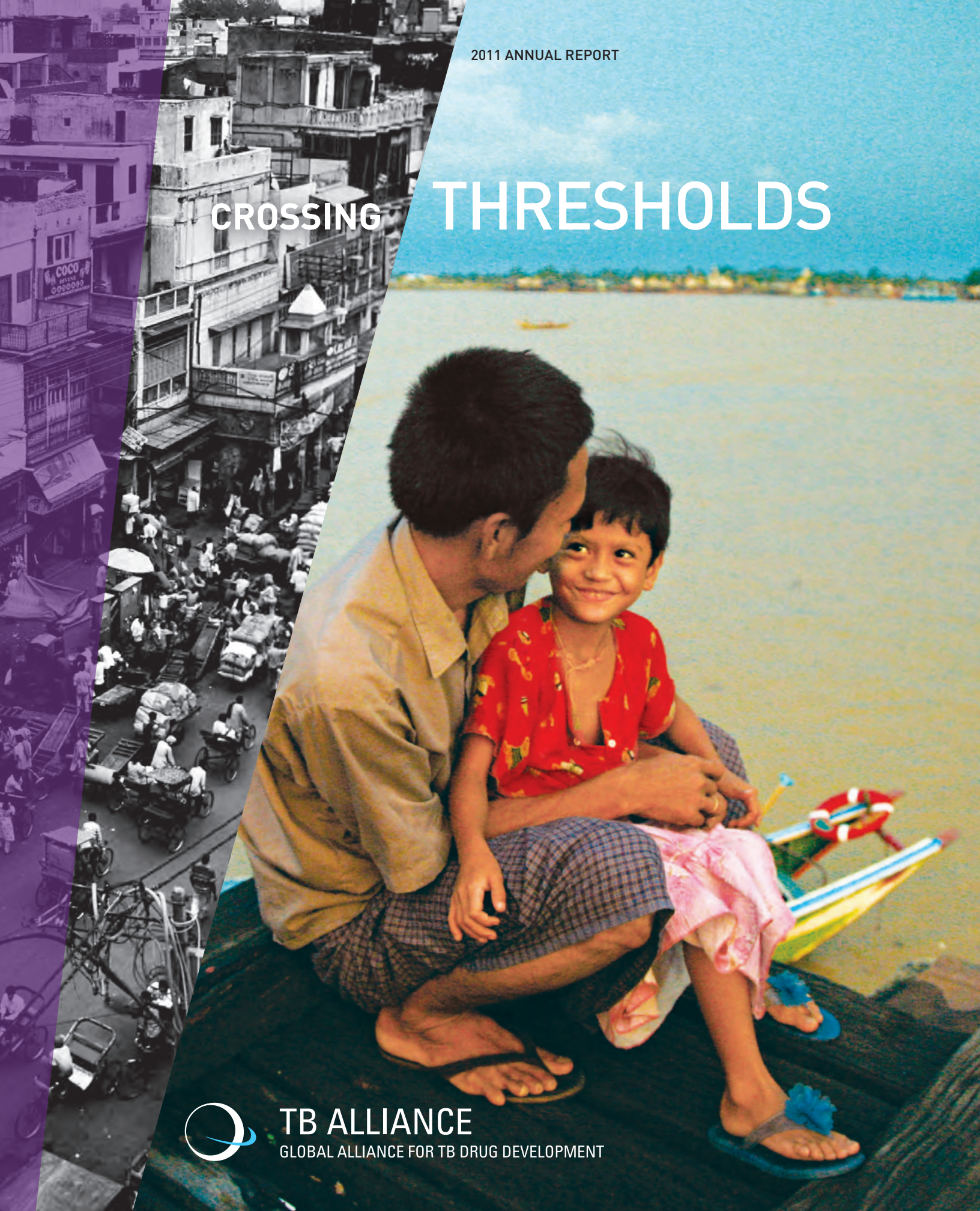
2011 ANNUAL REPORT

CROSSING THRESHOLDS



TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Welcome to the TB Alliance's 2011 Annual Report. This PDF is interactive and contains links to additional content housed on **tballiance.org** and other sites. Please take some time to get to know us better, and find out more about the progress we are making in the search for better, faster TB cures.

The global TB pandemic has plagued humankind for millennia; its death toll and economic cost to countries, communities, and patients are incalculable. Despite increased global efforts to improve TB control measures, there are more than **9 million new TB cases each year**—and still, the epidemic continues to worsen.

Where's the urgency? Where is the investment in global health?

Today, there is more TB in the world than ever before, and resistance to the available drugs is growing. **Better, faster-acting, affordable treatments are urgently needed** to stem the tide of TB, including drug-resistant TB. Without increased efforts to support new weapons against tuberculosis, the world cannot defeat this disease.

With nearly 2 million people dying each year from TB, we need to ask:

WHAT IS THE WORLD'S THRESHOLD FOR A PANDEMIC OF DEADLY TB?

HOW MUCH DEVASTATION BY TB CAN WE BEAR?

No new drugs in nearly 50 years...

TB kills someone every 20 seconds. Yet the current TB treatment is nearly 50 years old and inadequate to tackle today's pandemic. TB drugs must be taken for at least six months and up to 2 years. Many patients default on their treatment, contributing to a growing epidemic and increasing resistance to TB drugs, which is spreading to every corner of the world.

A worsening pandemic...

Current treatment for multidrug-resistant TB (MDR-TB) takes 18–24 months, with a host of medicines—more than a dozen pills per day—plus injectables. The cost and complexity mean that fewer than 10% of MDR-TB patients receive proper treatment. Of those who do, nearly half will still die.

Rising rates of TB forecast setbacks in HIV control...

TB and HIV are dual epidemics—and fatally synergistic. One-third of all HIV/AIDS patients are also infected with TB, making it the top killer of people living with HIV/AIDS. However, current first-line TB treatment is not compatible with commonly used antiretrovirals, leaving many patients without treatment options.

Robbing millions of health and hope...

TB and poverty combine to perpetuate a vicious cycle, the disease infecting those least able to afford it. TB will cost the world's poorest countries an estimated $1 to $3 trillion in development over the next 10 years, robbing nations, communities, and families of health and hope and a chance for economic prosperity.

THE TB ALLIANCE IS

CROSSING THRESHOLDS

IN DEVELOPING THE BETTER, FASTER-ACTING, AND AFFORDABLE TB CURES NEEDED TO STOP THE PANDEMIC.

