TB Alliance | 20 YEARS OF IMPACT

Gaining Ground

2020 Annual Report

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www.tballiance.org/annualreport2020

About TB Alliance

The world is in desperate need of improved, faster-acting and affordable tuberculosis drug regimens that are available to all who need them. These new cures can bring renewed health, hope and prosperity to millions. Since our inception in 2000, TB Alliance has contributed to the global search for and development of new TB drugs and regimens, catalyzing the field and convening cross-sector partnerships to forge the progress that is urgently needed for better TB treatments.
Learn more about TB Alliance here.

A Message from the CEO and Board Chair

This past year has been an extremely challenging year. The COVID-19 pandemic, which spanned virtually the entirety of 2020, continues to take a severe toll on lives and livelihoods around the world. In recognition of this once in a lifetime challenge, we stood in solidarity with other tuberculosis (TB) research leaders on World TB Day this past March in the fight against COVID-19 – a stance that is just as critical today as it was almost a year ago.

In this year's report, *Gaining Ground*, we detail the progress made under uniquely challenging conditions in developing new treatments that aim to improve the lives of TB sufferers around the world. The fact that we have managed to sustain momentum throughout this 20th anniversary year of the TB Alliance is a tremendous tribute to the dedication, capabilities, and hard work of our partners and staff.

Our treatment for highly drug-resistant forms of TB continued to reach major milestones toward global accessibility. The first regulatory approval in 2019 by the US Food and Drug Administration was followed this past year by approvals from the European Commission and Drug Controller General of India, as well as incorporation into World Health Organization (WHO) guidelines. Operational research programs are now underway in 9 countries, with many more expected to join in 2021 through programs like LIFT-TB, supported by the Republic of Korea through the Global Disease Eradication Fund. We profoundly thank our many partners and donors without whom this unprecedented rate of progress for a new TB drug could never have been achieved. We were also profoundly honored by the Prix Galien Award for Best Pharmaceutical Agent that was bestowed on pretomanid last year.

Despite the numerous headwinds presented by the COVID-19 pandemic, including lockdowns, travel restrictions, closing of TB hospitals, and diversion of TB staff, our three late-stage studies (Nix-TB, ZeNix, and SimpliciTB) have continued to progress well. Enrollment in the studies was completed in 2020 and top-line results will be available in 2021.

Similarly, multiple challenges arose for compounds in earlier stages of clinical development. Our progression of the drug candidates TBI-223, TBAJ-587, and TBAJ-876 has only been possible because of rapid flexibility on choosing Phase 1 sites that could operate through the COVID-19 pandemic, as well as our engagement with the Innovative Medicines Initiative (IMI). The development of TBA-7371 and sutezolid has also continued through a close partnership with the Gates Medical Research Institute.

Our earlier stage research has similarly progressed despite the challenges of COVID-19 – this includes our internal TB discovery programs, advances in our National Institutes of Health (NIH) Centers of Excellence for Translational Research program, as well as new research into new treatments for non-tuberculosis mycobacteria with support from the Cystic Fibrosis Foundation.

Our long-term vision, which is more urgent than ever in the wake of COVID-19, is a days- to weeks-long therapy that would serve to lift immense burdens from patients and health care systems alike. We are actively exploring new ways to achieve this beyond the conventional paradigms of antibiotic drug discovery. This includes taking advantage of advances in artificial intelligence and host-directed therapies, such as immunotherapeutics and therapeutic vaccines. We must continue to push the boundaries of scientific advances in fighting TB.

None of these achievements would have been possible without the dedication and determination of our partners, donors, stakeholders, and above all, our clinical trial participants. It is because of this engagement that we can envision a world in which the time it takes to cure TB is measured in days, not months, and ultimately this disease is vanquished.

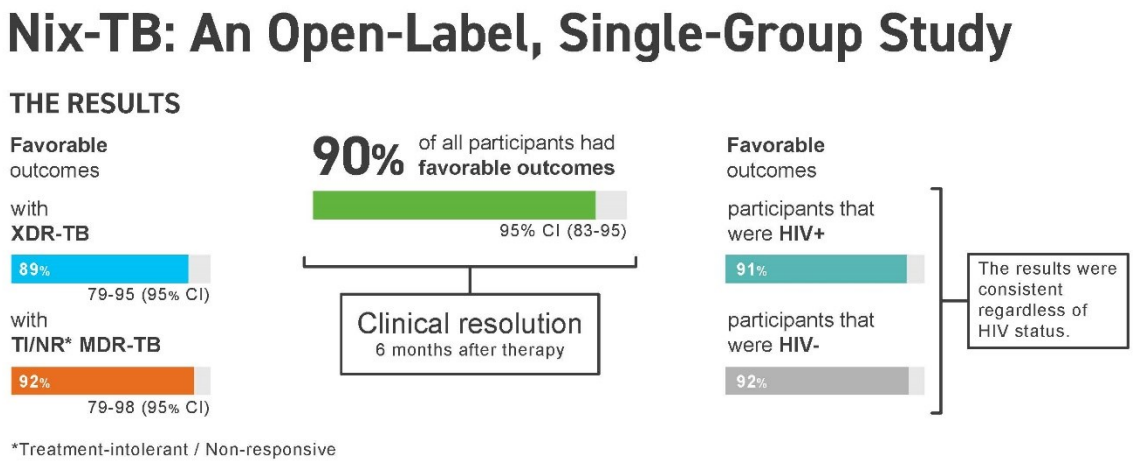
Mel Spigelman
President and CEO, TB Alliance

