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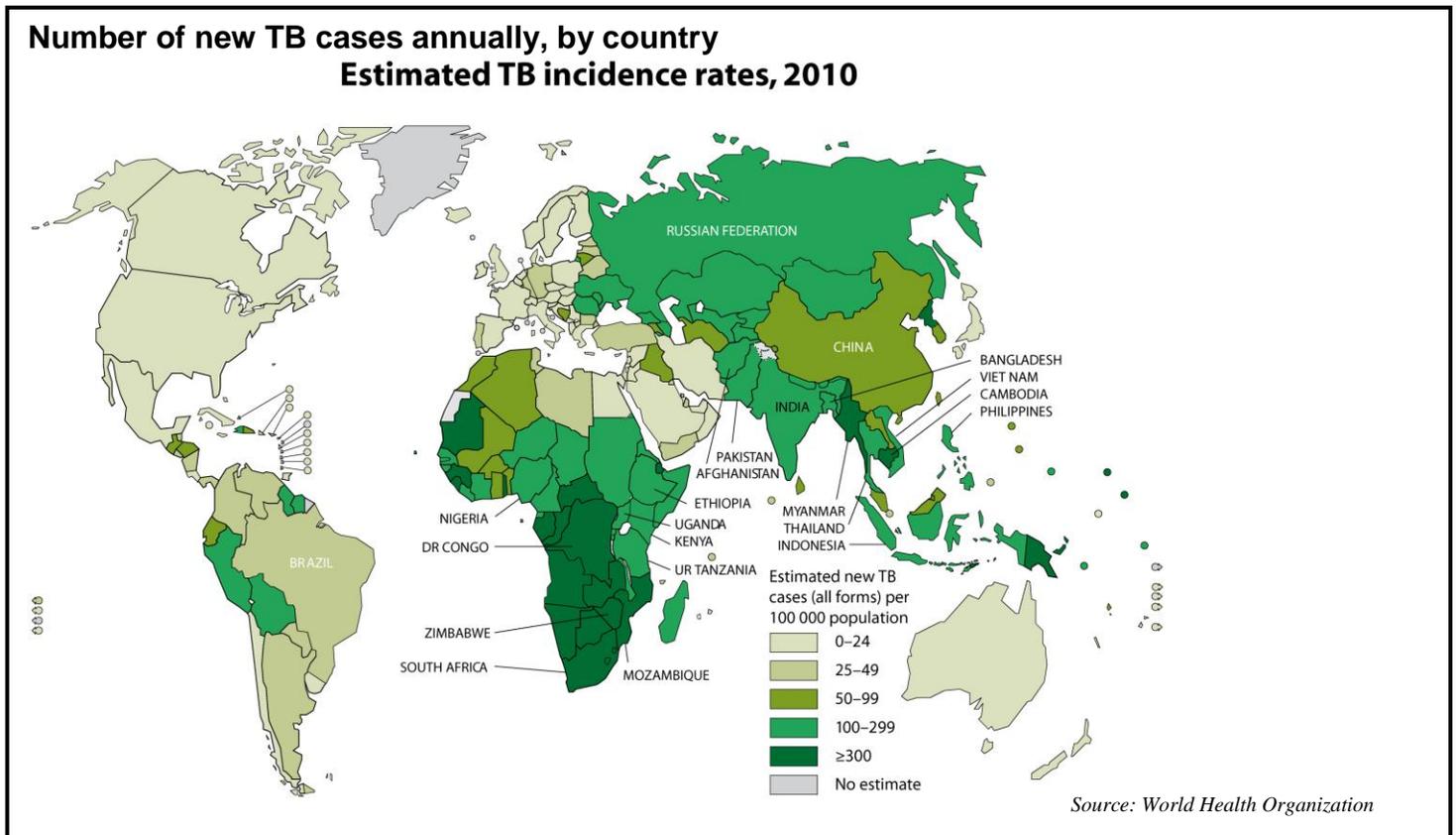
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TB Basics

TB in Numbers



- **2 billion people (one-third of the world's population) are infected with *M.tb***
- **~4,000 people die from TB daily**
- **~12 million people are co-infected with TB and HIV**
- **TB is the leading infectious killer of people living with HIV/AIDS**
- **There are currently 650,000 cases of MDR-TB around the world**

Last year, there were:

- **8.8 million new active TB cases**
- **~1.4 million deaths from TB**

What is TB?

Tuberculosis (TB) is a contagious disease caused by a bacterium called *Mycobacterium tuberculosis* (*M.tb*). The bacteria usually attack the lungs, but TB bacteria can attack any part of the body, such as the kidney, spine, and brain. TB in the lungs or throat can be infectious, while TB in other parts of the body is usually not infectious. If not treated properly, TB disease can be fatal.

Like the common cold, TB spreads through the air. *Only people with active TB disease can be infectious*. When infectious people cough, sneeze, talk, or spit, they propel TB germs, known as bacilli, into the air. A person needs only to inhale a small number of these to become infected.

Symptoms of TB depend on where in the body the TB bacteria are growing. TB bacteria usually grow in the lungs. TB in the lungs may cause symptoms such as:

- A bad cough that lasts 3 weeks or longer
- Pain in the chest
- Coughing up blood or sputum (phlegm from deep inside the lungs)

Other symptoms of active TB disease are:

- Weakness or fatigue
- Weight loss
- Loss of appetite
- Chills
- Fever
- Sweating at night



Colonies of *Mycobacterium tuberculosis* (*M.tb*). (Source: CDC).

Types of M.tb Infection

The appropriate TB treatment varies depending on which type of *M.tb* infection a person has. Some of the major categories are listed below.