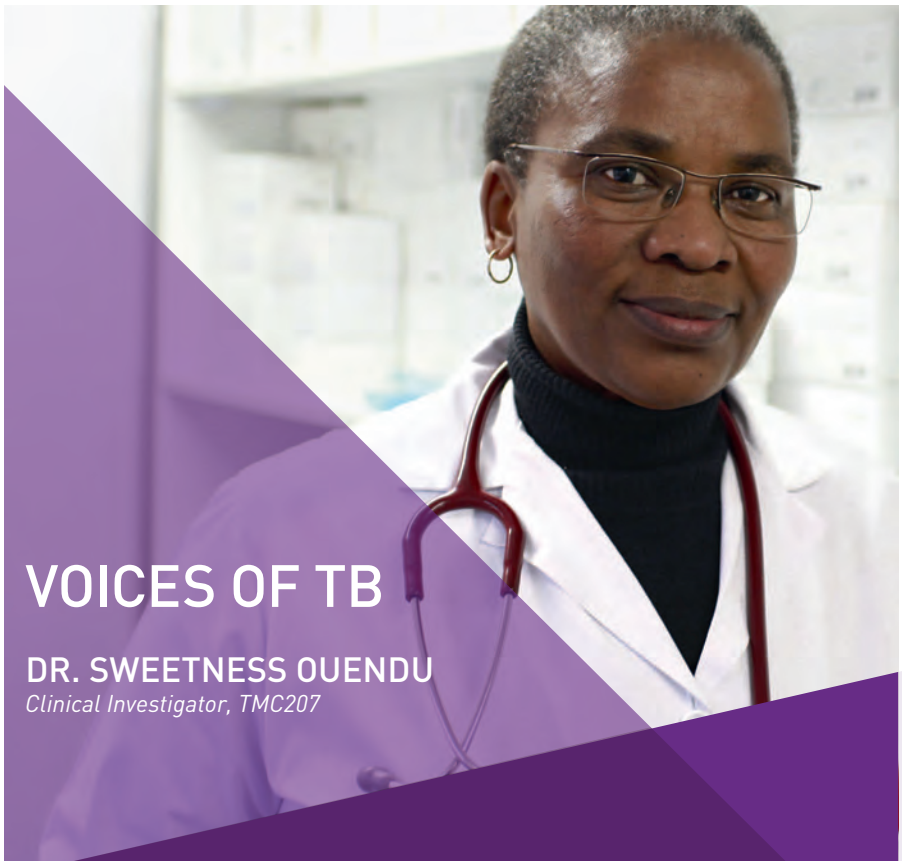
Armed with the world's largest TB drug pipeline and an innovative approach to speed clinical trials, the TB Alliance has revolutionized TB research and development. Today, working with our partners, we stand at the threshold of revolutionizing TB treatment itself.

1/2
of **MDR-TB** cases occur in China and India

More than
9 million
new cases of **TB** emerge each year, resulting in nearly 2 million deaths

TB IS THE #1 INFECTIOUS KILLER WORLDWIDE
of people with **HIV/AIDS**

PERU / Globally, each year more women die from TB than all maternal conditions combined.



VOICES OF TB

DR. SWEETNESS OUENDU

Clinical Investigator, TMC207

New, faster, and safer treatments are needed to scale up MDR-TB treatment and reduce its spread

Dr. Sweetness Ouendu is a clinical investigator on the TMC207 clinical trial, and based at Brooklyn Chest Hospital in Cape Town, South Africa. Her hospital is overrun with people suffering from MDR-TB and XDR-TB. Even with dedicated wards, the number of patients seeking treatment simply outstrips the hospital's capacity to care for them—many are left on waiting lists, while others are treated on an outpatient basis, returning home after taking their complicated daily course of treatment to overcrowded dwellings where they can easily infect others. Saddened, Dr. Ouendu explains that MDR-TB perpetuates the poverty cycle, with patients infecting others in their family who can ill afford the costly treatment and the time out of work. Current MDR-TB treatment can take up to two years, and nearly half of people with the disease die. Dr. Ouendu says that research to develop promising novel TB drugs, like TMC207, are desperately needed to help countries like South Africa control the epidemic.

TAHARQA ELNOUR

Community Engagement Officer

Clinic to Community: Empowering through Engagement

Within a community, says Taharqa Elnour, members should understand and participate in the TB research taking place. Working with TASK Applied Science in South Africa around the REMox TB clinical trial, Taharqa built towards that goal by catalyzing the development of a Community Advisory Board (CAB). "The CAB serves as a communication channel between the researchers and the community and works toward increasing awareness around TB," he explains. The CAB has spread information about TB through World TB Day events and other workshops, resulting in a more educated and empowered community. Taharqa, and Community Engagement Officers at other REMox TB sites, help TB researchers and local communities both get the most out of their shared experiences.

DR. DALI YIN

Professor, Medicinal Chemistry, Institute Materia Medica

Partners in the Fight

Dr. Dali Yin is a chemist working at the Institute of Materia Medica, in Beijing, China, where he is helping to develop a next-generation TB compound from the riminophenazine class. There is growing interest in this class of compounds, and its potential to yield components of tomorrow's TB and MDR-TB treatments.

Riminophenazines have intrinsic activity against *Mycobacterium tuberculosis*, which causes TB, but the team is working to develop improved analogs with fewer side effects.

Dr. Yin recalls a friend contracting active TB more than 20 years ago. He visited his friend during his 3 months of confinement in a hospital and saw the severe impact of the disease firsthand. The hospital at which his friend was treated is the Beijing Thoracic Tumor and Tuberculosis Research Institute (BTTTRI), another partner in this development program.

DR. ANNEKE HESSELING

Director, Paediatric TB Research Program, Desmond Tutu TB Centre

Pediatric TB: Passing TB from Parent to Child

Children are a barometer of a community's TB problems, says Dr. Anneke Hesseling, based at Stellenbosch University in Cape Town, South Africa. Researchers should not only study the disease in children, she said, but the disease in the context of childrens' families and communities. That's because the source of TB infection in children starts at home—with adults who pass on the disease.

Every 5 minutes, a child dies from TB. New TB drugs are instrumental in helping children receive appropriate and safe TB cures, and also to treat adults to stop the spread of the infection.

GERRY ELSDON

Celebrity and Activist

Using Fame to Further a Cause

TB is considered a disease of poverty, but it can infect anyone. Gerry Elsdon, a former model and celebrity TV show host, should know—she contracted the disease at the height of her career, just as she was trying to get pregnant and start a family.

At first, Gerry could not find out what was wrong. Finally, a physician identified that she had a TB infection in her womb, rendering her infertile.

As she sought treatment, the magnitude of the epidemic began to sink in. Instead of hiding her disease, Gerry decided to go public, appearing in magazines and in interviews and talking about TB. This work has continued long after her cure. Gerry now spends much of her time advocating for TB sufferers, and has used her platform to raise awareness of the disease.

FROM THEORY TO REALITY

A NEW CLINICAL DEVELOPMENT PARADIGM, REALIZED

CHENNAI, INDIA / India accounts for more than 20% of all estimated MDR-TB cases worldwide.