Bruce Carter
Chairman of the Board, TB Alliance

Research & Development

Results from Nix-TB Clinical Trial

The Nix-TB clinical trial demonstrated that a three-drug, six-month, all-oral regimen had a favorable outcome rate of 90 percent in people with highly drug-resistant forms of TB. According to the WHO, historic treatment success rates for multidrug-resistant (MDR) TB have been about 57 percent and about 43 percent for extensively drug-resistant (XDR) TB. Nix-TB is a Phase 3, open-label trial that enrolled 109 patients at three sites in South Africa. Of the 109 patients included in the clinical trial, 71 (65.1%) were classified as having XDR-TB, 19 (17.4%) as having MDR-TB that was non-responsive to treatment, and 19 (17.4%) as having MDR-TB but could not tolerate their therapy. Of all 109 patients, 56 (51.4%) were HIV positive. The 90 percent favorable outcome rate six months after the completion of therapy was similar for both HIV positive and HIV negative patients. Further results of this pivotal trial were published in the *New England Journal of Medicine* in March 2020.



TB and HIV Are a Deadly Duo

While fortunately more and more people are living with HIV, many of them are dying of TB – TB is the leading killer of people with HIV/AIDS. Because highly resistant forms of TB frequently afflicts HIV positive patients, they comprised just over half of the study population. The results of a HIV subgroup analysis were presented by Dr. Morounfolu Olugbosi, senior director of Clinical Development at TB Alliance, in July 2020 at the AIDS 2020 virtual conference. All 56 HIV positive patients were on antiretroviral (ARV) therapy during the study, and all except two had been receiving ARV therapy before enrolling. The results of the Nix-TB trial demonstrated a 90 percent favorable outcome in patients with highly resistant TB, and these results were consistent regardless of HIV status.

Phase 3 Clinical Research Updates

ZeNix

- The Phase 3 ZeNix clinical trial seeks to optimize the linezolid dosing that was used in the BPaL regimen in the Nix-TB study by evaluating the effects of both lower doses and shorter durations of linezolid administration.
- Patients from Georgia, South Africa, Russia, and Moldova are enrolled in the trial, and primary endpoint results are expected in 2021.

SimpliciTB

- The Phase 3 SimpliciTB clinical trial is evaluating a new regimen to treat both drug-sensitive (DS) and drug-resistant (DR) TB patients. The trial is testing a novel drug combination of bedaquiline (B), pretomanid (Pa), moxifloxacin (M) and pyrazinamide (Z) (known as the BPaMZ regimen).
- Despite challenges due to the emerging COVID-19 pandemic, and with a great effort from partners at clinical trial sites around the world, enrollment in SimpliciTB was completed in March 2020 with participants enrolled at 26 sites in eight countries on four continents.

Phase 1 Research

TBI-223

- In 2020, TB Alliance completed a SAD (Single Ascending Dose) study for TBI-223, with a MAD (Maximal Tolerated Dose) study to begin in early 2021.

TBAJ-876

- TB Alliance completed Investigational New Drug enabling studies and began Phase 1 trials for TBAJ-876 in 2020.

TBAJ-587

Clinical-stage testing began in 2020 for TBAJ-587. The compound was advanced in partnership with the Innovative Medicines Initiative (IMI).

Innovation in the EU

TB Alliance continued its partnership with the Innovative Medicines Initiative (IMI), a public-private partnership between the European Union and the European pharmaceutical industry, in order to facilitate the development of medicines, especially in areas of unmet need.

- As part of this program, the ERA4TB project is focused on developing new TB treatments, and in December 2020 a Phase 1 study of TB Alliance's new compound (TBAJ-587) began and the first dose was administered.