Latent TB

Latent TB is a condition in which TB bacteria are alive but inactive in the body. The WHO estimates that two billion people — one-third of the world's population — are infected with *M.tb*, but most have latent TB rather than active TB disease. People with latent TB infection usually have a positive skin test reaction when tested, but have no symptoms, don't feel sick, and can't spread TB to others. Although most people with latent infection will never develop active TB, an average of 10% of carriers will become sick in their lifetime. The likelihood of latent infection developing into active TB disease is greatly increased (by up 20-30 times) if an individual is HIV-positive.

Active TB

Once active, TB attacks the lungs and other organs, destroying body tissue. The disease is contagious, spreading through the air after a patient with active TB coughs, sneezes, or even talks. Approximately 9 million new active cases develop each year. At any given moment, approximately 12 million people around the world are suffering from an active infection, which must be treated with a four-drug combination for at least six months; this treatment regimen is also often referred to as “first-line” treatment. When treatment is not completed, drug-resistance often develops.

MDR-TB

WHO treatment standards require that at least four drugs be used to treat TB. Part of the reason for such a requirement is to prevent *M.tb* from developing resistance to any single drug. Unfortunately, in resource-limited settings treatment is often inconsistent and incomplete, which leads to the development of drug resistance anyway. Multidrug-resistant TB (MDR-TB) is defined by resistance to two of the most powerful drugs in the current four-drug regimen, isoniazid and rifampin.

There are 650,000 cases of MDR-TB cases around the world at any given time. So-called, “second-line drugs” are used to treat MDR-TB, but they are generally less effective. Further, some are toxic and can lead to adverse side effects. Second-line drugs must be taken for up to two years in order to eradicate the infection.

The costs of curing MDR-TB can be staggering — as much as 1,400 times that of regular treatment. This expensive treatment is often out of reach for patients who are infected with drug-resistant strains. At the same time, the cost and complexity of treating MDR-TB poses a significant challenge to national healthcare systems.

XDR-TB

Extensively drug-resistant TB (XDR-TB) is defined as MDR-TB that is also resistant to certain critical second-line drugs: any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin, and amikacin). This makes treatment of XDR-TB extremely complicated, with some strains proving to be virtually untreatable. XDR-TB is known to exist in at least 58 countries and is emerging as a dire health threat in many parts of the world.

The Dual Epidemic: TB/HIV co-infection

HIV/AIDS and TB form a lethal combination, each speeding the other's progress. TB is one of the most common *opportunistic infections* associated with HIV's attack on the immune system: people with HIV/AIDS are more likely to contract TB and more susceptible to active infection. *TB is the leading infectious killer of people with HIV/AIDS*, especially in sub-Saharan Africa, where it causes up to half of all AIDS-related deaths. Anti-retroviral (ARV) therapy is today's most effective available treatment option for controlling the progression of HIV, the virus that causes AIDS. Unfortunately, drug-drug interactions between the current first-line TB regimen and certain commonly used ARVs complicate treatment for co-infected patients.

TB and Poverty

TB overwhelmingly affects the poor because crowded living conditions where the disease can be more easily transmitted are common in poor areas, thereby increasing the risk of infection. Ninety-four percent of TB cases and 98 percent of TB deaths occur in developing countries.

TB also perpetuates poverty. Drug-susceptible TB treatment is often provided for free by national programs, but patients incur other costs related to transportation, hospital stays, and reduced working hours. The WHO calculates that the average TB patient loses three to four months of work-time, and up to 30% of yearly household earnings. Thus, TB creates a vicious circle: the disease exacerbates poverty, which in turn increases the likelihood of contracting TB.

Over the next decade, TB will rob \$1–3 trillion from the world's poorest countries. The World Bank estimates TB is responsible for a loss of productivity that is equivalent to 4–7% of the national GDP in some countries. Meanwhile, the burgeoning cost of TB medical care is a constant drain on those health systems whose infrastructures are least able to carry the load.

TB Treatment and Control

Current Treatment Standards

WHO-Recommended Treatment for Drug-Susceptible TB (New Cases)

The most common TB treatment regimen is for TB patients who have not been previously treated and have drug-susceptible TB. This treatment regimen consists of four medicines known as **first-line drugs**: isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E).

Treatment with this first-line drug combination works for active, drug-susceptible TB as long as patients complete treatment without interruption. Patients who are given incorrect or inadequate drug regimens, including sub-standard drugs, or who take their first-line drugs in an irregular way, are at greatly increased risk of treatment failure, relapse, and the development of drug-resistant TB strains. First-line treatment usually takes six to nine months to cure the disease.

First-line treatment consists of two months with all four first-line drugs (the initial phase) plus four to six months with two of the drugs (the continuation phase). During the initial period, the *M.tb* bacilli are killed rapidly. Infectious patients usually become non-infectious within approximately two weeks, and symptoms begin to abate.

The four-to-six-month continuation phase usually consists of a combination of isoniazid with rifampin or, less commonly, ethambutol. The continuation phase drugs eliminate the remaining *M.tb* bacilli and greatly reduce the likelihood of subsequent disease relapse.

Treatment for Multi Drug-Resistant TB (MDR-TB)

MDR-TB is defined as TB that is resistant to at least isoniazid and rifampin, two mainstays in today's first-line treatment course.

Treatment for MDR-TB must be done on the basis of sensitivity testing to determine which first-line drugs can still kill the *M.tb* bacilli. When sensitivities are known and the TB case is confirmed as resistant to both isoniazid and rifampin, the patient must undergo treatment with a combination of **second-line drugs**, many of which are less effective than first-line drugs and pose greater risks of adverse side effects.