2011 → **NC001** trial validates approach for developing better, faster novel TB regimens that can treat **TB**—including **MDR-TB**—with a single combination therapy → PaMZ could reduce treatment of **TB** and **MDR-TB** to **4 MONTHS**

The first novel TB drug regimen trial successfully validates the theory of regimen development—and reveals promising data on a novel combination.

The TB Alliance's first novel drug regimen trial was a pioneering study that validated a new clinical development paradigm's ability to speed development of improved novel treatment regimens. The NC001, or New Combination 1, trial was the first study to simultaneously test multiple novel TB drug candidates in a new development paradigm. In meeting its milestones, it shows the potential of a novel regimen to shorten, simplify, and transform treatment worldwide.

As the TB pandemic continues to spread and resistance to existing treatment grows, novel TB regimens are needed now more than ever. Novel regimens contain drugs for which there is little or no pre-existing resistance, therefore enabling the potential of these regimens to treat both drug-sensitive TB and MDR-TB in a single combination therapy. The novel three-drug regimen tested in NC001 could revolutionize TB treatment, particularly for drug-resistant disease, by reducing the duration of treatment from 2 years to 4 months—and costing a fraction of today's therapies. This could shorten and simplify TB therapy around the world, facilitate the global scale-up of MDR-TB treatment, and provide ARV-compatible TB treatment for those coinfected with HIV/AIDS.

Novel regimen development represents a major focus of the TB Alliance's R&D efforts and is positioned to emerge as the gold standard for all TB drug clinical development.

Today, more than a decade after the TB Alliance was established, there is a robust pipeline of promising TB drug candidates and an opportunity to test them in combination early in the development process to identify the most promising regimens for further development. But it takes more than promising science to speed new TB regimens to those in need; improvements in infrastructure, resources, and collaboration are necessary as well. It is on these fronts that the cross-sector initiative, the Critical Path to TB Drug Regimens (CPTR), has made much progress. Founded by the Bill & Melinda Gates Foundation, the TB Alliance, and the Critical Path Institute, CPTR is working to facilitate regimen development by bringing sponsors together to identify the most promising combinations and by identifying the regulatory pathways and other tools that accelerate the development process.

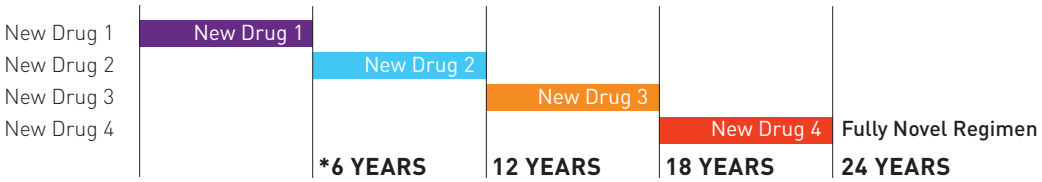
CPTR is also galvanizing the regulatory landscape. The US FDA issued draft guidance around combination drug development in December 2011. FDA's Dr. Janet Woodcock also co-authored an opinion piece in the *New England Journal of Medicine* proposing "co-development" as a useful paradigm to find new tools for life-threatening diseases. Dr. Woodcock specifically recognized the TB Alliance as an organization that was well positioned to continue to evolve and advance this paradigm for TB.

> "Drug developers must embrace a new paradigm that emphasizes sharing of information and collaboration in testing combinations...The TB Alliance and similar groups may be in a position to facilitate these kinds of studies."
>
> **JANET WOODCOCK, M.D.**
> Director, Center for Drug Evaluation and Research, FDA

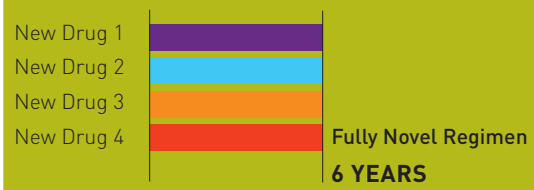
FROM THEORY...

Active TB must be treated with combinations of drugs for maximum efficacy and to prevent resistance. Previously, promising new compounds were tested by substituting or adding treatments into the current therapy, one drug at a time. However, this approach meant that developing a novel 4-drug regimen could take more than a quarter of a century. Today, for the first time in decades, there is a robust pipeline, and an opportunity to test TB drugs together early in the development cycle to speed the development of novel cures. Using a regimen-based development approach could reduce the time to develop a novel TB regimen by 75 percent.

TRADITIONAL TB DRUG DEVELOPMENT



INNOVATIVE CO-DEVELOPMENT PARADIGM



*Years are approximations, and regimens may not always consist of 4 drugs

THE PROMISE OF NOVEL TB DRUG REGIMENS

Novel TB drug regimens could have a transformational effect on the TB treatment landscape, reducing the burden of TB cures for patients and providers alike, and restoring health and hope around the world. These new TB drug regimens show:

- Potential to treat TB and MDR-TB with a single combination treatment
- Potential to dramatically reduce the cost of MDR-TB treatment, facilitating global scale-up of treatment
- Potential to shorten and simplify treatment for both TB and MDR-TB
- Validation of a clinical paradigm that speeds new drugs to people who need them

TO REALITY.

NC001 validates a new clinical paradigm, and shows the promise of a novel TB drug regimen.

NC001 was a Phase II Early Bactericidal Activity (EBA) trial launched in November 2010 and funded by the Bill & Melinda Gates Foundation, UK's Department for International Development, and the United States Agency for International Development. The six-arm, first-of-its-kind study tested the novel TB drug candidate PA-824, the antibiotic moxifloxacin, which is not yet approved for treatment of TB, and pyrazinamide, one of the four drugs in today's standard first-line TB therapy. The three-drug regimen (PaMZ) performed extremely well as compared to the standard of care, showing the potential for a single regimen to treat both drug-sensitive TB and MDR-TB in four months. Furthermore, PaMZ has potential for use by TB/HIV coinfected patients, with no anticipated drug-drug interactions with antiretrovirals.

A TRIAL OF A NOVEL THREE-DRUG COMBINATION MEETS ITS MILESTONES

75% FASTER

Novel regimen development can speed new drugs to patients in a fraction of the time.

The NC001 trial tested PA-824, moxifloxacin, and pyrazinamide in combination and showed the promise of this novel regimen to shorten and simplify treatment. A follow-up study is now being planned.

MAJOR FINDINGS OF THE NC001 STUDY

SUITABILITY OF PaMZ AS A REGIMEN. NC001 tested the efficacy of a novel regimen (PaMZ) and found that it compared favorably to the standard of care in drug-sensitive TB (isoniazid, rifampin, pyrazinamide, and ethambutol). We are now preparing for an 8-week study, which will begin in early 2012 and will test the PaMZ regimen in both drug-sensitive and drug-resistant patients, setting the stage for pivotal registration trials.

