor water and sanitation.

3 Hargreaves JR, Boccia D, Evans CA. The social determinants of tuberculosis: from evidence to action. *Amer J Public Health*. 2011;4:654–62.

BOX 5.3:

SOCIAL PROTECTION FOR TB IN PERU: The ISAT Project

This 2011 study looked at whether socio-economic interventions would increase the uptake of TB care and prevention services in more than 2000 people living in impoverished communities in Peru. Over nearly 3 years, the interventions aimed both to increase the uptake of TB care through education, community mobilization, and psychosocial support, and to reduce catastrophic costs through food and cash transfers, micro-credit, and vocational training.

The interventions increased household contact screening for TB from 82% to 96%, completion of TB treatment from 91% to 97%, and uptake of rapid MDR-TB testing from 67% to 92%.

These improvements were also associated with the creation of a civil society organization comprised of TB-affected households, who then began advocacy to improve services to match their needs. Some of the interventions were easier to administer than others; microcredit proved difficult, but psychosocial support was key in addressing the severe depression that contributed to peoples' reluctance to seek health care.

1 Lutge E, Lewin S, Volmink J. Economic support to improve tuberculosis treatment outcomes in South Africa: a pragmatic cluster-randomized controlled trial. *Trials*. 2013;14:154.

2 Tanimura T, Jaramillo E, Weil D. Financial burden for tuberculosis patients in low and middle income countries: a systematic review. *Eur Respir J*. 2014;43:1763–5.



Creating an enabling environment: Political will and policymaking

Advocacy within the TB community, led by NTP managers and health ministers, is key to raising the profile of TB, not only in the health sector but also in other sectors relevant to TB. This approach requires a major shift in mindset both within and outside of the community of people working on TB. One way to ensure the better integration of TB with other programmes could be for countries to set up a TB coordination council at the national level, similar to a national AIDS board, and to work closer with existing national health committees.

NTP managers are not the best positioned to lead coordinated efforts across several departments and ministries. However, if they can count on high-level political support as well as resources, NTP managers can effectively advise other programmes on how to incorporate TB into their activities. While TB programme managers may, for instance, be able to advise on the technical considerations of improving housing conditions, the political drive will need to come from a consortium of ministers and high-ranking government officials.

The way the argument is framed is also key; rather than insisting that TB take precedence over other public health priorities, for instance, TB experts should explain how focusing on TB will also improve performance in tackling these concerns and other UN Sustainable Development Goals. Another strong argument is that social protection interventions are likely to impact multiple diseases simultaneously, making their implementation more valuable and cost-effective.

As TB risk factors are diverse, policy approaches should contain a mix of TB-specific approaches (i.e. interventions that directly target people who have TB and aim to influence a particular TB indicator) and TB-sensitive approaches (i.e. interventions that target people who are at risk for TB and can indirectly reduce their vulnerability, such as better housing and ventilation, or agricultural policies aimed at improving nutrition).

Better data on the links between TB and socioeconomic actions should be collected in order to equip

decision-makers and parliamentarians with the evidence to change policy and allocate resources for social protection.

Addressing TB will require major systemic changes in regulatory capacity (to ensure the rational use of medicines and infection control, among other issues), health care financing (through improved health insurance schemes), and boosting the capacity of health care systems to ensure UHC.

BOX 5.4:

Social protection in Brazil

Brazil's Bolsa Familia, set up in 2004, is a cash transfer scheme that has benefited 11 million families, most with young children or pregnant or breastfeeding women.¹ Although families do not need to have a family member that is ill with TB to benefit from Bolsa Familia, evidence has shown that cash transfers are important tools in tackling TB.

A study carried out in Brazilian cities from 2004 to 2011 showed that TB incidence was lower among people who benefited from intermediate or high levels of coverage under the Bolsa Familia programme. Another study showed that the Bolsa Familia programme was associated with positive TB treatment outcomes.²

1 Soares FV, Ribas RP, Osorio RG. Evaluating the impact of Brazil's Bolsa Familia: cash transfer programmes in comparative perspective. IPC Evaluation Note. 2007;1.

2 Nery JS, Torrens A. Impact of social protection on TB incidence and treatment outcomes in Brazil: implications for the national TB control programme. Symposium of 45 Union World Conference on Lung Health; 2014.



6. NEW TOOLS



KEY MESSAGES

- ✦ The Global Plan presents an ambitious but critical set of priority investments for TB R&D. This ambition is essential in order to fully realize the goals of the End TB Strategy. We cannot afford business as usual.
 - ✦ Without new drugs, diagnostics and an effective vaccine, we will not achieve the steep reductions in incidence and mortality that we need, and millions more people will die from the disease.
 - ✦ Failing to invest in research and development for new tools immediately will result in huge financial costs in the future because of the large number of people that still require treatment. Delaying investment by just one year – 2017, rather than 2016 – will cause future treatment costs to increase by US\$ 1.3 billion. A five-year delay will result in extra costs of US\$ 4.2 billion. When lost productivity is factored in, this figure increases to US\$ 185 billion.
 - ✦ In addition to the financial costs, there will also be a tremendous human toll for failing to invest in R&D. A five-year delay in investing in R&D could result in an additional 8 million TB cases and 1.4 million TB deaths by 2030.
 - ✦ Patients' access to new tools must be considered alongside product development. And fast-track mechanisms for access to new tools must also be explored. There is no time for delay.
-

Introduction and the case for new tools

Without investment in research and development for new tools, the goals of the End TB Strategy will not be fully realized. Even if countries could manage to use existing tools to reach the 2020 and 2025 End TB milestones, there will still be 4 million new cases of TB a year in 2025. From that point on, existing technology will be insufficient to continue bending the curve down towards a 90% incidence reduction by 2035.

In addition to the missed opportunity in terms of saving lives and preventing infections and

antimicrobial resistance, failure to invest immediately in the tools needed to achieve the End TB milestones will result in huge human and financial costs. It is estimated that a five-year delay in investing in R&D could result in an additional 8 million TB cases and 1.4 million TB deaths by 2030. The financial cost of complacency is estimated at US\$ 1.3 billion for a one-year delay and US\$4.2 billion for a five-year delay, in costs for TB treatment alone. When productivity losses from TB deaths that could have been prevented by new tools are included, these costs climb to US\$ 55 billion and

US\$ 185 billion, respectively (see Chapter 7).

To avoid these costs and to achieve the rapid reductions in incidence and mortality required

by the End TB Strategy, a robust set of new tools must be available for use in 2025, preferably sooner.

THESE TOOLS INCLUDE:

1 A VACCINE that protects those of all ages who are not yet infected from getting TB disease – preferably one that can also prevent people with latent TB from becoming ill with the disease;

2 highly sensitive **DIAGNOSTIC TESTS** for all forms of TB that can be implemented at the point of care; and

3 DRUG REGIMENS (including regimens for TB infection caused by drug-resistant TB) that are not only highly effective, but also not unbearably lengthy or toxic.

New tools are also needed for the fight against TB in specific populations. Vaccines, diagnostics and treatment regimens that are suitable for children and safe and effective for people living with HIV are urgently needed, as is a better understanding of zoonotic TB and how to prevent, diagnose and treat it in both animals and humans.

Furthermore, all people – especially those who are most vulnerable – must have access to these new tools as they become available. For this to happen, TB programmes and partners must be aware of the processes, barriers, norms and policies affecting the introduction of new diagnostics, drugs and vaccines in different countries, with a view to being able to quickly adopt and scale up the use of new tools.

While it is essential to have new tools available after the period of the Global Plan, research and development to improve existing tools, including drugs and diagnostics that could become available within the next five years, will be vital in enabling countries to achieve the 90–(90)–90 targets as quickly as possible.

A total of around US\$ 9 billion is required for the research and development of new tools over

the course of the next five years. Failure to strive towards the Global Plan’s goals and failure to make this investment is tantamount to accepting the failure of the End TB Strategy. It also means accepting that 4 million people, equivalent to the population of Zhengzhou, Johannesburg or Los Angeles, will develop TB every year for the foreseeable future. Since validation and implementation take many years, we must urgently prioritize the development of new tools today.

Research and development in the End TB Strategy

The third pillar of the End TB Strategy focuses on the urgent need to promote, stimulate and intensify research and innovation worldwide, with special emphasis on the creation of research-enabling environments where the TB burden is greatest.

The Global Action Framework for TB Research lays out a vision and a plan to promote and intensify research and innovation both at country and global levels over the next 10 years. This Framework complements the objectives and activities outlined in the Global Plan.



The case for new drugs

Faster-acting and simplified TB drug regimens are required more urgently than ever in the fight against TB. Today's drug regimens, which take between 6 and 24 months to complete, are lengthy and complicated to administer, and can be highly toxic. Drugs to treat drug-resistant TB are expensive and extremely toxic. In addition, drugs to treat drug-sensitive TB are not compatible with certain common antiretroviral therapies used to treat HIV. Furthermore, all TB therapies must be available in appropriate dosage formulations for children of all ages.

The introduction of a new regimen of shorter duration (two to three months) and containing three or four new drugs with no pre-existing resistance would be a game-changer in the fight against both drug-susceptible and drug-resistant TB. Such a regimen could improve treatment adherence, stop the spread of drug-resistant TB, present significant cost savings (both direct and indirect) for national TB programmes and health care systems, and enable the global scale-up of MDR-TB treatment. A shorter and simpler universal treatment will not only help to cure those currently under care, but will also allow health workers to reach more people by significantly reducing the burden on national TB programmes.

A more effective treatment for latent TB is a long-term challenge, but one where success would also have a significant impact on the TB epidemic.¹

The case for new diagnostics

Every year, one in three who fall ill with TB are left undiagnosed or not registered by health systems. These "missed" 3 million people are at the root of why TB transmission continues to be at such high levels.

The scale up and more efficient implementation of current diagnostic tools will help to launch countries on the right trajectory to finding and treating these 3 million people. However, reaching the End TB Strategy milestones will require a drastic acceleration of these efforts – an acceleration that can only be driven by major advances in diagnostic capabilities.

Novel diagnostic tools and testing strategies are required in three categories: a range of tests for TB case detection that can be deployed at all levels of the health care system, including at the point of care; rapid and simple tests for the detection of drug resistance in decentralized settings; and tests for predicting the risk of progression from latent infection to active TB disease.

The case for new vaccines

New vaccines are necessarily a keystone of the global effort to eliminate TB. The only current vaccine – Bacille Calmette–Guérin (BCG), first used in 1921 – protects against severe forms of TB in children. However, BCG is inconsistent in protecting against pulmonary TB in adolescents and adults. New vaccines that protect against all forms of TB in all age groups and populations are urgently needed. Such vaccines will be essential to curbing the global TB epidemic and reaching the ambitious aims set forth in the End TB Strategy.

Recent modelling estimates indicate that a 60% efficacious vaccine delivered to just 20% of adults and adolescents globally, with a 10-year duration of protection, could stop approximately 60–70 million people from getting sick with TB globally in its first 25 years of use.² A significantly improved infant vaccine, relative to BCG, could potentially avert approximately 6–7 million new

1 Dye C, et al. Prospects for tuberculosis elimination. Annual Review Public Health. 2013;34:271–86.

2 Aeras. Modelling the health impact of new TB vaccines with specific vaccine product profiles. Applied Strategies Model; 2014.

cases of TB over that same period of time.^{1,2} The number of cases averted in each Global Plan country setting is shown in Table 6.1 and in Annex 5.³ The most recent analysis also indicates that new TB vaccines that prevent active disease are highly cost-effective health investments.⁴

New vaccines would also indirectly protect vulnerable and at-risk populations. Preventing TB disease in adolescents and adults will also prevent mortality in infants and young children, as well as those whose immune systems are too compromised to

effectively respond to vaccines. Recent modelling efforts show that targeting adolescents and adults with vaccines of 40–80% efficacy, providing 10 or more years of protection, would be a more effective strategy for protecting infants and young children from TB than direct pediatric vaccination with a similar vaccine, due to reduced transmission.⁵ In addition, new vaccines would protect equally well against multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. New drugs:

1 Aerias. Modelling the health impact of new TB vaccines with specific vaccine product profiles. Applied Strategies Model; 2014.

2 The modelling, which is separate to the impact modelling in Chapter 2 of the Plan, assumes that vaccines would be available in 2025, immunization campaigns would happen every 10 years, that two doses would be included in the regimen, that every country would be assigned a specific introduction date between 2025 and 2035, that the vaccine would have 60% efficacy, and that there would be a 20% coverage rate for adolescents and adults and 90% coverage for infants.

3 www.stoptb.org/global/plan/plan2/annexes.asp

4 Knight G, Griffiths UK, Sumner T, et al. Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries. PNAS. 2014;111:15520–5.

5 White, R. Indirect effects in infants on the force of TB disease from vaccinating adolescents and adults. TB Modelling Group, TB Centre, Centre for the Mathematical Modelling of Infectious Diseases; 2015.