WHO Stop TB Department and DOTS

In 1993, the World Health Organization (WHO) declared TB a global emergency, and the next year introduced a treatment plan to better fight the disease and control its spread.

DOTS or ***Directly Observed Treatment Short course*** has become the international standard strategy for TB control, recognized as the most efficient and cost-effective response with available tools. Among its standard components, DOTS calls for supervised treatment to help patients take their drugs regularly and completely. DOTS comprises five components:

- 1) Political commitment with increased and sustained financing
- 2) Case detection through quality-assured bacteriology
- 3) Standardized treatment with supervision and patient support
- 4) An effective drug supply and management system
- 5) A monitoring and evaluation system and impact measurement.

In 2006, the WHO adopted the Stop TB strategy, building on and enhancing DOTS to dramatically reduce the global burden of TB by 2015 in line with the United Nations' Millennium Development Goals and the Stop TB Partnership targets. The Stop TB objectives include:

- achieving universal access to high-quality diagnosis and patient-centered treatment;
- reducing the human suffering and socioeconomic burden associated with TB;
- protecting poor and vulnerable populations from TB, TB/HIV, and drug-resistant TB; and
- supporting development of new tools, including new drugs, and helping to enable their timely and effective use.

The Need for New Tools: Drugs, Diagnostics, and Vaccines

While great progress has been made in standardizing and expanding global TB control efforts, TB will never be defeated without new and more effective tools.

These include: simpler, faster drug regimens that treat all forms of TB; rapid, more accurate diagnostic tools to quickly detect TB; and a vaccine that will be effective in preventing TB in people of all ages. New tools will play a crucial role alongside the growing commitment to more aggressive TB control and broader treatment to end the needless burden of TB. However, the development of these new tools has been hampered by the fact that the markets for new TB technologies are both fractured and offer limited profit potential.

Drugs

The current TB drug regimen, a product of the best scientific advances of the 1960s, works for active, drug-susceptible TB as long as patients complete the six- to nine-month treatment. The problem is, many do not or cannot.

The length of TB treatment continues to impose tremendous demands on local healthcare systems, and on TB patients in treatment. Erratic or inconsistent treatment breeds drug-resistant strains that increasingly defy current medicines.

The growing global HIV/AIDS pandemic is fueling an increase in TB, and the numbers of co-infected are soaring. One in four patients who die from TB is HIV-positive, and TB is the leading infectious cause of death among patients with HIV/AIDS. However, some drugs in the current first-line TB drug regimen are not compatible with certain common antiretroviral (ARV) therapies used to treat HIV/AIDS.

Diagnostics

Today's most commonly used TB diagnostic, sputum microscopy, is more than 100 years old and lacks sensitivity, detecting only half of the world's new TB patients. Delay in proper diagnosis costs patients valuable time and money in receiving treatment. As new TB drugs are developed, the need for new, more advanced diagnostics will grow, as it will become even more important to identify which drugs should be used to treat a particular patient's disease

Vaccines

Today's TB vaccine, the Bacille Calmette-Guérin (BCG) vaccine, which is more than 85 years old, provides some protection against severe forms of TB in children, but is unreliable against pulmonary TB, which accounts for most of the worldwide disease burden.

Developing New Tools through Public-Private Partnerships

Driven by its deadly synergy with HIV/AIDS, complicated by drug-resistant strains, and amplified by the effects of poverty, today's epidemic is threatening to destabilize gains in TB control. The promise of TB control efforts will only be fully met when patients and healthcare workers are given the best tools that modern science can deliver.

Research is currently underway to develop these critically needed new tools through innovative partnerships that maximize the likelihood of success and minimize costs. Three not-for-profit **Product Development Partnerships (PDPs)**; see page 12) are leading the global effort to develop new TB tools:

- The Global Alliance for TB Drug Development (**TB Alliance**) is developing new affordable TB drugs that will dramatically shorten treatment time, work against drug-resistant TB, be compatible with HIV antiretrovirals and improve treatment of latent TB.
- **FIND** is developing rapid, accurate, and affordable TB tests and point-of-care diagnostics to more efficiently detect TB and drug-resistant forms of TB.
- **Aeras** is developing new, safe, effective and affordable vaccine regimens to protect against all strains of TB (including MDR-TB and XDR-TB) to prevent TB in children, adolescents, and adults, and to be safe for use in people infected with HIV.

Harnessing the collective resources of government, industry, academics, and philanthropies, FIND, the TB Alliance and Aeras have created the largest pipeline of new TB diagnostics, drugs, and vaccines in history.

Nevertheless, increased investments and support for this research are needed to speed development of better TB tools and ensure access for those who need them most.