"BUILDING BLOCKS" OF FUTURE REGIMENS. NC001 also tested promising two-drug combinations that can serve as the building blocks, or components of future regimens. Importantly, TMC207 and PA-824, each combined with pyrazinamide, were found to be much more efficacious than either drug alone.

NEW ENDPOINTS THAT ALLOW SCALABILITY. The study lent further support to the suitability of time to positivity (TPP) in addition to the more widely accepted Colony Forming Unit (CFU) as an appropriate endpoint in short-term studies. The ability to use TPP as an endpoint would eliminate the need for specialized, cost-intensive mycobacteriology laboratory capabilities, which severely restrict the sites available for the conduct of EBA trials.

THE MOUSE MODEL IS PREDICTIVE. The NC001 trial has provided the first positive, truly prospective testing of mouse model predictions in TB patients. Importantly, it confirmed the murine findings of the utility of the PaMZ regimen; the synergy from the combination of TMC07 and pyrazinamide; the additivity of PA-824 and pyrazinamide; and also the lack of additivity of TMC207 and PA-824.

THE PROMISE OF OUR PIPELINE

The TB Alliance advanced on all fronts throughout 2011 in the pursuit of its mission to develop faster-acting, affordable drugs to fight TB. In addition to the NC001 trial, there were many notable successes this past year.

Along with its partners, the TB Alliance continued to enroll participants in its Phase III clinical trial, REMox TB, to test the ability of two moxifloxacin-containing regimens to reduce treatment time of drug-sensitive TB from 6 months to 4 months. In 2011, additional sites were opened in India, China, and Africa. In particular, additional sites that are part of the NIH's AIDS Clinical Trial Group (ACTG) will participate in REMox TB with the goal of completing enrollment by the end of 2011. At many sites, there are active community engagement initiatives that empower community members with the knowledge to meaningfully participate in TB clinical trials.

Results from REMox TB, which requires 1-year follow-up post-treatment to ensure patients don't relapse, are scheduled to be available by 2014.

Meanwhile, the TB Alliance's preclinical and discovery portfolios continued to advance. The preclinical novel drug combination study, initiated four years ago in collaboration with Johns Hopkins University and the University of Illinois at Chicago, has identified multiple novel drug regimens that could potentially shorten therapy to 2 months or less based on mouse models. These promising regimens, containing both novel and existing drugs, are being evaluated systematically for their suitability for further development to treat both drug-sensitive and drug-resistant TB.

Two late-stage discovery programs, the nitroimidazoles and riminophenazines, have completed lead optimization and are entering final candidate selection. If the lead compounds meet drug candidate criteria, they will be advanced into development and add valuable new

DISCOVERY

TARGET- OR CELL-BASED SCREENING	LEAD IDENTIFICATION	LEAD OPTIMIZATION
Natural Products IMCAS	**Whole-Cell Hit to Lead Program** GSK	**Mycobacterial Gyrase Inhibitors** GSK
TB Drug Discovery Portfolio NITD		**Diarylquinolines** Tibotec/U. of Auckland
Topoisomerase I Inhibitors AZ/NYMC	**Gyrase B Inhibitors** AZ	**Riminophenazines** IMM/BTTTRI
	Folate Biosynthesis Inhibitors AZ	**Pyrazinamide Analogs** Yonsei
	Whole-Cell Hit to Lead Program AZ	
	RNA Polymerase Inhibitors AZ	
	Energy Metabolism Inhibitors AZ/U. Penn	

PRECLINICAL DEVELOPMENT

Nitroimidazoles
U. of Auckland/U. Ill Chicago

Preclinical TB Regimen Development
JHU/U. Ill Chicago

agents to the TB compound pool from which future regimens will be identified.

Projects within "mini-portfolios" in collaboration with GlaxoSmithKline, AstraZeneca, and Novartis continue to make progress and, importantly, leverage the resources of all partners involved. Several novel compound classes have demonstrated efficacy in *in vivo* mouse models and are positioned to enter into preclinical development in the coming year or two.

In addition, the TB Alliance, through active portfolio management, has terminated projects that no longer fit strategically within the larger global pipeline or failed to meet milestones. The following projects were discontinued during the past year: Protease inhibitors, Phenotypic Screening, Malate Synthase Inhibitors, InhA Inhibitors, and Menaquinone Biosynthesis Inhibitors.

NEW PROMISE FROM A FAMILIAR CLASS

Clofazamine is a drug from the riminophenazine class that was developed in the 1950s for use against leprosy, but which has also shown activity against *M.tb.* Unfortunately, riminophenazines cause a particularly problematic side effect—skin discoloration—that exacerbates the stigma associated with TB. But researchers are finding new promise in this old compound as a component of shorter, faster-acting novel regimens.

Since 2007, the TB Alliance has been working with the Institute of Materia Medica (IMM), the Chinese Academy of Medical Sciences, and the Beijing Thoracic Tumor and Tuberculosis Research Institute (BTTTRI) to discover improved next-generation riminophenazines. IMM, in collaboration with the TB Alliance, has designed and synthesized close to 1,000 riminophenazine analogs, and identified a short list of anti-TB compounds that are potent, safe, and stable, and that demonstrate efficacy in murine models of acute infection. Our partners, supported by Chinese government grants, have worked with the Shanghai Institute of Materia Medica and the National Institute for the Control of Pharmaceutical and Biological Products, bringing in further resources to enable the conduct of pharmacokinetic and safety studies. Further excitement around this chemical class is based on its potency and synergy as identified through the preclinical drug combination studies. A lead candidate for preclinical development is expected in 2012. With continued success, a pivotal building block for future novel TB regimens could be on the horizon.

CLINICAL DEVELOPMENT

CLINICAL PHASE I	CLINICAL PHASE II	CLINICAL PHASE III
	PA-824 Novartis	**Moxifloxacin (+ H, R, Z)** Bayer
	TMC207 Tibotec	**Moxifloxacin (+ R, Z, E)** Bayer
	PA-824 / Pyrazinamide	
	TMC207 / Pyrazinamide	
	PA-824/TMC207	
	PA-824 / Moxifloxacin / Pyrazinamide	

Current first-line TB treatment consists of Isoniazid (H) + rifampicin (R) + pyrazinamide (Z) + ethambutol (E)

Novel TB regimen development

OUR R&D PARTNERS

- AstraZeneca (AZ)
- Bayer Healthcare AG (Bayer)
- Beijing Tuberculosis and Thoracic Tumor Research Institute (BTTTRI)
- GlaxoSmithKline (GSK)
- Institute of Materia Medica (IMM)
- Institute of Microbiology, Chinese Academy of Sciences (IMCAS)
- Johns Hopkins University (JHU)
- Johnson & Johnson / Tibotec (Tibotec)
- New York Medical College (NYMC)
- Novartis Institute for Tropical Disease (NITD)
- Novartis Pharmaceutical (Novartis)
- University of Auckland (U. of Auckland)
- University of Illinois at Chicago (U. Ill Chicago)
- University of Pennsylvania School of Medicine (U. Penn)
- Yonsei University (Yonsei)

GAINING CRITICAL MASS:

NEW PARTNERS

IN THE FIGHT AGAINST TB

- The economic impact of TB on India reaches $24 billion per year.
- More than 400 people die from TB every day in China.