TABLE 6.1. TB CASES AVERTED BY GLOBAL PLAN COUNTRY SETTINGS

Global Plan Country Settings	Adolescents Adults Incident Cases Averted (millions)	Infants Incident Cases Averted (millions)	Cumulative Deaths Averted (millions)
1. High MDR Burden, Centralized Care	.3	0	0
2. High TB/HIV, SADC	3.6	.4	.4
3. High TB/HIV, non SADC	5.8	.5	.6
4. Moderate Burden, COE	1.5	.1	.1
5. High Burden, Private Sector	6.0	.3	.5
6. Moderate Burden, Middle Income	10.6	.4	1.3
7. India	12.4	2.3	1.2
8. China	21.1	2.6	1.0
9. Low Burden, High Income	1.3	0 (not vaccinated)	.1



New drugs: Progress report

The US Food and Drug Administration's conditional approval of Janssen's bedaquiline in 2012 marked the first novel TB drug approval in over 40 years by a stringent regulatory authority. As such, it represents a long overdue, but still largely inadequate, contribution towards the medical needs for TB. In addition, delamanid has more recently been conditionally approved by the European Medicines Agency. While it has not yet been registered in high-burden countries, Otsuka is advancing the drug rapidly through the required Phase III and pediatric studies, and it is available through a compassionate use programme. In an uncontrolled trial in Bangladesh, a nine-month multidrug-resistant TB regimen also resulted in high cure rates.⁶

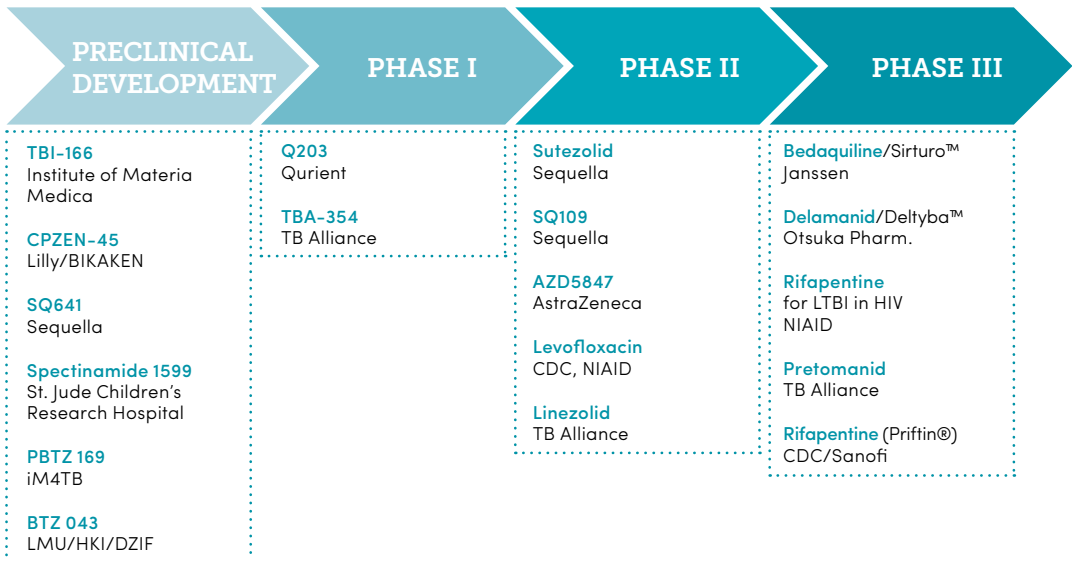
Overall, however, progress in the development of new drugs has been modest. This can be attributed to a mix of poor commercial incentives, high attrition rates, and the need for lengthy and costly trials.

Fig. 6.1 represents an overview of new anti-TB molecules that are in development. While there

has been progress, the clinical development pipeline for TB drugs contains relatively few truly innovative chemical scaffolds and new modes of action. Six new chemical entities (NCEs) are presently in clinical studies; these represent four chemical classes and three broad modes of action.

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

FIGURE 6.1. OVERVIEW OF NEW ANTI-TB MOLECULES IN DEVELOPMENT





Roadmap to new TB drugs

Multiple different drug regimens are needed to reach the End TB milestones. These include a shorter first-line regimen; a safer, shorter and more effective regimen for MDR-TB; appropriate dosing and regimens for children; and safer, more effective regimens for preventive therapy among people with latent TB.

THE NEW DRUGS STRATEGIC FRAMEWORK 2016–2020 GUIDES WORK TOWARDS THIS VISION THROUGH THE FOLLOWING EIGHT OBJECTIVES:

OBJECTIVE 1

Sustaining the pipeline through the basic discovery of TB drugs

OBJECTIVE 2

Increasing clinical trial site capacity

OBJECTIVE 3

Developing a shorter regimen for drug-sensitive TB

OBJECTIVE 4

Developing a safer, higher efficacy and shorter regimen for MDR-TB

OBJECTIVE 5

Improving treatment for children in parallel to efforts for adults

OBJECTIVE 6

Developing a safer, high-efficacy regimen for latent TB

OBJECTIVE 7

Ensuring adoption of new TB drugs and regimens at the country level

OBJECTIVE 8

Engaging community and civil society in the entire process of drug development and access.

The milestones, major activities, and costs of the New Drugs Strategic Framework are summarized in Annex 5.¹

Four of the main objectives are related to the development of new regimens. The ultimate, strategic goal is a universal regimen for all forms of TB that is based on a regimen including at least three NCEs.² In the interim, however, different, overlapping regimens are needed to treat various populations. A number of new regimens including bedaquiline or delamanid are

being evaluated clinically. These are shown in Table 6.2, along with the approximate delivery timelines that could be realized with sufficient funding.

In addition to new regimens, the Global Plan calls for a focus on basic discovery for TB drugs to sustain the pipeline; maintaining trial site capacity; ensuring adoption of TB drugs at the country level; and engaging community and civil society in the process of drug development and access.

The pursuit of new tools should not be carried out in isolation and new forms of collaboration between the public and private sector are

¹ www.stoptb.org/global/plan/plan2/annexes.asp

² Lienhardt C, Raviglione M, Spigelman M, et al. New drugs for the treatment of tuberculosis: needs, challenges, promise, and prospects for the future. *J Infect Dis.* 2012;205 Suppl 2:S241–9. doi:10.1093/infdis/jis034.

TABLE 6.2. SELECTED NEW COMBINATION REGIMENS

Treatment	Indications	Treatment duration(s), months	Status/next phase	Trial IDs
Rifapentine-isoniazid	Latent TB	3	The Rifapentine-isoniazid combination (3 months, LTb) received FDA approval in December 2014. Overcoming affordability barriers will now be critical to expand patient access.	
Delamanid	MDR-TB	6 (as component in combination)	In Phase III since September 2011, estimated end date is May 2016 (Cortellis). Wider registration is critical to expand patient access.	2010-022271-59; 242-09-213; NCT01424670
Pretomanid-moxifloxacin-pyrazinamide	DS-TB; MDR-TB	4; 6	In Phase III. Initial File for Registration at 12 months: May, 2018 (TBA CPRT DST Review, Sept 2014). This regimen could enter the market before 2020.	PHRR150114-000899; STAND; NC-006-(M-Pa-Z); NMRR-14-702-21522; NC-006-(M-Pa-Z) 21522; 2014-CT0249; NCT02342886
Pretomanid-bedaquiline-[an oxazolidinone]	XDR-TB	var.	This phase III study is estimated to run between February 2015 and Oct 2021; Primary endpoint completion date is 31-Oct-2018 (Cortellis)	NiX-TB-(B-L-Pa); NCT02333799
Pretomanid-bedaquiline-pyrazinamide	DS-TB; MDR-TB	3-4; 4	The estimated end date of this Phase II is 29-Feb-2016; Primary endpoint completion date 30-Nov-2015 (Cortellis estimates)	NCT02193776; NC-005-(J-M-PA-Z)
Bedaquiline: STREAM regimens	MDR-TB (including Pre-XDR/XDR TB) when an effective regimen cannot otherwise be constructed	9 & 6	STREAM Stage 2 (Phase III) is part of the post-approval requirements for bedaquiline from both the USFDA, EMA and other Health authorities, and is an alternative to the initially planned Phase 3 trial. STREAM2 has two bedaquiline containing arms, including an all-oral option; in addition, uses for pediatrics are being investigated.	STREAM stage 2, NCT02354014
High-dose rifamycin based regimens	DS-TB	4 or 6	Results announced in Feb 2015 indicated this regimen could shorten treatment. Another trial for TB meningitis was started in July 2014	NCT02169882
A5343: Bedaquiline and Delamanid, alone and in combination	MDR-TB		Expected to start 3Q2015. A Limited Center Trial of the AIDS Clinical Trials Group (ACTG); Sponsored by: The National Institute of Allergy and Infectious Diseases	



needed. Also, new drug regimens and diagnostics need to be introduced together as a single package that provides an integrated solution for triaging and diagnosing people with TB so that they are given the right regimen.¹

Addressing basic knowledge gaps

More basic research is needed to understand fundamental issues in TB biology and the mechanisms that lead to disease. Discovery activities have produced interesting molecules, but too few of these have progressed into development, suggesting that additional linkages and collaborations are needed between early discovery and clinical development.

The highest priority for basic research is the discovery of new candidate drugs based on new molecular scaffolds, and new modes of action that maximize synergy with existing drugs and preclude or at least delay the development of resistance. Reaching this goal requires the design of novel screening assays, which in practice requires combining the best biology and assay development (often found in academia)

with the best compound libraries and medicinal chemistry (often found in pharmaceutical companies).

Another high priority is the availability of validated biomarkers that help to expedite regimen selection. Biomarkers are also urgently needed to predict the activation of latent TB to active disease.

Animal models that improve on current rodent or other species models may better reflect human disease and predict clinical treatment outcomes.

In addition, other *in vitro* systems, such as the hollow fiber model, may provide predictive pharmacokinetic and pharmacodynamic information. However, these models are still difficult for TB; the bacteria grow slowly and thus studies are long and expensive.

Other major areas of basic research that cannot be ignored include understanding the host response to inform new strategies for TB therapeutics; investigating the effectiveness of novel ways to administer TB drugs such as inhalation; understanding the bacteria in latency; and revealing the unique factors of the disease in children and persons living with HIV in order to produce better treatment outcomes.

1 Nathan, C.. Cooperative development of antimicrobials: looking back to look ahead. *Nature Reviews Microbiology*. 2015; 13(10), 651-657

New diagnostics: Progress report

Global partnerships and unprecedented efforts by funding and technical agencies have contributed to significant progress in strengthening laboratory services and improving testing capacity. As a result, new rapid diagnostic technologies, such as liquid culture, rapid speciation and the line probe assay have been introduced in central laboratories and integrated into national TB programmes. Test results may now be delivered within a few days or weeks^{2,3}, compared to the two or three months required for conventional culture and drug-sensitivity testing (DST). The roll-out

2 Kwak N, et al. Diagnostic accuracy and turnaround time of the Xpert MTB/RIF assay in routine clinical practice. *PLoS One*. 2013;8(10):e77456.

3 Naidoo P, et al. A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus line probe assay and Xpert® MTB/RIF-based algorithms in a routine operational setting in Cape Town. *PLoS One*. 2014;9(7):e103328.



and use of these new diagnostic tools, including DST, has contributed to significant progress in the detection of MDR-TB cases.

In 2010, WHO recommended the Xpert® MTB/RIF – a simpler and faster test for detecting TB and rifampicin resistance in decentralized settings – and in 2013 issued a policy update extending the recommendation to children and people with extrapulmonary TB. Although the introduction of Xpert represents a significant step forward, the roll-out of this new technology has highlighted some critical gaps. Effective Xpert deployment has been constrained by the test's costs and infrastructure requirements. These factors have made scale-up and decentralization challenging in many endemic countries, thus resulting in uneven implementation and decreased impact.^{4,5}

Ultimately, the launch and implementation of Xpert MTB/RIF has demonstrated the need for comprehensive solutions tailored to the setting to accompany new tests. The introduction of new, highly performing technologies alone does not necessarily translate into improved patient management or a public health impact on TB epidemics. In order for new technologies to be a game-changer, adequate access to diagnosis, linkage to care, and earlier treatment initiation are also required.









Fig. 6.2 presents an overview of TB diagnostic assays in the pipeline at the time of writing the Global Plan. Although it includes a high number of molecular tools at various stages of development, the diagnostic pipeline has relatively few low-complexity tests and requires further biomarker development and validation efforts.

Among the highlights are tests that aim for higher sensitivity, are suitable for use at lower levels of the health system, and are compatible with existing platforms; tools that are being developed due to enhanced R&D capacity in BRICS countries; and technologies automating smear microscopy.

4 Theron G, et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. *Lancet*. 2014;383(9915):424–35.

5 Churchyard G, et al. Effect of Xpert MTB/RIF on early mortality in adults with suspected TB: a pragmatic randomized trial. 21st Conference on Retroviruses and Opportunistic Infections, 3–6 March 2014, Boston. Oral Abstract 95.