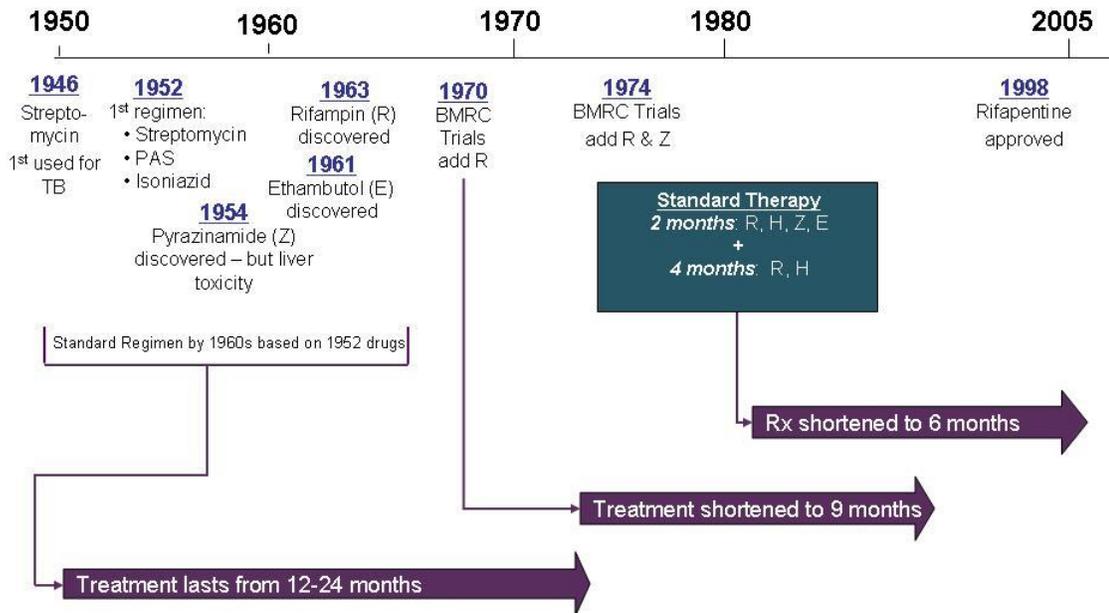
Developing New TB Drug Regimens

The History of TB Drug Development

Today's first-line TB drug regimen is a product of the best scientific advances of the 1960s and consists of four medicines (known as first-line drugs): isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E).

The following timeline illustrates the history of anti-TB drug approvals. As one can see, there have been no new classes of first-line TB drugs in more than 40 years.

TB Treatment Evolution



Pharmacological Profile of a New TB Drug Regimen

Scientists agree that to improve today's standard TB therapy, ideal drug candidates must show promise to deliver on the following:

- **Shorten and simplify the treatment of active, drug-sensitive TB**
- **Display novel mechanisms of action (must attack the bacterium in a new or different way)**

- **Be compatible with antiretrovirals (ARVs), allowing simultaneous treatment of TB and HIV/AIDS**
- **Improve therapy of latent TB.**

The limitations of current TB treatment drive the need for shorter, simpler, yet still-affordable regimens to treat active, drug-sensitive TB. A markedly shorter treatment regimen for active TB would have an extraordinary impact on TB patients and public health systems, rendering treatment adherence much easier and, therefore, drastically reducing the development of new drug-resistant strains of *M.tb*. Achieving this goal will, however, require overcoming the many challenges in a field in which there are knowledge and resource gaps.

Safer, more easily tolerated and more efficacious drugs, with novel mechanisms of action, are needed to treat drug-resistant strains of *M.tb*.

Other ideal properties of TB drug candidates include:

- **Low cost of treatment**
- **Orally available**
- **Once daily or intermittent therapy**

The Need for the TB Alliance and the TB Alliance's Early History

Although a consensus was forming on the need for new TB drugs, prior to the creation of the TB Alliance there was almost no activity in the area due to the lack of financial incentives for pharmaceutical companies. Subsequent work by the TB Alliance has estimated the global market for first-line TB drugs as just over \$300 million, split between four drugs and countless countries, many of which source their drugs locally. This alone is not enough to prompt a for-profit company to invest in research to find new TB drugs.

In response to this problem, the TB Alliance was conceived at a February 2000 meeting in Cape Town, South Africa, where 120 representatives from academia, industry, major agencies, non-governmental organizations, and donors gathered to discuss the problems of TB treatment. Participants stressed the need for new TB drugs, highlighting the unprecedented scientific opportunities and the economic rationale for developing new medicines. The resulting "Declaration of Cape Town" provided a road map for TB drug development, outlining the need for the creation of the TB Alliance. Cape Town signatory institutions formed the original Stakeholders Association for the nascent organization.

The TB Alliance was formally launched in October 2000, at the International Conference on Health Research for Development, in Bangkok, Thailand. In her keynote address, Dr. Gro Harlem Brundtland, then Director General of the World Health Organization, called the TB Alliance "a shining example of public and private sector partnerships to bridge the gap between market opportunities and peoples' needs."

Since then, the TB Alliance has received generous support from the Bill & Melinda Gates Foundation, the Rockefeller Foundation, Irish Aid, the Netherlands Ministry of Foreign Affairs (DGIS), the United Kingdom Department for International Development (DFID),

European Commission, United States Food and Drug Administration, and the United States Agency for International Development (USAID). The organization has a diverse donor base comprising private foundations and enterprises, governments, and multilateral donors. Since its inception in 2000, the TB Alliance has received pledges for more than \$250 million in financial contributions

The TB Alliance has also received substantial in-kind support, often in the form of scientific and strategic expertise and resources from partners in academia, private industry, public research institutes, and non-governmental organizations.

How the TB Alliance Operates

The Global Alliance for TB Drug Development (TB Alliance) is a not-for-profit **product development partnership (PDP)** accelerating the discovery and development of new TB drugs that will:

- shorten treatment;
- be effective against susceptible and resistant strains;
- be compatible with HIV/AIDS antiretroviral therapies; and
- improve treatment of latent infection.

Working with public and private research laboratories worldwide, the TB Alliance is leading the advancement of the most robust portfolio of TB drug candidates in history.

Maximizing our Leverage: Two for the price of one

A partnership-based approach enables the TB Alliance to build a stable of in-kind contributors and leverage these partnerships to impact our bottom line. Each dollar invested in the TB Alliance leverages two dollars worth of services rendered by the TB Alliance and its partners.