TIAJIN, CHINA / Researchers undergo training to support the expansion of the REMox TB trial into several new sites in China.

In 2010, **TB** was responsible for
MORE THAN 5 TIMES
as many deaths as all natural disasters combined

MORE PEOPLE IN SOUTH AFRICA DIE FROM TB EACH YEAR THAN GRADUATE COLLEGE

1/3
of the more than 42 million people living with **HIV** worldwide are infected with **TB**

In Afghanistan, a woman is
more likely to die of TB
than as a result of violence

The TB Alliance is extending our reach across the globe through platforms and collaborations that enable us to cross new thresholds.

New mechanisms help ensure that the TB Alliance and other stakeholders can mount a long-term, sustainable fight for new tools and deliver the improved TB regimens the world so desperately needs, even in the face of financial, scientific, and other challenges.

Coordinating Capabilities through CPTR

The TB Alliance continues to play a lead role in charting the course of the Critical Path to TB Drug Regimens, a cross-sector initiative that aims to speed the introduction of shorter, safer, more effective new TB drug regimens. By expediting testing of promising TB drug candidates in combination and by identifying new regulatory pathways and other tools to accelerate the development process, CPTR aims to facilitate the delivery of dramatically improved treatment to TB patients worldwide.

Since its launch in March 2010, CPTR has grown in size and scope. Now that NC001 has proven the underlying premise of regimen development, CPTR plays an increasingly important role in bringing TB drug sponsors together to identify promising future regimens. Several sponsors have now signed on to share information that will facilitate identification of promising drug combinations and testing.

1. BEIJING, CHINA / The GHRC is expected to play a major role in TB drug development in China and abroad. **2. SOUTH KOREA /** TB Alliance research conducted in partnership with collaborators around the world has produced the largest portfolio of new TB drug candidates in history.

Critical Path to TB Drug Regimens

The Critical Path to TB Drug Regimens is a cross-sector initiative that aims to speed the development and introduction of shorter, safer, more effective new TB drug therapies.

CPTR-PARTICIPATING ORGANIZATIONS:

TB Alliance
Bill & Melinda Gates Foundation
Critical Path Institute

Anacor
AstraZeneca
Bayer
European & Developing Countries Clinical Trials Partnership
GlaxoSmithKline
Johnson & Johnson
Novartis
Otsuka
Pfizer
Sanofi-Aventis
Sequella
Treatment Action Group
Vertex

WATCH THE CPTR LAUNCH—ADDRESSED BY FDA COMMISSIONER DR. MARGARET HAMBURG
WWW.TBALLIANCE.ORG/NEWSCENTER

The Global Health Research & Development Center—China's first PDP

For the fight against TB to be successful, emerging economies and other endemic countries need to be actively engaged in both finding and financing solutions. To that end, in 2011, the TB Alliance worked with the International Scientific Exchange Foundation of China (ISEFC) to launch the Global Health R&D Center (GHRC) of China, the first-ever Chinese Product Development Partnership. This organization will focus on the development of new technologies to combat public health threats in China and abroad, including TB, HIV/AIDS, and malaria.

The TB Alliance will help support the efforts of ISEFC in establishing the GHRC by contributing projects, intellectual property, and disease-specific expertise. The GHRC will facilitate collaboration between public and private entities both in China and around the world, including the Chinese government, pharmaceutical companies, academic institutions, and others in the pursuit of new, affordable innovations that address neglected diseases and improve global health.

This initiative has the potential to leverage new capabilities and resources in the fight against TB within one of the world's highest-burden countries. The GHRC is also viewed as a mechanism to help develop Chinese life sciences capabilities, and to help traverse the nation's "innovation gap" by translating scientific ideas into actual products that will improve health in China and around the world.

Funding, and a Future, for Regimen Development

This past year, the donor community has offered TB Alliance its vote of confidence. The organization received a landmark donation from the Bill & Melinda Gates Foundation for a 5-year renewal grant totaling $165 million to support regimen development.

In addition, the TB Alliance also gained a new donor, the United States Food and Drug Administration (FDA), which is a contributor and a partner in a consortium dedicated to discovering and developing biomarkers, which can, if successful, drastically accelerate the pace of TB drug development. In addition, the FDA is supporting programs to help further establish and improve the accuracy of preclinical models for predicting sterilizing activity and resistance suppression for novel drug combinations.

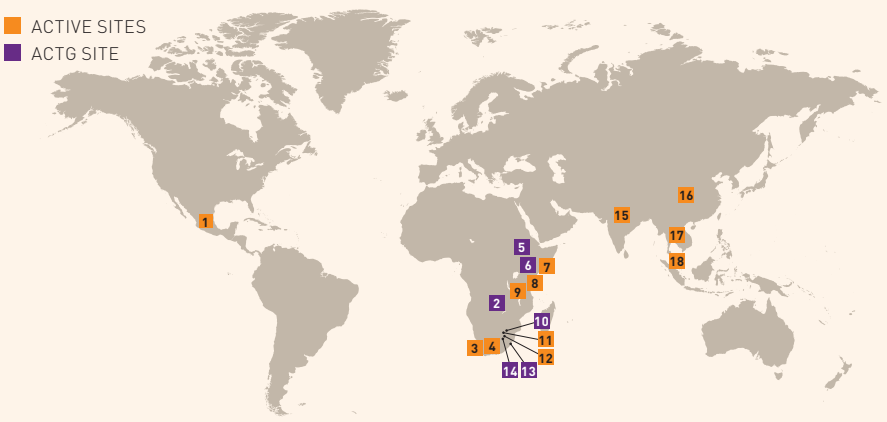
These commitments enable the TB Alliance to perform the work necessary to unleash the promise in our pipeline, but they are also an acknowledgement of the essential nature of our mission, an affirmation of our performance, and recognition of our scientific accomplishments and capabilities.

HARMONIZING TB AND HIV/AIDS RESEARCH THROUGH PARTNERSHIP

Advocacy surrounding the harmonization of diagnosis and treatment of TB and HIV/AIDS continued throughout 2011. But there are also opportunities to harmonize management of the co-epidemic further upstream—beginning with the clinical development of new tools. This year, the TB Alliance has partnered with the United States National Institute of Allergy and Infectious Diseases (NIAID) to use available clinical trial sites from NIAID's AIDS Clinical Trial Group (ACTG) for use in TB drug development trials. The addition of these new sites to the REMox TB clinical trial network will help expand capacity as the REMox TB Phase III global clinical trial advances toward completion of enrollment.