FIGURE 6.2. OVERVIEW OF TB DIAGNOSTIC ASSAYS THAT ARE CURRENTLY IN DEVELOPMENT, CATEGORIZED BY DEVELOPMENT PHASE AND LEVEL OF COMPLEXITY.

	Early development	Late or completed development	On pathway to WHO evaluation	
High complexity assays	MOLECULAR-DETECTION/DST			
	New TruArray MDR-TB (Akkoni) COBAS TaqMan MTB + DST(Roche) Hydra 1K (Insilixa) Mycobacterium Real-time MDR (CapitalBio) MTB Detect (Great Basin Scientific) Aries (Luminex) PNAclap (Panagene) AccuPower TB&MDR (Bioneer)	TRC Rapid MTB (Tosoh) VereMTB (Veredus Laboratories) LiPA Pyrazinamide (Nipro) Fluorotype MTBDR (Hain) TBMDx (Abbott) Meltpro (Zeesan) Mycobacteria RT PCR (CapitalBio) REBA MTB-XDR (YD Diagnostics) EasyNAT TB (Ustar) BD Max (BD)	GenoTYPE MTBDRsl (Hain) REBA MTB-Rifa (YD Diagnostics)	
	CULTURE-BASED-DETECTION/DST			
	BNP Middlebrook (NanoLogix) Rapid colorimetric DST	TREK Sensitive MYCOTB (Trek)		
Moderate complexity assays	MOLECULAR-DETECTION/DST			
	Xtend XDR (Cepheid) Alere Q (Alere) Enigma ML (Enigma Diagnostics) Q-POC (QuantuMDx) EOSCAPE (Wave80) TBDx system (KGI) XI (Xagenic) MTB Detection (Tangen Biosciences) TB POC (Qiagen) Savanna (NWGHF/Quidel)	Genedrive MTB/RIF (Epistem) Truelab/Truenat MTB (Molbio) Xpert Ultra/Omni platform (Cepheid)	TB LAMP (Eiken)	
	CELLULAR RESPONSE-DETECTION/LATENT AND LATENT TO ACTIVE PROGRESSION			
	T-Track TB (Lophius) TAM-TB (LMU/Alere) ESAT-6/CFP-10 skin test (SSI)		QuantiFERON-TB PLUS (Qiagen) Diaskin (Generium)	
BREATH BIOMARKER-DETECTION				
BreathLink (Menssana) Prototype breathalyzer (Next Dimensions Tech) TB Breathalyser (Rapid Biosensor Systems) Aeonose (The eNose Company) Breath analysis instrument (Metabolomx)				
AUTOMATED MICROSCOPY & IMAGING-DETECTION				
TBDx (Applied Visual Sciences) Fluorescent microscopy (ID-FISH Tech.) Automatic TB Screener (Fluorobot) Cellscope (UCSF)	Microimager (BD) CAD4TB (Delft Imaging Systems)			
Low complexity assays	ANTIGEN, ANTIBODY AND BIOMARKER-DETECTION			
	LAM in sputum (Standard Diagnostics) IRISA-TB-pleural/pericardial/ascitic fluid (Antrum Biotec)		Alere Determine TB-LAM in urine (Alere)	
ENZYMATIC-DETECTION/DST				
β-lactamase reporter (Global BioDiagnostics)				





Roadmap for new diagnostics

The overall vision of the New Diagnostics Working Group's Strategic Framework 2016–2020 is to achieve early and universal diagnosis of people with all forms of TB, and to foster progress towards TB elimination by making appropriate and affordable diagnostic solutions available at the right setting and ensuring that diagnostic results are linked to treatment.

THE FRAMEWORK SETS THE FOLLOWING GOALS AND CORRESPONDING DIAGNOSTICS THAT WILL BE REQUIRED TO REACH THE GOAL OF ENDING TB BY 2035:

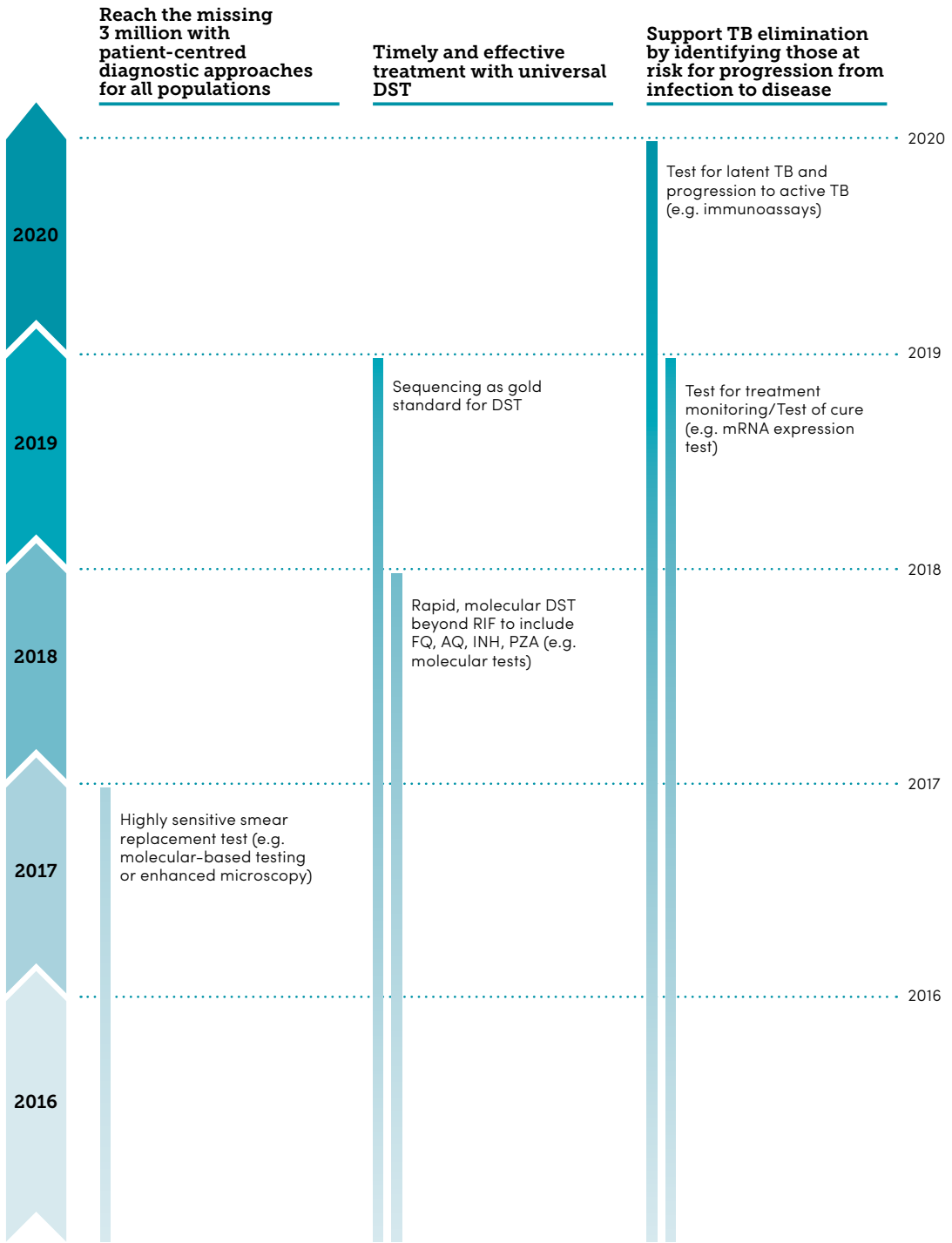
- 1** Reduce the current gap of 3 million cases missed each year and improve TB case detection. This will require a range of tests that can be used in a patient-centred fashion and deployed at all levels of the health care system, including at the point of care, for all populations, including children and those living with HIV. It will also require innovative diagnostic strategies to ensure better outreach to people with TB.
- 2** Enable timely and effective treatment to reduce mortality and ongoing transmission, and prevent antimicrobial resistance by ensuring universal access to DST. This will require rapid and simple tests for the detection of drug resistance to existing and future drugs in decentralized settings, as well as tests to assess response to therapy and cure.
- 3** Support the goal of disease elimination by addressing the reservoir of TB infection and efficiently introducing targeted preventive therapy. This will require tests for predicting the risk of progression from latent infection to active TB disease.

The milestones, major activities, and costs of the New Diagnostics Strategic Framework are summarized in Annex 5.¹

The timelines in Fig. 6.3 indicate when evidence for different types of tests could be available for policy review during the period of the Global Plan, provided that sufficient funding is available.

¹ www.stoptb.org/global/plan/plan2/annexes.asp

FIGURE 6.3. PRIORITY NEEDS UNTIL 2020 REQUIRED TO ACHIEVE THE END TB STRATEGY.



The timelines indicate when evidence for different types of assay could be available for policy review in the period of the Global Plan (provided that sufficient funding is available)



To focus efforts on the three goals listed above, the TB community has agreed on a set of target product profiles (TPPs), defining the performance and operational characteristics that the tests should meet in order to respond to the needs of target populations.

THE HIGH-PRIORITY TPPS ADDRESSING CATEGORIES 1 AND 2 ARE:

- 1** a point-of-care non-sputum-based test capable of detecting all forms of TB by identifying characteristic biomarkers or biosignatures (biomarker test);
 - 2** a point-of-care triage test that should be a simple, low-cost test to be used by first-contact health care providers to identify those in need of further testing (triage test);
 - 3** a point-of-care sputum-based test to replace smear microscopy for detecting pulmonary TB (smear-replacement test);
 - 4** a rapid drug-susceptibility test that can be used at the microscopy-centre level of the health care system to select first-line regimen-based therapy (rapid DST).
-

The biomarker-based test has been identified as the one most urgently needed. As it is difficult to obtain sputum samples from children, such a test would greatly facilitate the diagnosis of childhood TB and have significant benefits for young patients. The TPP therefore considers specific test characteristics to address the needs of children.

To address the diagnostics in category 3, experts are in the process of defining the TPP and the design of clinical trials aimed at the evaluation of a predictive test for the progression of latent TB infection.

The TB community has also expressed the need to ensure the affordability of new diagnostic tools, as well as the need to develop additional tests to identify difficult-to-diagnose patients (e.g. children, people living with HIV and people with extrapulmonary TB).

Overall, in order to ensure the greater impact of new diagnostic tests, comprehensive packages of supporting tools will have to be developed

and delivered together with new technologies in a solution-based approach. These will include innovations in sample transportation and connectivity solutions, such as e-health and m-health solutions, to help increase the number of notified cases, along with the improved use of molecular tools for the confirmation of results.

In addition to developing individual tools, it will also be important to develop effective and efficient diagnostic algorithms that synchronize technologies in implementation plans, and for new diagnostics and drug regimens to be implemented together.



Making strides: Objectives

The New Diagnostics Working Group's Strategic Framework includes four main objectives for the 2016–2020 period.

THESE OBJECTIVES ARE DESIGNED TO GUIDE PROGRESS TOWARDS THE OVERALL GOALS:

OBJECTIVE 1

To ensure that critical knowledge is available to enable the development of new diagnostic tools and solutions, including alternative approaches to case finding;

OBJECTIVE 2

To develop a portfolio of new diagnostic tools coupled with a package of accompanying solutions to ensure that results translate into patient treatment;

OBJECTIVE 3

To evaluate the portfolio of new diagnostic tools and solutions, including new detection strategies, approaches for optimized use, and innovative delivery mechanisms, in order to demonstrate patient benefits and predict the likely impact for entire health systems and populations;

OBJECTIVE 4

To ensure that fully validated new diagnostic tools and solutions are widely available and appropriately used in endemic countries.

The Framework's objectives and key supporting activities are summarized in Annex 5.¹

¹ www.stoptb.org/global/plan/plan2/annexes.asp

New vaccines: Progress report

Thirteen vaccine candidates are currently being tested in clinical trials. In addition, there are promising activities for the development of new biomarkers, and, for the first time in decades, basic information on safety and immune responses to a variety of first-generation TB vaccine candidates is available.

Nevertheless, the next five years will be a critical and challenging period in TB vaccine R&D. Although the clinical pipeline is well populated (see Fig. 6.4), there is a growing concern that it lacks diversity in its immunological strategies and approaches, necessitating a boost in early-stage research. The recent trial of the MVA85A² vaccine in infants showed a lack of

efficacy, demonstrating that much work remains to be done.

Lessons learned from the past 5–10 years of vaccine R&D in TB and other disease areas will help to inform the strategy of the TB field in the period of the Global Plan.