\$1 invested = **\$2** leveraged

Catalyzing the field: Concentric benefits of the TB Alliance's work

In addition to the direct leveraging of donor funds, the TB Alliance's mission-driven approach enables the entire global health field to benefit from its work. The Alliance maintains transparency regarding its research strategy and generates significant knowledge, resources, and capacity that benefit the field of TB drug development, and sometimes even broader research areas – in one instance, The TB Alliance has shared compounds that show potential efficacy against other neglected disease areas with Drugs for Neglected Disease Initiative (*DNDi*) for potential development. This resulted in new global health research programs and significant cost-savings to *DNDi*. Such are examples of how the work of the TB Alliance can benefit others at no additional cost.

What is a PDP?

A PDP is a non-profit organization that builds partnerships between the public, private, academic, and philanthropic sectors to drive the development of new products for under-served markets.

Through their unique, collaborative efforts, PDPs are able to access a variety of funding sources, and to apply a wide range of tools and knowledge to their programs. PDPs utilize various partnership models and retain direct management oversight of their projects, though much of the work is done through external research facilities and contractors.

In the global health arena, PDPs have been established to accelerate the development of new technologies that fight TB, AIDS, malaria, and a wide range of neglected diseases. PDPs are created for the public good; their products are made affordable to all those who need them.

How PDPs Work



TB Alliance Collaborators

The TB Alliance operates as a virtual R&D organization — acquiring, in-licensing, or co-developing promising compounds, with laboratory research outsourced to public and private partners. Every project is different, with each program designed to move drugs forward as efficiently as possible.

Projects are overseen by TB Alliance staff members with input from its Scientific Advisory Committee and outside consultants. There are predefined, measurable milestones, and clear go/no-go decision points with common evaluation criteria. Innovative intellectual property agreements ensure the affordability of the developed drugs, especially in poorer, high-endemic countries.

Additionally, our work in the area of Market Access requires a wide and diverse network of partners to assist in the facilitation of the adoption and uptake of new TB treatment technologies.

Selected TB Alliance Partners

<u>Pharma Partners</u>	<u>Access Partners</u>	<u>Clinical Trial Sites</u>
<ul style="list-style-type: none"> • AstraZeneca (UK/India) • Bayer HealthCare AG (Germany) • GlaxoSmithKline (UK/Spain) • Johnson & Johnson/Tibotec (USA/Belgium) • Novartis (Switzerland/Singapore) 	<ul style="list-style-type: none"> • Global Drug Facility • IMS Health • Liverpool School of Tropical Medicine • Management Sciences for Health • STOP TB Dept. (World Health Organization) • TB Alliance pharmaceutical partners • Treatment Action Group 	<ul style="list-style-type: none"> • Aurum HIV Vaccine Research and Treatment Centre (South Africa) • Beijing Chest Hospital (China) • Chest Diseases Institute ((Thailand) • Durban International Trials Unit (DICTU)(South Africa) • Helen Joseph Hospital (South Africa) • Hospital General de Occidente de la Secretaria de Salud del Estado de Jalisco (Mexico) • Indian trial sites used in REMox TB (29 sites) • Institute of Respiratory Research (Malaysia) • Kenya Medical Research Institute • Kilimanjaro Christian Medical Center (Tanzania) • Madibeng Center for Research (South Africa) • Mbeya Referral Hospital (Tanzania) • Rajanathi Hospital (Thailand) • Shanghai Pulmonary Hospital (China) • Soweto CTU (South Africa) • Tianjin TB Control Center (China) • UKZN CAPRISA HIV/AIDS CTU(South Africa) • University of Cape Town Lung Institute (South Africa) • University of Stellenbosch (South Africa) • University Teaching Hospital (Zambia)
<u>Academic Partners</u>	<u>Research Institutes</u>	
<ul style="list-style-type: none"> • Colorado State University (USA) • Johns Hopkins University (USA) • New York Medical College (USA) • University of Auckland (New Zealand) • University of Cape Town (South Africa) • University College London (UK) • University of Illinois at Chicago (USA) • University of Pennsylvania (USA) • Stellenbosch University (South Africa) • Yonsei University (Korea) 	<ul style="list-style-type: none"> • Beijing TB and Thoracic Tumor Research Institute (China) • British Medical Research Council (UK) • Centers for Disease Control and Prevention (USA) • Institute of Materia Medica (China) • Institute of Microbiology (China) • Medical Research Council (South Africa) • Research Triangle Institute (USA) • Scripps Research Institute (USA) 	

The Basic Discovery and Development Pathway for New TB Drugs

The TB drug development process consists of a discovery stage, a clinical stage, and, ultimately, processes that lead to registration and adoption.

Discovery Stage

The discovery process begins with large libraries of chemical compounds or chemical variants of probable leads. Carefully selected chemicals are tested directly against the molecular drug targets, or for their ability to kill drug-susceptible and drug-resistant *M.tb*. Some of these *in vitro* tests mimic conditions in the *M.tb*-infected human lung, so that this early stage has the best chance of uncovering drugs relevant for treating disease.

Compounds that perform well are then tested for activity against TB disease in animals, usually mice. These tests assess safety and ability to kill active bacteria, further narrowing down the potential compounds.

Once drug candidates have been selected, *in vivo* studies in animals define the best possible dosages, drug combinations, and frequency of treatment to help ensure safety before they reach the clinic.

Clinical Stage

All drug candidates, including any proposed TB drug, must go through a strictly defined series of clinical trials in people to ensure safety and efficacy.

Initial Phase I studies are small, limited tests of the safety and metabolic and pharmacologic profiles of drugs. These studies, which are standard for all drug development, are usually conducted in healthy volunteers.