REMox TB: A GLOBAL PHASE III TRIAL

Additional sites have been launched to enable the REMox TB trial to complete enrollment by the end of 2011.



New **ACTG** sites have been added to the REMox TB clinical trial network

REMox SITES AND COUNTRIES

1 GUADALAJARA
2 LUSAKA (2)
3 CAPE TOWN
4 STELLENBOSCH
5 KERICHO
6 ELDORET
7 NAIROBI
8 MOSHI
9 M'BEYA
10 TEMBISA
11 BRITS
12 JOHANNESBURG
13 DURBAN (3)
14 SOWETO
15 INDIA (30)
16 CHINA (3)
17 THAILAND (2)
18 MALAYSIA

CROSSING THE ULTIMATE THRESHOLD:

THE PATIENT'S DOOR

- A person dies from TB every 20 seconds.
- There are nearly 500,000 new MDR-TB patients each year.

CAPE TOWN, SOUTH AFRICA / WHO estimates that one million children suffer from TB each year.

The TB Alliance will not be satisfied until new treatments cross the ultimate threshold—and reach patients in need. That's why we are planning today for product launch, to ensure the rapid uptake of new and improved TB treatment regimens tomorrow.

New TB drug regimens will only have their intended major public health impact when they reach the millions of patients in need. Our commitment to access is defined by our "AAA Mandate"—that is, that new and improved TB regimens will be available to, adopted by, and affordable for those who need them. It is through this work that we link clinical research to the realities experienced by patients, providers, and programs, thereby ensuring that our efforts, above all else, benefit people around the world suffering from TB.

As the date for the introduction of new TB drugs approaches, the TB Alliance continues to build on its foundational work in mapping the pathway from pipeline to patients. Over the past year, the TB Alliance has defined key dynamics of the global TB market, informed the field, brokered important collaborations, and advocated for mechanisms to support the introduction of new, improved TB treatment.

Collaborations as Cornerstone

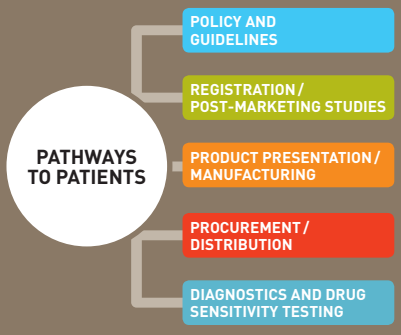
As a Product Development Partnership, the TB Alliance operates based on a model of collaboration. This concept extends to the area of access, where meaningful global partnerships are needed to ensure that new TB treatments are available to, adopted by, and affordable for those who need them.

As the organization looks forward, expanding our partnerships is a critical step in preparing for the launch of TB drugs, starting with a moxifloxacin-based regimen. Over the past year, there have been many efforts to coordinate and leverage the full expertise of additional PDPs, which have relevant experience and also share similar challenges. In so doing, the groups are realizing efficiencies that can help advance global health.

The TB Alliance continues to lead the PDP Access Steering Committee, a group formed in 2008 to enhance the capabilities of PDPs in the area

PLANNING FOR LAUNCH

The TB Alliance works with partners to map the pathway from pipeline to patients.



Several areas demand focus when planning for access to new global health technologies. For more on access, visit the newly launched website, **www.pdpaccess.org**, developed by the TB Alliance in collaboration with other Product Development Partnerships.

WATCH DR. WILLIAM WELLS—ADDRESSING THE LARGE AND MESSY TB DRUG MARKET
WWW.TBALLIANCE.ORG/NEWSCENTER

THE PRIVATE SECTOR— TOO MANY PATIENTS TO IGNORE

TB is widely considered a public health concern and its treatment a public sector responsibility, but the reality of public and private sector involvement was highlighted by TB Alliance and IMS Health research published in the *PLoS ONE* journal. This study found that in some countries, the volume of TB drugs sold in the private sector equals or exceeds the volume distributed in the public sector. Additionally, TB drug dosages sold in the private sector varied widely. The resulting irregular TB treatment practices could be driving treatment failures and contributing to the emergence of MDR-TB.

This research fundamentally shifts the global understanding of the TB market, showing the need for the private sector to become a partner in the provision of rational, appropriate TB treatment. It is the first detailed study of the private TB drug market across multiple high-burden countries. Sixty percent of the world's TB burden is present in the 10 study countries.

Since publication, TB Alliance staff has been speaking with government officials and other key constituents about the importance of scaling up public-private mix programs for TB care and investing in quality improvements of private sector TB care.

The average **TB** patient loses nearly

1/3

of yearly household earnings

NEW, MORE AFFORDABLE

MDR-TB drug regimens will help enable scale up of treatment

of access. We manage a grant from the Netherlands Directorate-General for International Cooperation on behalf of the group, which has funded eight discussion papers on critical topics including pharmacovigilance, manufacturing and supply, economics and financing, and country decision-making, and also a summit on access with an eye toward improving the efficiency and cost-effectiveness of PDPs. The TB Alliance also participates in the PDP Regulatory Group, which identifies the information needed to make informed decisions that reduce delays in product introduction and the added costs often associated with the regulatory process.

Building on the 2010 *Open Forum* conference, we continue to collaborate, both formally and informally, with National TB Programs, WHO, and regulators. Over the past year, the TB Alliance has participated in reviews of National TB Programs in Indonesia and Nigeria. These visits provided opportunities to improve TB treatment today, and to gain an in-depth view of these TB programs and the challenges they face—information that can be fed back into the R&D process and the market access strategy to ensure that the most useful and promising TB treatments are developed and made available for tomorrow.

Getting the Word out: Past and Future Regimen Change

As part of our continuing commitment to inform the treatment landscape, this year the TB Alliance published two research studies in the *International Journal of Tuberculosis and Lung Disease*. The papers are based on a study by the TB Alliance and Management Sciences for Health in which country stakeholders in 21 TB high-burden countries were interviewed. The papers offer a wake-up call to the TB community on the need for planning and preparation to speed regimen change.