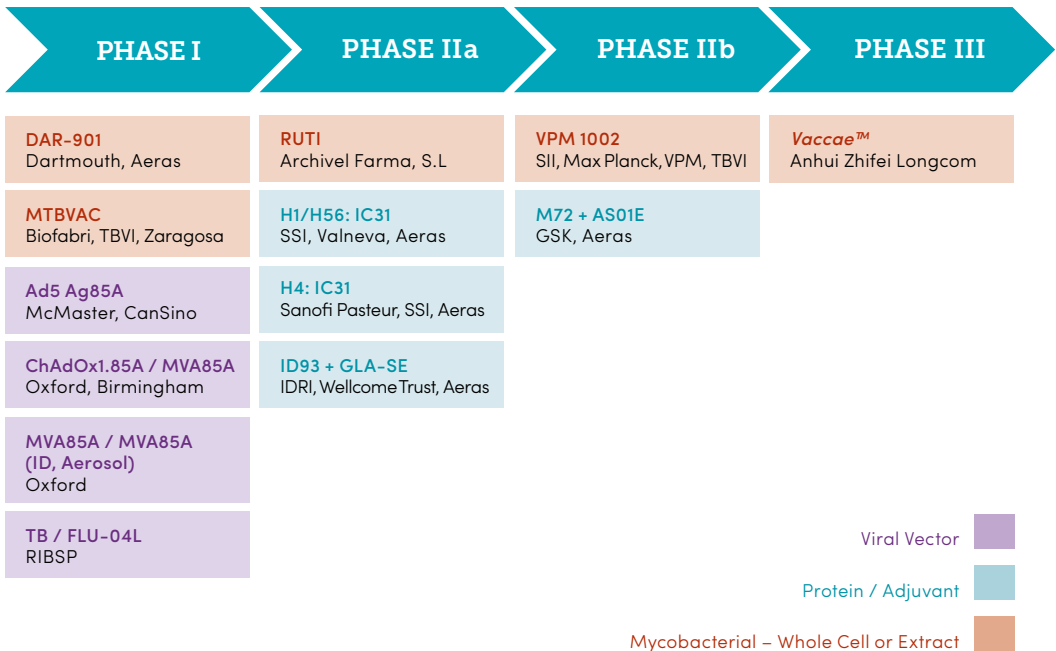
² Tameris M, et al. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. *Lancet*. 2013;381(9871):1021–8.



KEY TAKEAWAYS ARE THAT:

- 1** Success will be dependent on evaluating a diverse portfolio of vaccine candidates that interrogate different aspects of the human host immune response to *M. tuberculosis*.
- 2** It is necessary to reduce the risk of candidates failing at earlier stages of development.
- 3** Robust, high-quality efficacy trials conducted to stringent regulatory requirements have been shown to be feasible in high-burden countries and should be pursued on the most promising candidates.
- 4** Harmonized global portfolio management will help to ensure optimized use of limited resources, prevent duplication of effort, and facilitate collaboration and cooperation. The TB vaccine R&D community has published an agreed set of objective "stage-gate" criteria on which to base Go/No-Go decisions for the advancement of preventive vaccine candidates through development. These will continue to evolve as animal models and our understanding of them are improved and/or as alternate functional assays are developed.

FIGURE 6.4. THE GLOBAL CLINICAL PIPELINE OF TB VACCINE CANDIDATES



The information in the Global Vaccine Clinical Pipeline is as of November 2015, and is reported by vaccine sponsors



Roadmap for new TB vaccines

The core vision that guides the Strategic Framework for New Vaccines 2016–2020 is the development of new, more effective vaccines that will directly and safely prevent TB in all age groups and populations.

To achieve this vision, greater investment is required for TB vaccine R&D, from basic research to clinical trials. There must also be investment in the development of both the scientists and scientific infrastructure necessary to ensure the robust and sustainable development of novel vaccine candidates. Progress will also be greatly facilitated by the creation of bioinformatics platforms and repositories that allow for broad access to the data and analytic tools required to evaluate both preclinical and clinical data.

At a high level, the strategy for vaccine development should focus on four overarching principles:

1. INCREASING FOCUS ON EARLY-STAGE RESEARCH TO IMPROVE THE DIVERSITY OF IMMUNOLOGICAL STRATEGIES AND APPROACHES IN THE CLINICAL PIPELINE.

This will include developing novel study designs, broadening preclinical approaches and antigen selection strategies, and developing evaluation strategies for new TB vaccine candidates that move forward into clinical trials.

2. FOCUSING ON ADOLESCENTS AND ADULTS AS AN INITIAL TARGET POPULATION.

New vaccines targeted at adolescents and adults should be prioritized because, while the ultimate goal is a universal vaccine for all age groups, adolescents and adults bear approximately 94% of the disease burden globally and are the major source of TB transmission. Given concerns about the safety of BCG in infants with HIV, efforts to develop vaccines that will be safer and more effective in infants and children than the current BCG should continue to be supported.

3. DEVELOPING VACCINES FOR MULTIPLE INDICATIONS.

Due to the complex interaction of humans with the bacteria that cause TB, a preventive vaccine might work in any one or more of the following ways: the vaccine could prevent infection of a healthy person altogether; it could prevent latent TB infection from progressing to active TB disease; and it could protect those already infected from getting re-infected. New vaccines that could be used as an adjunct to chemotherapy to shorten treatment, known as therapeutic vaccines, are also under development.

4. EXPLORING NEW VACCINE DELIVERY PLATFORMS.

Researchers and product developers are working to develop new delivery systems and platforms, including a needle-free delivery system and vaccines that do not require a cold chain, in order to overcome key challenges in vaccine delivery.

Advancing the vaccine pipeline and expanding the portfolio

Given the knowledge gaps and financial and infrastructural constraints that exist, advancing the vaccine pipeline will require a globally harmonized portfolio management structure that employs specific, rigorous criteria for stage-gating – a process for deciding whether a vaccine proceeds to the next stage of development.

THE KEY OBJECTIVES ARE AS FOLLOWS:

OBJECTIVE 1

CONTINUE TO ADVANCE THE CLINICAL PIPELINE OF TB VACCINE CANDIDATES. This includes conducting clinical trials, exploring novel trial designs to identify promising vaccines, ensuring sufficient manufacturing and trial site capacity, and conducting epidemiological research at trial sites to optimize site selection and clinical trial design.

OBJECTIVE 2

ENHANCE KNOWLEDGE THROUGH EXPERIMENTAL MEDICINE. Several small, early-phase human studies of TB vaccine concepts should address specific scientific hypotheses and provide data to inform future vaccine development.

OBJECTIVE 3

INCREASE EMPHASIS ON EARLY-STAGE AND DISCOVERY RESEARCH. Increased investment and focus on early-stage research, including the development of novel vaccination targets, will be essential to diversifying the TB vaccine portfolio, enhancing the knowledge and understanding of the pathogen, and identifying breakthroughs that will advance the field and accelerate the TB vaccine R&D process.

OBJECTIVE 4

IMPROVE ANIMAL MODELS. Refined animal models that better mimic human disease and/or reflect natural TB transmission, and allow for the preclinical readout of vaccines that are possibly capable of preventing sustained infection, will be essential to the development of new and improved vaccines.

OBJECTIVE 5

IMPROVE PRECLINICAL AND CLINICAL READOUTS, STANDARDIZING REAGENTS AND HARMONIZING ASSAYS. This should include the use of advanced imaging in conjunction with immunological and transcriptional profiling in order to better define correlates of protective immunity.

OBJECTIVE 6

LAY THE GROUNDWORK FOR ADOLESCENT AND ADULT VACCINATION CAMPAIGNS. This involves conducting strategic access and implementation research, including studies of cost-of-goods, TB cost-effectiveness, country vaccine readiness, and vaccine landscape.

The milestones, major activities, and costs of the Strategic Framework for New Vaccines are summarized in Annex 5¹:

¹ www.stoptb.org/global/plan/plan2/annexes.asp

Developing access strategies for new tools

Access strategies for new drugs

The process of taking an interesting molecule ('hit') through to the next stage of development can be challenging. Similarly, the entire spectrum of research and development of new TB drugs is extremely challenging, both technically and financially. Research institutions are under-resourced, and not enough pharmaceutical companies are investing in research and/or development

within their business plans, further slowing the advancement of potential novel candidates into the commercial realm. Furthermore, the global infrastructure required for the responsible stewardship of new drugs needs to be strengthened. Research-based incentives, regulatory harmonization, and multi-faceted public and private cooperation in the discovery, development, delivery, support and maintenance of new drugs and regimens are therefore to be encouraged and supported.

Improving the way we work together to bring TB drugs to people with TB

Ideally, clinical development needs to be accompanied by the further expansion of trial capacities in TB-endemic countries, preferably with the involvement of representatives from the affected communities: investigative researchers, physicians, nurses and statisticians. Several NGOs play important roles in strengthening TB programmes and improving early access to new tools; the TB Alliance and the National Institute of Allergy and Infectious Diseases (NIAID) play important roles in product development research. In addition, there are umbrella organizations such as the Critical Path to TB Drug Regimens (CPTDR), which are playing an increasingly important role in coordinating a variety of activities. It is important that the communities in which clinical trials will be conducted are fully engaged, as laid out in the Good Participatory Practice Guidelines for TB Trials.¹

A frequent obstacle to accessing drugs is the lack of transparency in the registration of new drugs. There is often no forum for interaction or discussion between the drug sponsor applicant, regulatory authorities, and communities in the registration process. The present lack of regulatory harmonization has resulted in a staggered, country-by-country approval procedure

for new TB drugs, resulting in deadly delays. Regulatory harmonization could streamline the process from clinical development to regulatory submission and regional approval. This process should be accompanied by WHO-issued guidance as a prelude to country policy setting and adoption.

It is important to understand barriers to patient access. Compassionate use programmes offer a good example of providing early access to life-saving drugs during the development stage. The supply chain must be better coordinated and strengthened, ensuring reliable and high-quality supply through organizations such as the Global Drug Facility (GDF). Better forecasting and availability of stockpiles would improve manufacturing and distribution inefficiencies in order to avoid stock-outs. The costs and energy associated with these aspects are underestimated and need to be addressed in order to make scale-up and product introduction successful. This cannot be achieved without engaging local communities

Access strategies for new TB diagnostics

Adoption of a test does not necessarily result in increased case notifications or the augmentation of the number of patients treated.

The introduction of Xpert MTB/RIF has made it clear that additional effort in implementation – not just the improvement of diagnostic technology – is needed to efficiently integrate innovative assays into existing, interdependent health care procedures.

Appropriate integration of new diagnostic solutions in the broader health system will require country-specific solutions, with several common measures to build capacity for the appropriate scale-up of new tools. These include the provision of training and other technical assistance; improved quality assurance; monitoring of supply; TB/HIV laboratory integration; reinforcement of e-health solutions; better integration of

¹ Critical Path to TB Drug Regimens. Good participatory practice: guidelines for TB drug trials; 2012 (<http://www.cptrinitiative.org/downloads/resources/GPP-TB%20Oct11%202012%20FINAL.pdf>).



the private sector; planning and budgeting for technical support and maintenance; and reduction of pricing through improved manufacturing and efficient supply-chain management. Such efforts should provide comprehensive support at the country level and enable ministries of health to develop national guidelines and implementation plans.

In addition, operational research is needed to guide the implementation of patient-centred use and, ultimately, to improve the impact on patient outcomes across the wide variety of settings into which each new diagnostic test must be integrated. These improvements will, in turn, create market incentives by reducing the investment risks for developers. Finally, harmonized regulatory and registration frameworks for diagnostics for high-priority diseases such as TB are needed.

Access strategies for new TB vaccines

TB vaccine R&D and vaccine administration and delivery must be considered together from the outset in order to achieve maximum health impact, particularly in new populations. New TB vaccines targeted at adolescents and adults are most likely to have the greatest overall impact on the global epidemic, but present greater challenges for access. New and innovative public health programmes can take decades to implement, and the challenges surrounding adolescent and adult vaccination are complex.

To effectively address this gap in adolescent and adult immunization structure and programmes, comprehensive 'strategic access' implementation research is needed through 2020.

Research, including evaluations and studies of cost-of-goods, pricing criteria, target product profile (TPP) cost-effectiveness, country vaccine readiness, and vaccine landscape, will identify the factors to facilitate efficient implementation and overcome the barriers to adolescent and adult vaccination. It will also be important to understand the programmatic suitability for prequalification (PSPQ) early in the development process, so that licensed products will likely be preapproved for procurement by GAVI Alliance and UNICEF.

It will also be important to identify and advocate for broader programmatic approaches that may target the adolescent and adult age group, such as administration along with the human papillomavirus and potentially herpes simplex virus, when a vaccine is available.

Global access for new TB vaccines must integrate evidence, technology, policy, funding, and, later, global and country politics. End users, communities, physicians and national TB programmes should be actively engaged in this process. These activities will help to ensure the alignment and smooth transition of new vaccines from R&D to worldwide markets in order to achieve maximum public health impact.