Because of the peculiar nature of the disease, the next round of TB clinical trials is conducted differently than most new drug trials. Since TB must be treated with multiple drugs, a potential new TB drug must be evaluated in patients first by itself, and then subsequently in combination with other first-line TB drugs, as part of a treatment regimen.

Phase II trials are usually the first opportunity to test new TB drugs in patients. Phase IIa trials study the short-term potency of a single drug, given by itself, to TB patients. Although the drug alone is not expected to be a cure (and the trial participants are given standard combination therapy immediately after the trial), these Early Bactericidal Assays (EBAs) give a preliminary indication of potential efficacy. They measure the killing of *M.tb* in patients' lungs as represented by how many live bacteria remain in the patients' sputum.

If EBA results are positive, Phase IIb studies are used to test the drug as part of a full combination therapy for TB, with a two-month assay or test as an initial indicator of the drug's effectiveness.

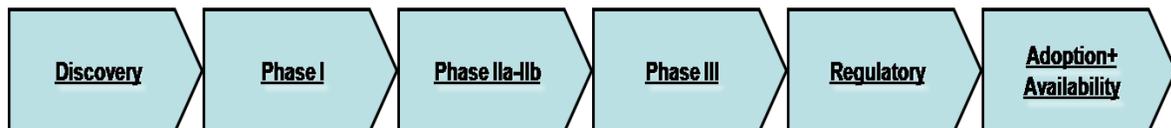
As with other diseases, the final proof of safety and efficacy before registration or regulatory approval comes from longer Phase III trials in larger numbers of patients. In traditional TB research, a single new drug candidate has been tested by substituting it for a drug in the standard first-line regimen. More recently, the TB Alliance has helped advance a new model of TB drug research, which tests multiple TB drug candidates simultaneously, in combination. This model offers the potential to substantially accelerate the time required to develop fully novel TB regimens. (See page 18).

Phase III TB drug trials for drug-susceptible disease continue to test for disease relapse for a year or more after the completion of a full course of combination treatment. This dynamic contributes to the length, cost, and difficulty of completing TB drug trials.

Following completion of large-scale Phase III testing, drug candidates must be evaluated and licensed by regulatory bodies, such as the U.S. Food and Drug Administration, before they can be administered to patients. Drugs are registered on the basis of their performance in clinical testing.

Generally, after a new TB drug is registered it must be adopted as part of a treatment regimen by National TB Programs (NTPs). Adoption requirements are complex, with standards often differing greatly from country to country. Considerations include but are not limited to cost, burden on national healthcare providers, and recommendations of intergovernmental bodies, like the WHO.

The TB Drug Development Process at a Glance:



- **DISCOVERY:** Identify lead structural series; optimize activity *in vitro*, efficacy in animals, and other pharmacological properties. Perform preclinical safety studies allowing filing of a new drug application. Use combination testing to identify the best potential new regimens for clinical development.
- **PHASE I:** Test drug candidates and regimens in small numbers of healthy volunteers for safety, tolerability, and pharmacokinetic properties.
- **PHASE IIa-IIb:** Evaluate single drug candidates (Phase IIa) and multidrug regimens (Phase IIb) in TB patients for potential efficacy and further assessment of safety.
- **PHASE III:** Test multidrug regimens in large numbers of TB patients for efficacy and safety in well-controlled clinical trials.
- **REGULATORY APPROVAL:** Regulatory authorities license the drug/regimen after reviewing all preclinical and clinical results (also called registration)
- **ADOPTION/ AVAILABILITY:** National TB control programs adopt the new drug/regimen, ensuring that it is available to those who need it.

Challenges in TB Drug Research and Development

The unique biology of *M.tb*, the low level of research expenditure in TB drug development over the past 40 years, and the length of the current TB drug regimen all present significant challenges for TB drug research and development.

Researchers require a better understanding of how to kill persisters—the subpopulation of *M.tb* that can persist in animals and humans for long periods, despite drug treatment.

Reliable animal models are needed to test early-stage treatments before giving them to humans. Mice, and sometimes guinea pigs, are used currently, but a drug candidate that cures these animals does not always cure humans.

Testing the drugs in humans takes a long time because the end point is a lack of relapse after 6 months' treatment and an additional 1-2 years' observation time. One way around this is to use biomarkers—molecular or clinical indicators that can signal, sometimes very early on, that a treatment is working. Good biomarkers for TB treatment are still needed.

TB trials are also more challenging because current TB treatments, although very lengthy, are highly efficacious. This is especially true in the well-controlled setting of a clinical trial. Therefore, large numbers of patients are needed to statistically prove that the new (usually shorter) treatment is curing at least as many of the patients as the old, lengthy treatment.

Additionally, the relative lack of TB drug development over the past 40 years has led to a shortage of clinical trials sites that can meet the internationally accepted standards of good clinical practice and good laboratory practice that is required for a registration-grade trial. Compounding this hurdle is the fact that many of the countries with high TB burdens prefer, if not require, data collected from patient populations within their own countries; TB research and development is truly a global endeavor. Evaluating and preparing potential trial sites are elements of the complex and enormous undertaking that is TB drug development.

Overcoming Obstacles: New initiatives in TB Drug Development

Critical Path to TB Drug Regimens



CPTR is a multi-sectoral initiative established to address various challenges associated with TB drug development by bringing together the world's leading pharmaceutical and other drug developers, global regulatory agencies, and civil society organizations to support the advances needed to facilitate the development and availability of new TB drug treatments. Co-founded by the Bill & Melinda Gates Foundation, the Critical Path Institute, and the TB Alliance and launched in March 2010, CPTR is working with stakeholders around the world to speed new TB drug regimens to patients. CPTR is organized into three arms, each led by a founder of the initiative.