Preparing for Launch

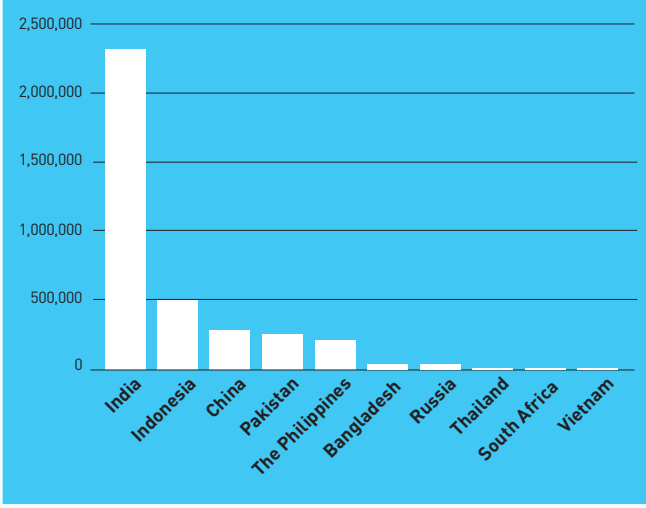
Today, the TB Alliance is taking steps toward product introduction. This includes gathering patient perceptions of the moxifloxacin-based regimen and also patient expenditure data to understand the full cost of first-line treatment, not only to the health system but also to patients. Additionally, the TB Alliance has formed an Access Advisory Committee, which will help guide TB Alliance strategy while also championing the introduction of new regimens.

INFORMING THE TB TREATMENT LANDSCAPE

- **35% of all TB drug dosages sold in the private sector fall outside national and international treatment recommendations. There were 111 different first-line TB drug dosages and combinations detected in the private sector, compared with the 14 deemed necessary. The dissemination of non-standard treatment can contribute to escalating rates of MDR-TB.**
- **Several of the highest-burden countries had particularly large private markets. In India, Indonesia, Pakistan, and the Philippines, enough TB drugs are sold in the private sector to treat all, or nearly all, incident TB patients with a full TB drug regimen. This is without even considering the 60 to 80 percent of cases covered by the public sector.**
- **The private sector is distributing drugs to treat fewer than 10% of MDR-TB patients, indicating that the gap in access to MDR-TB treatment in the private sector mirrors that of the public sector in many countries.**

TB Drug Volume in Private Sector

(x-axis) # Cases potentially covered by private market

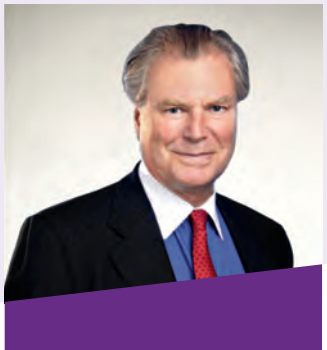


DEAR DONORS, STAKEHOLDERS, PARTNERS AND PATIENTS,

As we look back on the significant accomplishments over this past year, it is clear that the TB Alliance—and the field of TB drug development—has crossed a threshold. Since 2000, the TB Alliance and our partners have been working to build history's largest TB drug portfolio. But in 2011, with the successful completion of the landmark NC001, or New Combination 1, trial, we have entered a new era. NC001 validated an innovative clinical paradigm that builds on our previous advances by testing promising combinations of TB drugs together. In so doing, the approach can dramatically speed the development of novel TB drug regimens, fast tracking scientific breakthroughs that would have previously taken decades to achieve.

Novel TB drug regimens show promise to be shorter, simpler, and safer TB cures, and can transform the epidemic by treating TB and MDR-TB in a single combination pill. Today, regimen development represents the focus of the TB Alliance's efforts and is an emerging gold standard for the field at large.

DR. MEL SPIGELMAN
President and CEO



DR. BRUCE CARTER
Chairman of the Board

Nearly 2 million people die each year from TB. Although the new tools to turn the TB tide are on the brink of becoming a reality, the challenging funding environment demands that we mount more long-term sustainable approaches to support the development of new TB cures. Over the past year, the TB Alliance has forged several new partnerships that help us achieve that goal, and open new doors that multiply our impact around the world.

These collaborations include a new Product Development Partnership in China—the country's first—and a collaboration with the National Institute of Allergy and Infectious Diseases' AIDS Clinical Trial Group to provide clinical trial site capacity to help us complete the Phase III REMox TB trial. Additionally, the Critical Path to TB Drug Regimens initiative continues to gain momentum as several companies with clinical-stage TB drugs have agreed to share information about their drug candidates with one another, with the goal of assembling and developing the best possible TB regimens, regardless of sponsor.

Indeed, we have reached a new era in the search for TB cures, but the final threshold is still before us—getting new treatments into the hands of those who need them. To this end, we are working all over the world, connecting with National Treatment Program managers, the WHO, governments, regulators, and other key players to secure the necessary partnerships critical to ensuring that improved new TB treatments are adopted, available, and affordable to those who need them.

In the face of heightened global economic fears and an unrelenting TB pandemic, the TB Alliance remains focused and committed to our mission. We are grateful for the support and vision of our donors and partners, but still more is needed. We invite all those committed to global health, international development, and a healthy and TB-free world to join us in our quest to vanquish one of humanity's most resilient pandemics—once and for all.

All the best,

Dr. Mel Spigelman
President and CEO, TB Alliance

Dr. Bruce Carter
Chairman of the Board, TB Alliance

FINANCIALS AND ACKNOWLEDGEMENTS

Statement of Financial Position

YEAR ENDED DECEMBER 31,		2010
ASSETS:		
Cash and cash equivalents	$	51,318,691
Assets limited to use		916,043
Investments at fair value		—
Accounts receivable		2,833,938
Pledges receivable		—
Other assets		294,533
Fixed assets, net		2,296,844
	$	**57,660,049**
LIABILITIES AND NET ASSETS:		
Liabilities:		
Accounts payable and other liabilities	$	10,678,121
Accrued payroll and payroll-related liabilities		1,015,892
Deferred revenue (Note 6)		14,600,176
Deferred rent		935,078
Total Liabilities	**$**	**27,229,267**
Commitments	**$**	**—**
Net assets:		
Unrestricted net assets	$	30,430,782
	$	**57,660,049**

Statement of Activities

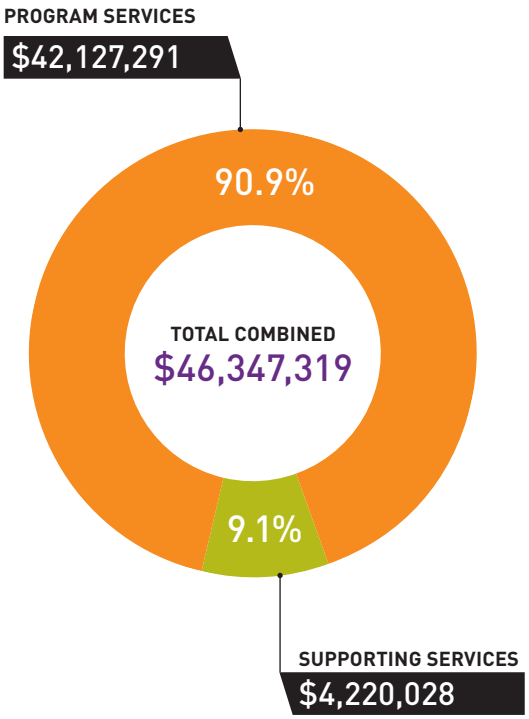
YEAR ENDED DECEMBER 31,		2010
PUBLIC SUPPORT AND OTHER REVENUE:		Unrestricted
Contributions	$	42,386,671
Grants		3,983,457
Interest and dividend income		107,983
Net realized and unrealized gains on investments		—
Miscellaneous income		114,321
Total public support and other revenue	**$**	**46,592,432**
Expenses:		
Program services:		
Research and development	$	38,973,162
Business development		494,009
Public affairs and policy		2,660,120
Total program services	**$**	**42,127,291**
Supporting services:		
Management and general	$	3,549,222
Fundraising		670,806
Total supporting services		**4,220,028**
Total expenses		**46,347,319**
Change in net assets before foreign translation gain		**245,113**
Foreign translation gain		**(377,985)**
Change in net assets		**(132,872)**
Net assets, beginning of year	**$**	**30,563,654**
Net assets, end of year	**$**	**30,430,782**