Advocacy and community engagement for new tools

Ending TB can only be achieved if there is a massive increase in global awareness about the scale of the TB problem and the measures required to address it, including the development and implementation of new tools. Strengthened advocacy efforts to raise awareness are therefore an essential part of reaching the End TB milestones. Specific steps include:

SUPPORT FOR ADVOCACY FUNDING. Funders of R&D for new TB tools should recognize advo-

cacy as an integral part of research activities for which they should reserve dedicated



funds. Particular emphasis should be placed on strengthening R&D advocacy by in-country networks of activists in high-burden countries.

STRENGTHENING OF COMMUNITY ENGAGEMENT IN RESEARCH (see Chapter 4). Engaging with communities in all aspects of R&D will create new groups of advocates who can effectively communicate the benefits of TB R&D to governments, regulatory authorities, funders and other institutions.

INCLUSION OF ADVOCATES IN DECISION-MAKING STRUCTURES AND SCIENTIFIC FORUMS. Framework gatherings such as global meetings, research conferences, and policy meetings that direct funding should include community and civil society representatives in governance roles, and should offer scholarship opportunities, travel support, or advocacy and civil society abstract tracks.

Specific milestones for advocacy for new tools are provided in Annex 5¹.

¹ www.stoptb.org/global/plan/plan2/annexes.asp





7. RESOURCE NEEDS

KEY MESSAGES

- ✦ Significantly increased upfront investments are urgently needed in order to hit the End TB Strategy milestones and the 90-(90)-90 targets. Over the next five years, a total of US\$ 56 to 58 billion is needed to implement TB programmes, and another US\$ 9 billion is needed to fund R&D for new tools.
 - ✦ By implementing the Global Plan’s standard investment scenario, countries will reach the 2020 End TB Strategy milestones, prevent 38 million people from falling ill with TB and saving 8 million lives. The return on investment would be US\$ 27 for each dollar invested.
 - ✦ Implementing the accelerated investment scenario would achieve even greater impact by 2020, preventing 45 million people from getting ill with TB and saving 10 million lives. The return on investment for the accelerated investment scenario would be US\$ 85 for each dollar invested.
 - ✦ For Global Fund-eligible countries, with even the most optimistic domestic funding forecasts and with external funding maintained at current levels, an additional US\$ 7.4 billion must be mobilized in order for countries to reach the 2020 milestones.
 - ✦ While the bulk of these investments should come from domestic resources and international donors, the mobilization of alternative funding sources – social impact bonds, micro levies or taxes, and pooled donor trusts – could dramatically accelerate the pace of scale-up.
 - ✦ Continuing with current levels of investment and effort is not an option, as it will miss the 2020 End TB Strategy milestones and also result in escalating future costs.
 - ✦ New tools will be essential to meeting the milestones of the End TB Strategy. Delaying investment in these new tools, even by one year, will have a significant impact on the future in terms of lives lost, infections and disease not prevented, increased treatment costs, and lost productivity.
-

Investment requirements to achieve the 90-(90)-90 targets

A significant increase in resources for both current interventions and new tools is needed in order to reach the 90-(90)-90 targets. If these funds are mobilized, the benefits will be dramatic – both in human and economic terms. Over the next five years, a total of **US\$ 56 to 58 billion** is needed for implementing TB programmes, and **US\$ 9 billion** is needed for R&D for new tools.

Fig. 7.1 shows the resource needs for implementing the TB response globally, in non-OECD countries, and in countries eligible for Global Fund financing. The resource needs in non-OECD countries are estimated at US\$ 51.9 billion,

while the resource needs in countries eligible for Global Fund financing are estimated at **US\$ 29.4 billion** over the 2016–2020 period.

FIGURE 7.1. GLOBAL RESOURCE NEEDS FOR IMPLEMENTATION 2016–2020

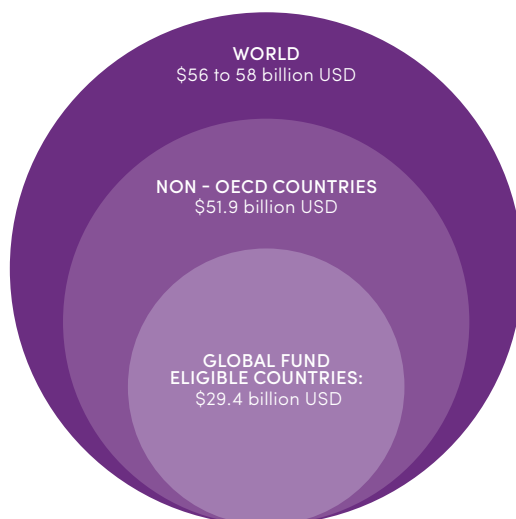


Fig. 7.2 shows the projected global funding needs over the next five years to reach the Global Plan’s 90–(90)–90 targets.

Two investment scenarios are considered: standard and accelerated. In the standard investment scenario, investments increase gradually at a level sufficient to set the world on course to reach the 90–(90)–90 targets by 2025. This level of investment will be just enough to ensure that the 2020 End TB Strategy milestones are reached.

In the accelerated investment scenario, investment increases sooner, setting the world on course to reach the 90–(90)–90 targets by 2020 and exceed the End TB Strategy milestones.

These two investment scenarios are presented in comparison to a baseline, where efforts to fight TB continue at their current levels. As shown in Fig. 7.2,

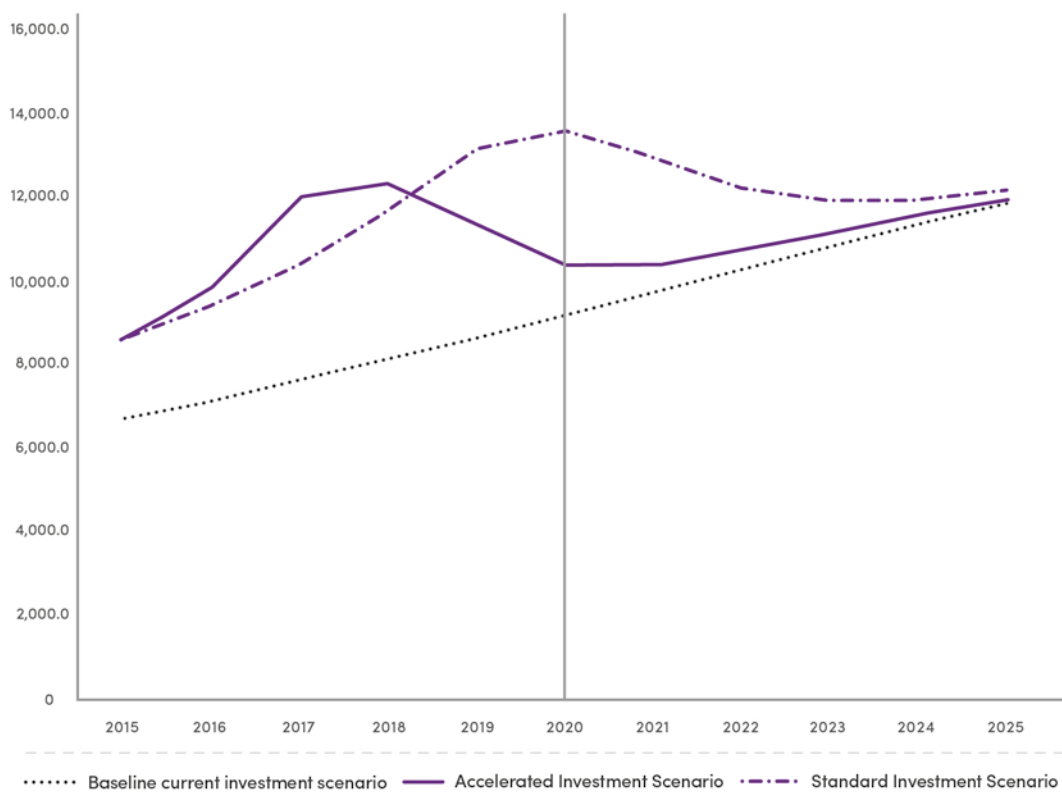
in 2015, there is already a gap of approximately US\$ 2 billion a year between TB budgets and the amount of funding available.

Without any scale-up (i.e. remaining at baseline), annual costs are expected to follow the trend of the past five years, steadily increasing from around US\$ 6.7 billion in 2015 to around US\$ 8.6 billion by 2020.

In the standard investment scenario, annual costs steadily increase to a peak of US\$ 13.6 billion in 2020 before declining and then resuming a gradual increase in line with the baseline.

In the accelerated investment plan, the funding required increases more quickly, then decreases sharply after reaching a peak in 2018. This peak of US\$ 12.4 billion is lower than in the standard investment plan.

FIGURE 7.2. RESOURCE NEEDS FOR THE GLOBAL TB RESPONSE (IN US\$ MILLIONS): STANDARD INVESTMENT SCENARIO, ACCELERATED INVESTMENT SCENARIO, AND BASELINE CURRENT INVESTMENT SCENARIO.



Three conclusions can be drawn from the cost predictions depicted in Fig. 7.2.

First, without any scale-up, the baseline cost of TB would increase steadily due to the large number of people still requiring TB care, combined with increasing costs per case.

Second, in both the standard and accelerated investment scenarios, **countries that accelerate their efforts to find and treat people with TB would see the increases in upfront costs pay off, as less investment would be needed over time.** This decline is due to the reduced number of people needing TB care and lower imple-

mentation costs (compared to future years).

Third, **the most ambitious scenario is also the most cost-effective** in the long run. Implementing the accelerated investment scenario would lead to a much earlier reduction in the number of people becoming ill with TB, resulting in more dramatic cost savings compared to the standard investment scenario.

In the accelerated scenario, the total investment in TB in the year 2020 would be about US\$ 10.5 billion, only US\$ 1.2 billion or 13% more than in the baseline scenario where no scale-up is implemented at all. As described later in this

chapter, the accelerated scenario would also significantly increase the number of lives saved and return on investment in the period covered by the Global Plan.

Tables 7.1 and 7.2 show the total financial resource requirements for the period 2015–2020, broken

down by countries' income status, eligibility for Global Fund financing, and Global Plan country setting. Table 7.1 shows the resource requirements for the standard investment scenario, and Table 7.2 shows the resource requirements for the accelerated investment scenario.

TABLE 7.1. TOTAL RESOURCE REQUIREMENTS FOR THE STANDARD INVESTMENT SCENARIO (US\$ BILLIONS).

	2016	2017	2018	2019	2020	Total
GLOBAL TOTAL						
Total (Global, including OECD countries)	9.5	10.4	11.7	13.2	13.6	58.4
Total (Global, excluding OECD countries)	8.3	9.2	10.4	11.8	12.2	51.9
BY INCOME STATUS						
Low income	0.9	1.0	1.3	1.6	1.7	6.5
Lower-middle income	2.2	2.5	2.9	3.4	3.5	14.4
Upper-middle income	2.5	2.7	2.9	3.2	3.3	14.6
High income	3.8	4.2	4.7	5.0	5.2	22.9
GFATM ELIGIBLE COUNTRIES, BY INCOME STATUS						
Low income	0.9	1.0	1.3	1.6	1.7	6.5
Lower-middle income	2.2	2.5	2.9	3.4	3.5	14.4
Upper-middle income	1.5	1.6	1.7	1.8	1.9	8.5
Total	4.6	5.1	5.8	6.8	7.1	29.4
GLOBAL PLAN COUNTRY SETTINGS						
High MDR burden, Centralized Care	3.9	4.2	4.6	5.0	5.1	22.7
High TB/HIV, SADC	0.9	1.0	1.1	1.2	1.2	5.4
High TB/HIV, non SADC	0.5	0.6	0.7	0.9	1.0	3.7
Moderate Burden, COE	0.2	0.3	0.3	0.4	0.5	1.7
High Burden, Private Sector	0.9	1.1	1.3	1.7	1.7	6.7
Moderate Burden, Middle Income	0.7	0.8	0.9	1.0	1.0	4.4
India	0.6	0.6	0.7	0.8	0.7	3.4
China	0.5	0.6	0.7	0.7	0.8	3.3
Low Burden, High Income	1.2	1.3	1.5	1.5	1.5	7.1
BRICS (BRA, CHN, IND, RUS, ZAF)						
Total	4.4	4.9	5.4	6.0	6.2	26.9

TABLE 7.2. RESOURCE REQUIREMENTS FOR THE ACCELERATED INVESTMENT SCENARIO (US\$ BILLIONS)

	2016	2017	2018	2019	2020	Total
GLOBAL TOTAL						
Total (Global, including OECD countries)	9.9	12.0	12.4	11.4	10.4	56.1
Total (Global, excluding OECD countries)	8.7	10.8	11.2	10.2	9.4	50.3
BY INCOME STATUS						
Low income	1.0	1.6	1.6	1.4	1.2	6.8
Lower-middle income	2.4	3.2	3.3	2.9	2.5	14.3
Upper-middle income	2.6	2.9	2.8	2.7	2.5	13.5
High income	3.9	4.4	4.6	4.4	4.2	21.5
GFATM ELIGIBLE COUNTRIES, BY INCOME STATUS						
Low income	1.0	1.6	1.6	1.4	1.2	6.8
Lower-middle income	2.4	3.2	3.3	2.9	2.5	14.3
Upper-middle income	1.6	1.8	1.8	1.7	1.6	8.5
Total	5.0	6.6	6.7	6.0	5.3	29.6
GLOBAL PLAN COUNTRY SETTINGS						
High MDR burden, Centralized Care	4.0	4.5	4.6	4.5	4.3	21.9
High TB/HIV, SADC	1.0	1.2	1.2	1.1	1.1	5.5
High TB/HIV, non SADC	0.6	0.8	1.0	0.8	0.7	3.9
Moderate Burden, COE	0.3	0.5	0.5	0.4	0.3	1.9
High Burden, Private Sector	1.0	1.5	1.6	1.4	1.2	6.7
Moderate Burden, Middle Income	0.8	0.9	0.9	0.8	0.7	4.1
India	0.6	0.8	0.7	0.6	0.6	3.3
China	0.5	0.5	0.5	0.5	0.5	2.5
Low Burden, High Income	1.3	1.4	1.3	1.2	1.1	6.3
BRICS (BRA, CHN, IND, RUS, ZAF)						
Total	4.5	5.3	5.4	5.2	4.9	25.3

The methodology for estimating the cost of reaching the 90-(90)-90 targets is presented in Annex 6.¹

Fig. 7.3 shows the disaggregation of total costs by

category over the five-year period.