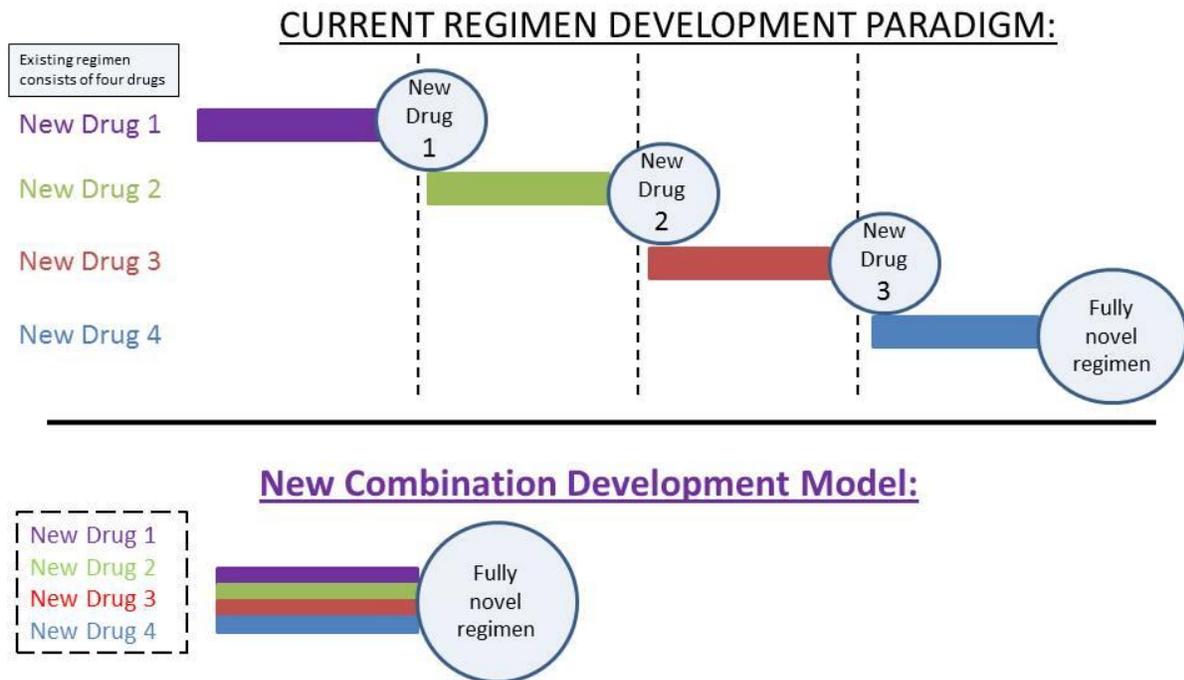
- **CPTR DRUG COALITION**—Drug sponsors work together to select and assemble the most effective treatment regimens, regardless of sponsor.
- **REGULATORY SCIENCE CONSORTIUM**—Stakeholders support a new regulatory framework that enables global authorities to evaluate new multidrug TB treatments.
- **RESEARCH RESOURCES GROUP**—Interested parties advance the development of infrastructure by addressing clinical trial capacity, resource generation for late-stage clinical trials, and access and appropriate use of new TB drug regimens.

Under CPTR, drug sponsors developers allow their TB drug candidates to be tested in combination with one another early in the development process to identify and develop the most promising regimens. The selection of compounds is informed by a program the TB Alliance oversees in partnership with Johns Hopkins University and the University of Illinois at Chicago, which tests preclinical combinations to determine those that are the most promising.

Co-development: A New Paradigm for TB Drug Development

Active TB must be fought with combination therapy to achieve maximum efficacy and combat the development of drug-resistance. Today's four-drug first-line TB treatment, evolved through the addition and substitution of single new drugs into an existing regimen. Each trial to amend the regimen can take six or more years to complete, thus the development of a fully novel treatment regimen could take decades. With nearly 2 million people dying from TB yearly, this is absolutely too long to wait.

In order to speed the development of new TB treatment regimens, the TB Alliance and its partners pioneered a new paradigm to develop entirely new treatment combinations for both TB and MDR-TB by testing multiple drugs together, in combination, at the same time. This new approach is championed by the CPTR initiative.



New Combinations and PaMZ

In 2011, the TB Alliance concluded the first clinical trial testing a novel TB drug regimen in human patients. This regimen performed exceedingly well in this trial (NC001) and is set to undergo further testing in its path toward pivotal registration trials, and ultimately regulatory approval.

This regimen, known as PaMZ, consists of:

PA-824 (a new TB drug candidate)

+

Moxifloxacin (an existing antibiotic, not currently approved for TB use)

+

Pyrazinamide (an existing TB drug)

The potential benefits of this regimen include:

- The ability to reduce the treatment of both TB and MDR-TB to 4 months
- The ability to treat both TB and MDR-TB with a single regimen
- A profound simplification of MDR-TB treatment
- A significantly cheaper MDR-TB treatment
- The ability to facilitate wider scale-up of MDR-TB treatment

NC002 and Beyond:

The next trial testing the PaMZ regimen will be known as NC002. This trial, scheduled to begin in early 2012 will test PaMZ in both drug-sensitive and drug-resistant patients for a 2-month duration.

Additional trials of new regimens are also on the horizon. Trials scheduled to begin later in 2012 and 2013 could include additional compounds from various companies' portfolios combined to form new regimens. Early studies of some regimens show potential to treat TB in as little as six weeks.