Comprehensive 2010 TB Alliance financial statements are available at:
www.tballiance.org/newscenter/publications.php

Statement of Cash Flows

YEAR ENDED DECEMBER 31,		2010
CASH FLOWS FROM OPERATING ACTIVITIES:		
Change in net assets	$	(132,872)
Adjustments to reconcile change in net assets to net cash provided by operating activities:		
Depreciation and amortization		430,256
Loss on disposal of fixed assets		—
Realized gain on sales of investments at fair value, net		—
Unrealized losses (gains) on investments at fair value		—
(Increase) decrease in assets:		
Assets limited to use		(2,819)
Accounts receivable		(2,020,439)
Pledges receivable		1,439,551
Other assets		42,916
Increase (decrease) in liabilities:		
Accounts payable and other liabilities		2,052,886
Accrued payroll and related liabilities		92,108
Deferred revenue		1,503,038
Deferred rent	$	(83,611)
Net cash provided by operating activities	**$**	**3,321,014**
CASH FLOWS FROM INVESTING ACTIVITIES:		
Purchase of investments		—
Proceeds from sale of investments		3,000,000
Purchase of fixed assets		(23,947)
Net cash used in investing activities		**2,976,053**
Net increase in cash and cash equivalents		**6,297,067**
Cash and cash equivalents, beginning of year	**$**	**45,021,624**
Cash and cash equivalents, end of year	**$**	**51,318,691**
SUPPLEMENTAL DISCLOSURE OF CASH FLOW INFORMATION:		
Cash paid for interest	$	—

Program Services Vs. Supporting Services



TB Alliance Stakeholders Association

American Lung Association

American Thoracic Society

Association of the British Pharmaceutical Industry

Bill & Melinda Gates Foundation

Community Representative, Francis George Apina

Eli Lilly and Company

European Commission

GBC Health

Global Fund to Fight AIDS, TB and Malaria

Global Health Advocates

Indian Council of Medical Research

Infectious Diseases Society of America

International Union Against Tuberculosis and Lung Disease

Irish Aid

JATA Research Institute of Tuberculosis

KNCV Tuberculosis Foundation

National Institute for Research in Tuberculosis, India

New Jersey Medical School Global Tuberculosis Institute

Novartis India, Ltd.

Oswaldo Cruz Foundation

Partners in Health

RESULTS

RTI International

Sequella, Inc.

South African Medical Research Council

Stop TB Partnership

TB Alert

Treatment Action Group

Tropical Disease Foundation

U.K. Department for International Development

U.S. Agency for International Development

U.S. Centers for Disease Control and Prevention

UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases

Wellcome Trust

World Health Organization

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Senior Vice President, Business Development

Zhenkun Ma, Ph.D.
Chief Scientific Officer

Carl Mendel, M.D.
Senior Vice President, Research and Development

Colleen Pero, M.A.
Chief Administrative Officer

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Chairman of the Board,
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Bill & Melinda Gates Foundation

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Julia Gregory
Formerly, President & Chief Executive
Officer, Five Prime Therapeutics

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Symphony Capital LLC

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Director, Center for Technological
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Oswaldo Cruz Foundation (FIOCRUZ)

James T. Morris
President, Pacers Sports
and Entertainment

Mel Spigelman, M.D.
President & Chief Executive Officer,
TB Alliance

Recognition of Support

Bill & Melinda Gates Foundation

European Commission

United Kingdom Department
for International Development

United States Agency for
International Development

United States Food and
Drug Administration

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About the TB Alliance
The Global Alliance for TB Drug Development is a not-for-profit, tax-exempt organization recognized under section 501(c)3 of the United States Internal Revenue Code; contributions are tax-deductible in the United States. Its Belgium branch office was also registered in the Annex of the Belgian State Gazette for non-profit organizations on February 28, 2002.

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Concept and Design
Ideas On Purpose, ideasonpurpose.com

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SOUTH AFRICA / PDPs have more than 140 technologies in their collective pipelines. The molecules depicted on these children's shirts represent neglected disease drug candidates with the potential to elevate global health, and provide hope and opportunity to billions.

ON THE BRINK: THE CRITICAL NEED FOR

MORE FUNDING

$1=$2

The multiplier effect—total value of TB Alliance programs is more than **twice** our investment, meaning every dollar given to the TB Alliance produces roughly $2 in impact.

MORE FUNDING
MEANS
MORE IMPACT

Thank you for your ongoing support of our mission to find better, faster-acting drugs to treat tuberculosis. With your help, we can transform lives.

The TB Alliance wishes to thank its donors for their help in pursuit of our vision—a world without TB. Through this support, working with our partners worldwide, we can continue to cross scientific and other thresholds to ultimately transform our vision into reality.

The TB Alliance has also been able to deepen its impact and extract greater value from its funds due to the generous in-kind contributions from its partners. For instance, every dollar given to the TB Alliance produces roughly $2 worth of output. This leveraging of resources makes donors' contributions go further and accomplish far greater impact than otherwise possible.

More Support is Needed for a Better Cure

TB perpetuates the poverty cycle and is one of the world's worst killers, yet it is among the most neglected and underfunded diseases in the world. The TB Alliance is working to stop this deadly pandemic and has created the largest pipeline of TB drugs in history. However, with this success comes the need for additional support to mount the late-stage clinical trials to bring promising new regimens through the final stages of development. New tools offer hope for transforming the epidemic—and for crossing the final threshold to create a world without TB.

Please support us in finding new and faster cures for TB.

TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

The TB Alliance accelerates the discovery and development of faster-acting and affordable drugs to fight tuberculosis. Through innovative science and with partners around the globe, we aim to ensure equitable access to faster, better tuberculosis cures that will advance global health and prosperity.

TBALLIANCE.ORG