The health system category (20% of total) includes hospitalization and ambulatory care costs, together with distribution costs related to TB commodities.

¹ www.stoptb.org/global/plan/plan2/annexes.asp

The anti-TB drugs, both first line (FL) and second line (SL), and diagnostics category (13%) includes costs of first-line and second-line drugs, diagnostics for drug-susceptible and drug-resistant TB, and treatment monitoring tests.

Drug resistant TB (DR-TB) case management (12%) includes all costs related to the management of people with MDR-TB and XDR (excluding anti-TB drugs, diagnostics for DR-TB, and health systems).

TB/HIV collaboration (3%) includes TB/HIV coordinating bodies, joint training and planning, HIV testing for TB patients, TB screening for people living with HIV, isoniazid preventive therapy, and

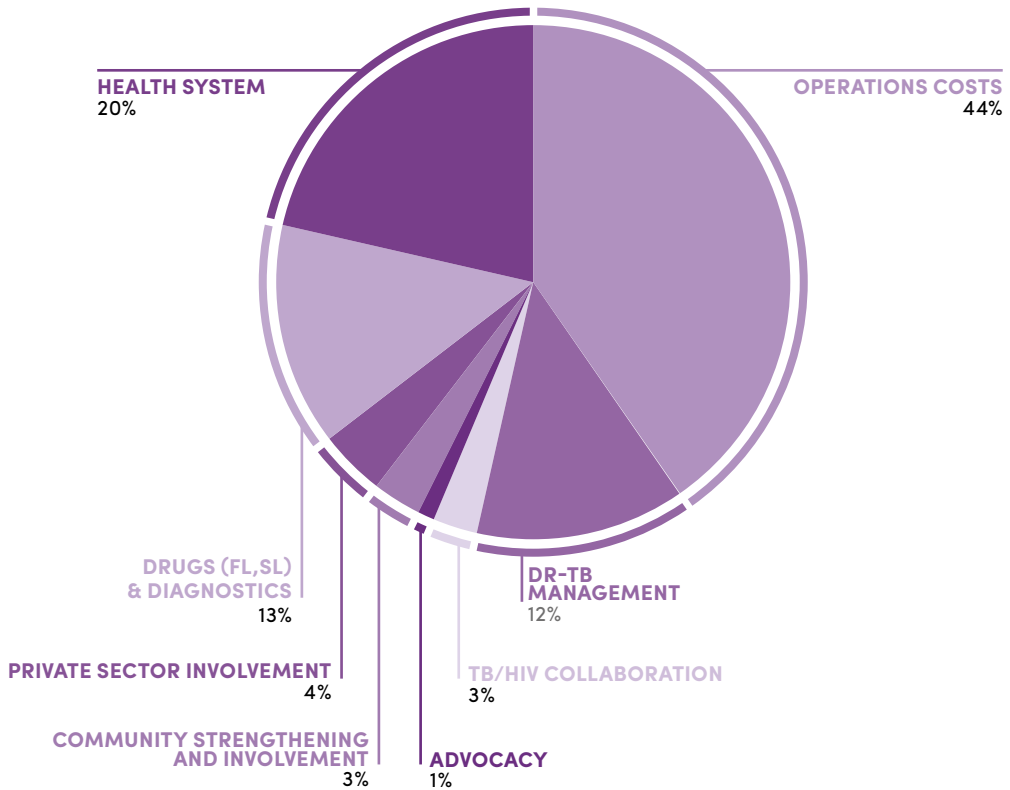
joint TB/HIV information and education. It does not include ART.

Community systems strengthening and community involvement at all levels (3%) represents activities related to community involvement, community TB care, the strengthening of community-based organizations and patient groups, policy development, incentives, and enablers.

Four percent of the budget is allocated to the private health sector.

The advocacy category (1%) represents funding estimates needed for advocacy work at the global, regional and national levels.

FIGURE 7.3. DISAGGREGATION OF COSTS FOR THE STANDARD INVESTMENT PLAN (NON-OECD COUNTRIES)



Several cost categories have been grouped together under “Operations Costs” (44%) due to limitations in data availability and precision. Operational costs include human resource costs, transport and facilities, monitoring and evaluation, training, operational research, surveys, overall programme management, etc.

As described in Annex 6¹, several cost categories are expected to increase, especially the categories of community system strengthening and private sector engagement, which are expected to reach 5% in 2020 at the global level.

Costing approach and limitations

To calculate costs, the Global Plan draws from financial data reported by countries to WHO (described in detail in Annex 6)¹. The costing approach is subject to certain limitations. The manner in which the different cost categories are bundled together (see above) and reported

to and by WHO varies. Furthermore, the costing for the period 2016–2020 does not factor in the introduction of new diagnostics or drugs to come.

To overcome these limitations, a global approach has been used, adjusting the growth rates of different types of unit costs. The decline in resource requirements shown after 2020 is linked to the decline in TB burden. However, this prediction needs to be interpreted with caution due to uncertainties around the availability and cost of new tools.

Going forward, the Global Plan recommends more robust collection of financial data from national TB programmes, national health accounts, and international development partners, along with increased investment in tracking and improving unit costs, costs of new interventions, and domestic investments. In addition, the different cost categories should be disaggregated at the point of data collection for a better understanding of the financial implications.

¹ www.stoptb.org/global/plan/plan2/annexes.asp

What will the Global Plan achieve?

Lives saved and cases averted

The impact modelling carried out for the Global Plan shows that implementing the standard investment scenario would set countries on track to achieve the 2020 End TB milestones – a 20% reduction in the number of people becoming ill with TB and a 35% reduction in deaths from TB – in just five years. The modelling also demonstrates that an accelerated investment scenario would have an even more dramatic epidemiological impact.

The standard and accelerated investment scenarios would treat 32 and 29 million people for TB, respectively. Less people will be treated in the accelerated investment scenario because of more rapid decline in incidence.

Implementing the standard investment scenario would prevent 38 million people from having TB and save 8 million lives when compared to no TB-related care.

The accelerated scenario would have even greater impact, preventing 45 million people from falling ill with TB and saving 10 million lives.

Given the cost-effectiveness of front-loading investments and the additional lives saved, the Global Plan's clear recommendation is for countries to fund and implement the accelerated investment scenario.

Reducing the burden of disease on society

The Global Plan has calculated the number of DALYs – a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death – that would be averted by achieving the 90-(90)-90 targets.

The DALYs averted were calculated using the TIME model and a standard life expectancy of 82.5 years for women and 80 years for men. The calculation was applied to 12 countries that represent about 50% of the world's population and TB burden, and an extrapolation method was used to estimate DALYs averted for the remaining countries.

The results are shown in Table 7.3. Implementing the standard investment scenario would avert an additional 51.2 million DALYs. The accelerated investment scenario would more than double that impact between 2016 and 2020, averting 144.7 million DALYs.

TABLE 7.3. DALYS AVERTED BY COUNTRY SETTING AND GLOBALLY

Country Settings	Standard investment plan	Accelerated investment plan
	Additional DALYs Averted	Additional DALYs Averted
High MDR burden, Centralized Care	900	2700
High TB/HIV, SADC	7800	21 000
High TB/HIV, non SADC	13 100	37 400
Moderate Burden, COE	4700	13 400
High Burden, Private Sector	10 700	31 100
Moderate Burden, Middle Income	1300	3700
India	10 600	30 400
China	2000	4800
Low Burden, High Income	80	200
Global (thousands)	51 180	144 700

Return on investment

When a TB programme provides people with effective treatment – preventing death and disability – these people receive spillover economic benefits. First, it is possible that the prevention of TB may save household expenditures on health care. Second, when TB is prevented (or effectively treated), household members are able to continue or resume productive work.

Although disease programmes can thus bring real economic gains to households, they do not necessarily translate into large gains at the societal level. In many TB-affected countries, high levels of unemployment complicate this equation. For example, if a worker dies or leaves the workforce due to disability, his or her household may be worse off, but another person who steps into the job may be better off. Consequently, society as a whole may not suffer from the loss of the first worker.

Similarly, comparing countries’ economic status using GNI per capita alone misses important aspects of social welfare, such as life expectancy. The Global Health 2035 Lancet Commission¹ has developed another way to measure return on investment. The method assigns a “monetary value” to health gains based on the “full income” approach to measuring a society’s economic welfare. In this way, “full income” accounting monetizes life expectancy gains and combines them with consumption gains to get a fuller picture of improvements in welfare.

To estimate the return on investment of the Plan, a similar method was applied to the nine countries modelled in the Global Plan and extrapolated to the remaining countries in each setting.

To estimate the return on investment projection for the period 2015–2020, the value of life years expressed as multiples of GNI per capita was multiplied by DALYs averted. The results are shown in Table 7.4.

The overall return on investment would be about US\$ 530 billion for the standard investment plan – a return on investment ratio of about 27. The accelerated investment plan would return US\$ 1.2 trillion, or US\$ 85 for each dollar invested.

¹ Global health 2035: a world converging within a generation. Lancet. 2013;382(9908):1898–955 (<http://www.thelancet.com/commissions/global-health-2035>).

TABLE 7.4. RETURN ON INVESTMENT (ROI) ESTIMATES FOR 2016–2020 BY COUNTRY SETTING AND GLOBALLY

By Country Settings	GNI per capita 2013 (AVG)	ROI for standard investment (US\$ millions)	ROI for accelerated investment (US\$ millions)
High MDR burden, Centralized Care	9000	15 000	1700
High TB/HIV, SADC	3200	185 000	7800
High TB/HIV, non SADC	1500	159 000	41 200
Moderate Burden, COE	800	12 000	158 500
High Burden, Private Sector	2400	60 500	41 000
Moderate Burden, Middle Income	8200	16 200	407 200
India	1600	52 900	364 000
China	6700	29 200	52 600
Low Burden, High Income	40 900	3000	134 500
Total	11 000	532 800	1208 500

The return on investment is positive in all country groups, ranging from ratios below 10 in settings such as high-MDR and fragile-state settings, to a ratio of 90 in high TB/HIV settings in SADC countries.

Permanent health systems gains as a result of investing in TB

Investments in TB strengthen health systems permanently, increasing their ability to fight other diseases and outbreaks. This strengthening can be achieved in several ways.

First, investing in early and effective TB diagnosis builds lasting diagnostic, laboratory and case-finding capacity in the health system. TB symptoms are not specific and occur in multiple diseases, and tools such as microscopes and X-rays have manifold uses beyond TB. Efforts to improve early TB case-finding therefore positively impact the early detection of other conditions, particularly those affecting the lungs.

TB laboratory networks are known for establishing standardization and quality assurance processes that can positively impact the quality of public health laboratories across the board. The Global Plan calls for the integration of TB laboratory and diagnostics into health systems and improved access through specimen transportation. It envisages well-integrated TB programmes as a conduit for strengthening health systems for early disease diagnosis.

Second, investments that strengthen contact investigation for TB will create a system that can be reliably called upon during infectious disease outbreaks, such as the Ebola outbreak in West Africa in 2014, which demanded the rapid mobilization of both health facilities and communities to conduct extensive contact investigations.

Third, fighting TB requires investment in airborne infection control practices. Such investment would build the capacity of health systems to quickly respond to other airborne infection outbreaks such as influenza and respiratory syndromes.

Fourth, as TB treatment requires lengthy interaction with patients and communities, TB investments can strengthen overall engagement with these communities to the benefit of other health programmes.