Success will require novel drug combinations

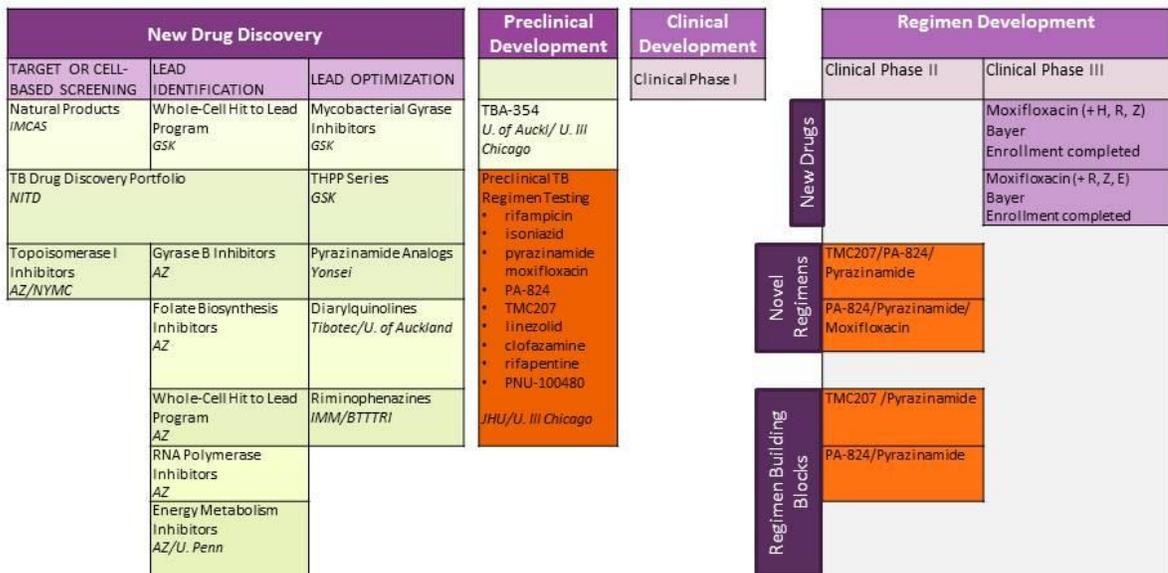
Today's New TB Drug Pipeline

The TB drug pipeline today is the largest it has ever been. A great number of the active projects are being overseen by the TB Alliance. The charts below outline the TB Alliance drug pipeline and the global TB drug pipeline.

TB ALLIANCE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

TB Alliance Pipeline

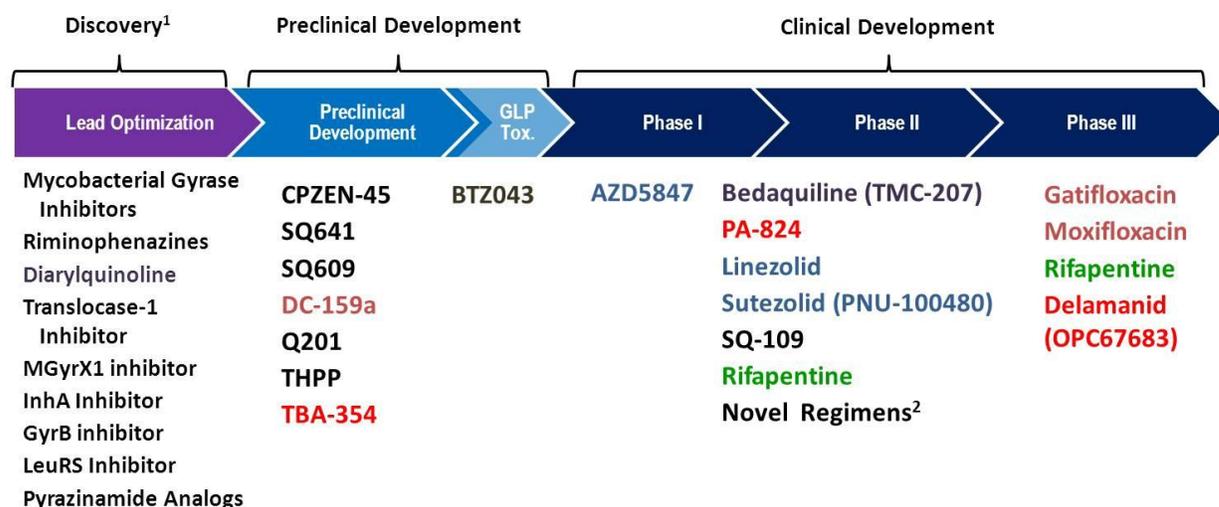
March 2012



Novel TB regimen development

Our R&D Partners			
AZ	AstraZeneca	NITD	Novartis Institute for Tropical Diseases
Bayer	Bayer Healthcare AG	Novartis	Novartis Pharmaceutical
BTTTRI	Beijing Tuberculosis and Thoracic Tumor Research Institute	NYMC	New York Medical College
GSK	GlaxoSmithKline	Tibotec	Johnson & Johnson / Tibotec
IMCAS	Institute of Microbiology, Chinese Academy of Sciences	U. of Auckl	University of Auckland
IMM	Institute of Materia Medica	U. Penn	University of Pennsylvania School of Medicine
JHU	Johns Hopkins University	Yonsei	Yonsei University

Global TB Drug Pipeline



Chemical classes:

fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

¹Ongoing projects without a lead compound series can be viewed at <http://www.newtbdrugs.org/pipeline-discovery.php>

² Combination regimens: first clinical trial (NC001) of a novel TB drug regimen testing the three drug combination of PA-824, moxifloxacin, and pyrazinamide.



www.newtbdrugs.org

Updated: November 2, 2011