Fifth, lengthy TB treatment demands strong and reliable drug supply chain systems. Further improvements in these systems, and greater integration of these systems into the wider health systems of countries, will directly benefit health systems seeking to improve supply chains for other diseases.

Finally, costs besides commodity-based or direct costs make up a large proportion of the costs. These costs involve laboratory strengthening, the improvement of health system components, and human resource development – all of which have the potential to make a lasting, positive impact on the overall strength of health systems.

The urgent need for funding for research and development

Countries can achieve dramatic gains by scaling up to meet the 90-(90)-90 targets. However, after 2025, existing tools will have a diminishing impact and will no longer be sufficient to bend the epidemic curve of TB steeply enough to meet the milestones of the End TB Strategy.

To sustain momentum and continue progress beyond 2020, new tools – including rapid point-of-care diagnostics, effective short-course drug regimens, and vaccines to prevent infection and disease – are urgently needed.

targets) is required for the research and development of new drugs, diagnostics and vaccines, according to the framework set out in Chapter 6.

US\$ 9 billion (which includes the roll-out of new and existing diagnostics to meet the 90-(90)-90

TABLE 7.5. TOTAL FUNDING REQUIRED FOR THE RESEARCH AND DEVELOPMENT OF NEW TOOLS, 2016–2020

	Objective	(US\$ millions)
NEW DRUGS	Sustaining the pipeline through the basic discovery of TB drugs	1050
	Maintaining trial site capacity	300
	Developing a shorter regimen for DS-TB	1400
	Developing a safer, higher efficacy, shorter regimen for MDR-TB	600
	Improving treatment for children	150
	Developing a safer, higher efficacy regimen for latent TB	90
	Ensuring country adoption of new TB drugs and regimens	500
	Engaging community and civil society in the entire process of drug development and access	65
	Total New Drugs	4155
NEW DIAGNOSTICS	Ensuring that critical knowledge is available and exploring alternative approaches to case finding	281
	Developing a portfolio of new diagnostic tools, coupled with a package of accompanying solutions to ensure that results translate into patient treatment	158
	Evaluating the portfolio of new diagnostic tools and solutions, including new detection strategies, approaches for optimized use, and innovative delivery mechanisms; demonstrating patient benefits; and predicting the likely impact within the health system	165
	Fully validating that new diagnostic tools and solutions are widely available and appropriately used in endemic countries (including roll-out)	2827
	Total New Diagnostics	3431 (including roll-out) 676 (without roll-out)
NEW VACCINES	Continuing to advance the clinical pipeline of TB vaccine candidates	537
	Enhancing knowledge through experimental medicine	220
	Increasing emphasis on early-stage and discovery research	200
	Improving animal models	150
	Improving preclinical and clinical readouts	71
	Laying the groundwork for adolescent and adult vaccination campaigns	12
	Engaging the community	60
	Total New Vaccines	1250
	Advocating and mobilizing resources for new tools	60
TOTAL	With roll-out of diagnostics	8836
	Without roll-out	6081

Many factors will impact the costs of R&D, such as new research findings, the evolving pipeline of new tools, and manufacturing complexity. Funding requirements will continue to evolve as new discoveries are made, results from pre-clinical and clinical research inform decisions, and new models and advances in knowledge streamline the R&D process.

The cost of inaction: What is the result of underfunding research and development?

One way to conceptualize the importance of upfront investment in new tools is to estimate the cost of inaction. This complacency is defined as the cost of future TB treatment and lost productivity that would accrue if the world achieved the 2020 milestones of the End TB Strategy, but failed to make the necessary investments in new tools between 2016 and 2020.

In order to estimate the cost of inaction, a series of simplifying assumptions are required:

- ✦ The annual percentage declines in TB incidence and mortality that were achieved without new tools in order to reach the 2020 milestones will continue through to 2030.

- ✦ Five years after the investment in new tools begins, the decline in incidence and mortality will increase steadily and to a degree sufficient to achieve the 2030 milestones. The impact of new tools is therefore only slowly realized over time – with greater impact in 2030 than in 2020.
- ✦ The cost of TB treatment will not increase above 2013 levels.
- ✦ A 3% annual discount rate is applied to all costs and DALYs, thereby reducing the value of future savings in costs and productivity (although undiscounted costs and outcomes are also presented).
- ✦ Health utility losses from TB are assumed to scale with TB mortality, and a standardized conversion is made of 41 DALYs averted per TB death averted (the ratio estimated by the 2010 Global Burden of Disease study).¹

Despite the conservative nature of these assumptions, the estimated cost of complacency is tremendous (see Fig. 7.4).

¹ Global burden of diseases, injuries, and risk factors study. Lancet (<http://www.thelancet.com/global-burden-of-disease>).

BY 2030, A FIVE-YEAR DELAY IN INVESTMENT FOR NEW TOOLS IS ESTIMATED TO RESULT IN:

- | | |
|--|--|
| <p>1 8.4 MILLION ADDITIONAL TB CASES</p> | <p>4 US\$ 5.3 BILLION IN ADDITIONAL COSTS FOR TB TREATMENTS
(US\$ 7.5 billion without discounting)</p> |
| <p>2 1.4 MILLION ADDITIONAL TB DEATHS</p> | <p>5 US\$ 181 BILLION IN LOST PRODUCTIVITY (US\$ 318 billion without discounting), valuing each DALY at per-capita GNI.</p> |
| <p>3 39.8 MILLION DALYs SUFFERED
(56.1 million without discounting)</p> | |

Thus, the total cost of complacency is estimated to be more than US\$ 185 billion. These costs are expected to increase even further beyond 2030. Even a one-year delay in investment after

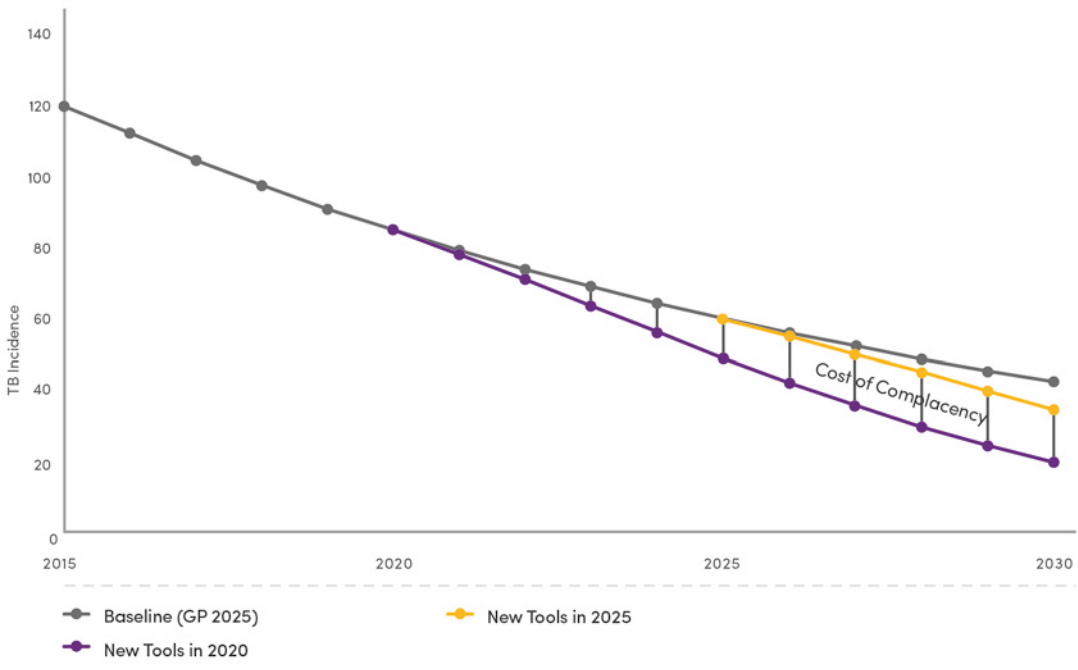
2016 would carry a tremendous cost: 2.4 million people having TB; 390 000 TB-related deaths; US\$ 1.6 billion in TB treatment costs (US\$ 2.2 billion without discounting); 11.6 million DALYs

(16.0 million without discounting); and US\$ 54 billion (US\$ 91 billion without discounting) in lost productivity.

It is certain that we cannot end the TB epidemic with the tools that we have today. And every day the epidemic continues to rage, the human and

economic costs only increase. To avert these costs, it is imperative that we urgently and rapidly scale up investments in new diagnostics, drug regimens and vaccines today. Delaying that investment by even one year could result in billions of dollars in additional treatment costs alone.

FIGURE 7.4. THE COST OF FAILING TO INVEST IN NEW TOOLS



Sources of funding for the Global Plan

The “global public goods”¹ nature of most of the TB investments makes it a priority for funding with a wide societal benefit. There are three broad sources of funding for implementation and research: domestic funding, external funding and innovative financing.

1 “Global public goods” are defined as those goods that are both “non-rival” (i.e. anyone can consume the good without affecting the utility derived from its consumption) and “non-excludable” (i.e. once the good is produced, no one can be prevented from enjoying it). World Bank (http://web.worldbank.org/WBSITE/EXTERNAL/EXTOED/EXTANNREVEVEFFE/EXT2008ANNREVEVEFFE/0_contentMDK:21903365~menuPK:5397143~pagePK:64829573~piPK:64829550~theSitePK:4683541_00.html). WHO (<http://www.who.int/trade/glossary/story041/en/>).



For the high-income countries, BRICS countries and upper middle-income countries, nearly all TB investments should flow from domestic resources. The BRICS countries and Indonesia are expected to see steep increases in public health spending over the coming years.¹

Russia and other eastern European countries may be able to finance a significant share of the expansion of TB services through cost savings within existing TB budgets: by decentralizing TB care, sharply reducing the number of patients that are hospitalized, and reducing hospitalization times.

Other middle-income, high-burden countries could rationalize their TB activities by better integrating them into general health services.

However, a paradigm shift focused on ending TB will only be possible if countries are prepared to dedicate special budget lines, as South Africa has done.

The economic realities are very different in lower middle-income and low-income countries. Most of the high-burden countries in this subset remain heavily dependent on external financing for their TB programmes. Moreover, large parts of TB budgets currently go unfunded in many of these countries.

Analysis performed by the Stop TB Partnership² shows that in the eight low-income, high-burden countries, domestic funding accounts for only 7% of national TB budget needs. In the nine lower middle-income, high-burden countries, domestic funding represents less than 26% of national TB budget needs. In both low-income and lower middle-income countries with high burden, around half of the national TB budget remains unfunded.

The figures provide a stark illustration of the need for increased international support. Without such support, none of these countries will be able to achieve the 90-(90)-90 targets.

A troubling trend has emerged in many countries whereby GDP growth does not translate into greater expenditure on public health. Instead, these countries tend to underinvest in public health or underfund public health services until they are close to reaching upper middle-income status. Meanwhile, they rely on international assistance. While the case should be made for increased domestic investments in TB programmes even in low-income and lower middle-income countries, it is important to be aware of this dynamic of delayed health investments and not be naïve about the ability of these countries to perform a significant scale-up of domestic funding for TB.

That being said, many countries do indeed require some degree of external support. In order to determine the right blend of funding sources to finance the efforts outlined in this Plan, the circumstances of each country need to be taken into account, as these vary widely.

It is important to track increases in domestic funding through better systems of financial reporting from countries, especially through national health accounts where they exist.

Fig. 7.5 shows that, even with the most optimistic scenario for increased domestic funding, a large funding gap in Global Fund-eligible countries (first bar) would remain. For the domestic scenario, the Global Fund 2015 estimates are used.

Increasing the efficiency of domestic TB programmes

The choices facing TB policy makers and programme implementers are daunting because of a persistently high burden of disease, limited

1 De La Maisonnette C, Oliveira Martins J. A projection method for public health and long-term care expenditures. Economics Department Working Papers No. 1048, OECD, Paris; 2013.

2 Stop TB Partnership Factsheet. Racing to the End TB finish line; 2015.

resources, and the need to compare emerging technologies with cheaper (but older and less effective) approaches.

This challenge requires a shift towards allocative efficiency, i.e. the maximization of health outcomes using the most cost-effective mix of health interventions, delivered to target populations in the highest priority areas via streamlined service delivery.

The Global Plan urges countries to use analytical approaches that incorporate data on the cost and effectiveness of interventions in real-world applications in order to estimate how the burden of TB can be addressed using available resources. It also encourages countries to seek ways to improve the efficiency of TB programme implementation without reducing quality.

Social health insurance

Social health insurance (SHI) is a mechanism by which funds within countries can be raised and pooled to finance health services.³ In European SHI systems, employees and their employers contribute to a package of services available to the insured and his or her dependents. Many

³ Thinking of introducing social health insurance? Ten questions. World Health Report background paper. Geneva: World Health Organization; 2010.

governments also subsidize these systems to ensure sustainability.

These contributions programmes are designed to ensure that the rich contribute more than the poor and that the sick do not pay more than the healthy. In addition, some governments have extended coverage to people who cannot pay, such as the poor and unemployed, by meeting or subsidizing their contributions.

This approach has benefits in the context of TB. As SHI schemes generally charge higher rates for coverage to wealthier people (who are less likely to have TB) and often provide free coverage to poorer people (who are more likely to have TB), SHI mechanisms can help to reduce health inequalities, avoid catastrophic costs for people with TB, and redistribute funds towards TB – increasing the overall levels of funding available for fighting TB.

A number of countries are planning to introduce and/or scale up SHI as part of their efforts to attain UHC. TB programmes must seize the opportunity to include TB care in the package of coverage provided by SHI. As much as possible, all forms of TB managed by both public and private health systems should be brought under the coverage of SHI schemes. Efforts should also be made to ensure that SHI schemes are inclusive and provide coverage to key populations, such as migrants.

INTERNATIONAL FINANCING



Fig. 7.5 provides an illustration of the need for increased international funding in Global Fund-eligible countries. It shows the funds that are anticipated from domestic sources, the Global Fund, and other external sources, as well as the additional funding that countries will require over and above these sources.

Given that the figures for domestic funding are based on the most optimistic forecast scenarios prepared by the Global Fund, it is clear that

there is a significant and increasing need for additional contributions from the Global Fund and from other international sources. Without such additional funding, the 2020 milestones of the End TB Strategy will not be met.

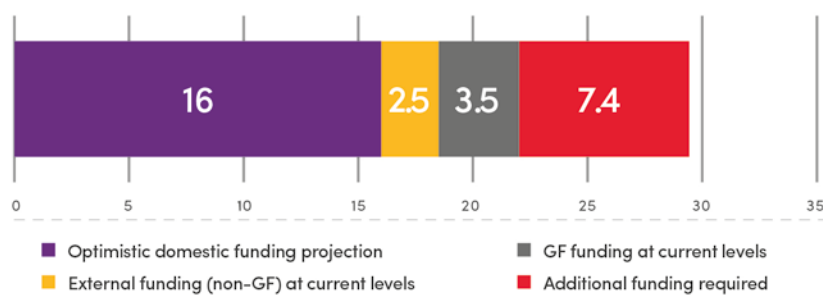
For Global Fund-eligible countries, the total resource need for the period 2016–2020 is US\$ 29.4 billion. The most optimistic scenario of increased domestic funding, along with continued external funding at current levels, will provide up to US\$ 22

billion, which leaves an additional funding requirement of US\$ 7.4 billion that needs to be mobilized.

If Global Fund-eligible countries implement the accelerated investment scenario – as the Global

Plan recommends – the total amount of funding required over the next five years will be roughly the same, but will need to be made available sooner.

FIGURE 7.5. RESOURCE NEEDS (IN US\$ BILLIONS) FOR GLOBAL FUND ELIGIBLE COUNTRIES FOR THE PERIOD 2016–2020 (TOTAL US\$29.4 BILLION), BY SOURCE OF EXPECTED FUNDING



THE ROLE OF INNOVATIVE FINANCING IN THE FIGHT AGAINST TB

Global health has a strong track record in developing innovative financing mechanisms. While still primarily backed by traditional donors, the Global Fund and UNITAID, for example, have developed innovative approaches to mobilizing, pooling, channelling, allocating and implementing resources in order to direct large amounts of funding rapidly to low-income and middle-income countries.¹

These mechanisms will continue to play a key role in the fight against TB. The Global Fund alone contributes nearly 70% of international financing.² But, there is a need to cultivate funding from non-traditional donors.

The Social Impact Bond

One instrument that may have the potential to secure additional funding is the Social Impact Bond. This is a financial scheme whereby investors pay in advance for interventions in order to achieve agreed-upon results. Then, they work with delivery organizations to ensure that those results are achieved. Outcome funders (governments and/or donors) make payments to investors if the interventions succeed, with the degree of returns linked to the level of success of the results achieved. In this sense, Social Impact Bonds are like other results-based approaches, but with upfront capital. This ensures finance at affordable rates for service providers.

In the context of TB programming, a Social Impact Bond could encourage investors to provide upfront capital to support the efforts of various service providers to improve TB diagnosis and treatment in high-burden communities.

1 Atun R, Knaul FM, Akachi Y, Frenk J. Innovative financing for health: what is truly innovative? *Lancet*. 2012;380(9858):2044–9.

2 Institute for Health Metrics and Evaluation. *Financing global health 2014: shifts in funding as the MDG era closes*. Seattle, WA: IHME; 2015.

These activities would have both social and financial benefits. The social impact would be generated from the reduced burden of disease and the increased productivity of a population with fewer active TB cases. Governments and companies providing TB care (for example in mining communities) would realize financial benefits through the reduced costs incurred in treating patients. The government would also benefit from the increased tax revenues generated from a more economically productive population. These savings would form part of the capital that would be paid back to investors.³

Blended finance

Blended finance is another framework that has the potential to increase the funding available for TB programmes and R&D. As the name suggests, this approach facilitates the blending of public and private capital to finance development goals.

Its principle aim is to unlock investment from the private sector. Typically, clinical trials for new tools (e.g. TB tests) constitute a high-risk activity with no guaranteed financial returns for a company. Blended finance seeks to reduce that risk by providing public sector and philanthropic funding to defray programme costs – such as technical support for study and intervention design – that a company would not be able to meet. The approach therefore has the potential to leverage private sector investment, innovation and expertise for projects that would otherwise be left on the shelf.

Micro levies/taxes

Taxes and micro levies on consumer goods can also generate resources for global health. The most cited example is a small tax on airline ticket

purchases. Started in 2006 in France, the tax has now spread to Cameroon, Chile, Congo, Madagascar, Mali, Mauritius, Niger, and South Korea. The funds raised support UNITAID in purchasing treatments for HIV, tuberculosis and malaria. From a tax of around US\$ 1 for economy-class tickets and US\$ 40 for business-class seats, UNITAID raised nearly US\$ 1.2 billion over five years (2007–2012). There remain numerous other opportunities in the areas of extractive industry, processing, consumption and finance where such taxes could be levied.

Pooled donor trusts

Donor-based trusts are pooled funds that distribute grants to organizations to meet defined social outcomes. Their main feature involves a multi-donor approach, which aims at better coordinating the funding for programmes, while raising awareness for issues that need additional attention.

Trusts can help to simplify the grant-making process and maximize impact. For example, the recently launched Power of Nutrition trust, hosted by the World Bank and UNICEF, is a US\$ 200 million fund that aims to increase the efficiency of funding for undernutrition and other specific health goals related to stunting and wasting. The fund requires countries to provide matching capital for efforts to tackle the issues.

³ Milken Institute. Innovative financing for global health R&D; 2012 (<http://assets1c.milkeninstitute.org/assets/Publication/InnovationLab/PDF/FIL-Global-Health-Report.pdf>).

Meeting the financing needs for research and development

There is a huge gap in financing for research and development for new tools to fight TB. In 2013, a total of US\$ 676.7 million was invested in TB R&D, just 33.8% of the US\$ 2 billion annual target set out in the 2011–2015 Global Plan to Stop TB.¹

Without an increase in funding, the End TB Strategy aims will not be met, and the resulting toll on economies and human lives will be tremendous. At current low levels of financing, researchers and product developers have nevertheless been able to advance research agendas, and pipelines continue to move forward, as demonstrated in Chapter 6. However, they must limit their research projects to fit within a constrained funding environment, stifling the creativity, innovation and experimentation needed for the development of tools. Crucially, insufficient resources limit the number of researchers willing to enter or stay in the field of TB R&D.

There are several reasons for the shortfall in TB R&D funding. The current market for TB drugs does not provide sufficient incentives for the development of new products. Developing diagnostic solutions is a financially high-risk activity, making it particularly challenging for small- and medium-sized companies. Furthermore, vaccine development is a costly and complex endeavour that has so far only attracted a narrow donor base.

To increase funding for TB R&D, action is required in the following key areas:

MAINTAINING AND INCREASING THE DONOR BASE. Maintaining current partnerships and increasing the funding base with new donors, investors and private sector actors are priorities.

These efforts must increase. Government, public sector and philanthropic donors, particularly the Bill & Melinda Gates Foundation, have provided essential funding for TB R&D, and some pharmaceutical industry partners have also contributed resources and expertise.

However, expanding investments from BRICS countries – countries that account for nearly half of all TB and have significant research infrastructure and capacity – would provide a major boost. The establishment of the BRICS New Development Bank (NDB), with its US\$ 50 billion in capital, represents one such opportunity for BRICS investment in TB R&D.

A number of additional funding sources exist, including pooled funding mechanisms such as the European and Developing Countries Clinical Trials Partnership and the Global Health Innovative Technology Fund. It is imperative that these initiatives be strengthened, supplemented, and adequately coordinated.

FUNDING PLATFORMS AND MECHANISMS.

The complexities, costs and risks of TB R&D will require multiple funding platforms and partners, and a combination of push and pull mechanisms. Push mechanisms, such as traditional grants, finance R&D activities up front, reducing the risk to researchers and developers. Pull mechanisms incentivize private sector investment in R&D. In 2007, for example, the US Food and Drug Administration introduced the priority review voucher, granted to companies that discover drugs for neglected diseases. These vouchers can be traded²; initially valued at US\$ 321 million, two vouchers were recently sold for US\$ 67 and US\$ 125 million. For diagnostics, expanding the market through widespread

1 Frick M. 2014 report on tuberculosis research funding and trends, 2005–2013. Treatment Action Group; 2015.

2 Noor W. Placing value on FDA's priority review vouchers. *In Vivo*. 2009;27(8):1–8.

implementation of existing solutions, while at the same time making new tools more affordable, would help to drive a virtuous cycle of demand creation.

Clearly, TB R&D funding requires more inno-

vative ideas and alternative financing mechanisms. The Push-Pull & Pooling Mechanism described in the Box 7.1 below is one such initiative that aims to bring together a variety of actors and market incentives to facilitate open collaboration.

BOX 7.1:

Collaborative Frameworks for Research and Development Funding: The 3P project

Despite the increasing health burden, underinvestment in TB R&D means that the pipeline for new drugs is sparse. Private sector companies lack the financial incentives to invest in R&D for new TB drugs due to the relatively low commercial revenues available. Developers are often unable to access the intellectual property of certain compounds to test their drugs in combination, meaning that the research into much-needed new regimens for TB can only happen after individual compounds have completed clinical development and are registered. Furthermore, there are no guarantees that patients will be able to access new TB treatments at affordable prices.

The 3P Project, an initiative of the *Medécins Sans Frontières* Access Campaign, is one example of an effort to tackle these issues by creating a collaborative framework that combines push-funding, pull-funding, and a pooling mechanism for scientific knowledge and intellectual property. In sum, the 3P Project aims to:

- 1** Offer milestone prizes for products at predetermined points in the drug development pipeline, for example, when a product successfully completes phase-one trials;
- 2** Obtain licenses for the TB indications of new compounds, thereby ensuring the feasibility of rapid development of the most promising TB drug regimens;
- 3** Fully compensate and reward researchers and developers up front for their investments, de-linking the financing of R&D from product prices and promoting access and affordability;
- 4** Pool licenses, thereby facilitating the development of optimized regimens independent of the inventors of any individual compound;
- 5** Provide research grants to encourage preclinical and clinical development of the most promising TB regimens;
- 6** Facilitate competitive production of the final regimens where market size allows;
- 7** Make eligibility for push or pull funding dependent upon willingness to share both data and relevant intellectual property rights within the 3P pool.

The 3P Project aims to transform TB R&D by using novel approaches to coordination and financing to encourage substantially increased levels of research activity, and to incentivize the development of a new set of regimen drugs capable of treating all forms of TB. The launch of 3P is planned for 2016.

STREAMLINING AND INVESTING IN R&D THROUGH PARTNERSHIP MODELS.

Product development partnerships (PDPs) have played a crucial role in advancing TB R&D, demonstrating efficient and effective use of limited resources, and bringing together partners to advance a common research agenda and coordinate activities. However, funding in 2013 for four of the primary TB PDPs was US\$ 22 million below 2008 funding levels.¹ Funding support for PDPs should be increased by US\$ 25–40 million a year in order to restore funding at least to 2008 levels and to increase funding as research progresses.

¹ Moran M, Guzman J, Chapman N, et al. G-FINDER 2014: Neglected disease research and development: emerging trends. Policy Cures; 2014 (<http://www.policycures.org/downloads/Y7%20GFINDER%20full%20report%20web%20.pdf>).

FIG: 7.6: TOTAL INVESTMENTS AND RETURNS UNDER THE ACCELERATED INVESTMENT SCENARIO FOR IMPLEMENTATION







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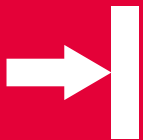
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Chemin de Blandonnet 2,
1241 Vernier
Geneva, Switzerland

www.stoptb.org