EU-PEARL is an IMI program aiming to reimagine how clinical trials are designed by making them more efficient and patient friendly. The project focuses on four disease areas: major depressive disorder, tuberculosis, the liver disease nonalcoholic steatohepatitis, and neurofibromatosis.

Spotlight: Dr. Suzette Oelofse

Suzette Oelofse, MBChB, is a Research Medical Officer at the Lung Institute, a part of the University of Cape Town. Dr. Oelofse provides clinical services and conducts research in the field of respiratory medicines, including TB. During the virtual 51st Annual Union Conference on Lung Health, Dr. Oelofse gave an Oral Abstract Presentation of findings on how the Phase 3 Nix-TB clinical trial compared to a prospectively recruited XDR-TB cohort. “I see many patients with these forms of highly resistant TB. I’ve seen how they’ve had to take thousands of pills over the course of many months, and sometimes years, and seen how the treatment still didn’t work for most of them,” said Dr. Oelofse, who treats TB patients in Cape Town, South Africa. “This three-drug, all-oral, six-month regimen has proven efficacy and offers a reduction in pill burden and duration of treatment that could have a meaningful impact for patients. Ongoing operational research programs and additional clinical studies will continue to generate valuable evidence for its safety and efficacy.”

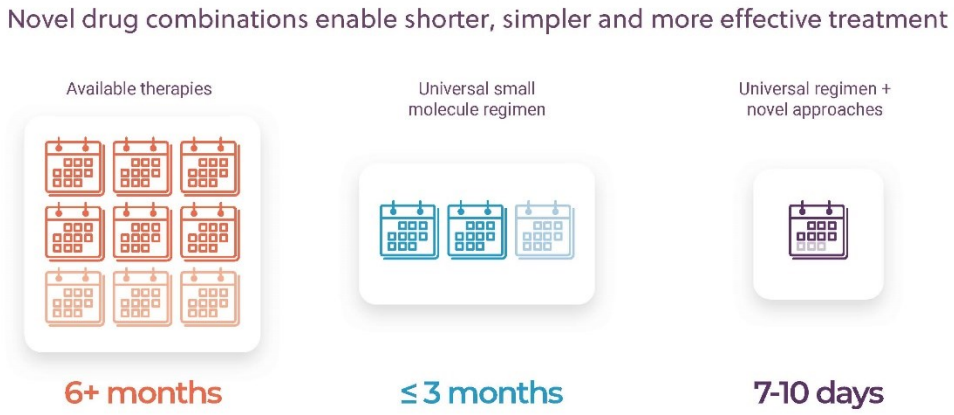
Discovery

The Future of TB Treatment

TB Alliance manages the largest pipeline of new TB drugs in history and has advanced multiple products to market. Projects with the potential to have the greatest impact on the disease, while being cost-effective and simple to administer, are prioritized. Finding short, effective, and simple regimens is our goal.

Our researchers are exploring ways to improve the treatment experience for patients. One area that may have potential is learning how immunotherapy can be used to improve the treatment experience for TB patients, and by learning from the success that the approach has had for people with other diseases like cancer.

Today, the advances that have been made in the understanding of immune modulation, as well as the biology of TB, coupled with progress in artificial intelligence, offers a real promise of achieving a significantly shorter treatment regimen that can help achieve global goals of ending the TB pandemic.



Leveraging Partnerships toward Global TB Drug Pipeline

Center of Excellence

- The National Institute of Allergy and Infectious Diseases (NIAID) awarded TB Alliance a Center of Excellence in Translational Research (CETR) grant for TB drug development, which is being carried out with partners at the University of Illinois at Chicago, Harvard University, Johns Hopkins University, and Research Triangle Institute. Throughout 2020, this partnership advanced the identification and optimization of various molecules and candidates through early-stage discovery phases. Despite many lab closures and complications due to the COVID-19 pandemic, CETR projects continued to meet program goals.

Artificial Intelligence

- In a partnership announced in June 2020, TB Alliance will make use of InveniAI's AI and machine learning platform, AlphaMeld®, to identify and accelerate transformative therapies for the management, treatment, and cure of TB through an AI driven analysis of immunomodulatory pathways and targets with greatest impact on bacterial clearance.

Spotlight: Developing Treatments against NTM

In 2019, the Cystic Fibrosis Foundation collaborated with TB Alliance to advance a drug discovery program in partnership with Johns Hopkins University for the treatment of nontuberculous mycobacteria (NTM), which are increasingly found among people with cystic fibrosis. In 2020, the initiative successfully identified lead compounds from two different series with the potential to treat NTM infections. NTM infections are difficult to treat, requiring antibiotics for a year or longer with no guarantee of a cure, and with a risk of serious side effects. Identifying these compounds will enable program researchers to develop a new treatment, or treatments, that are improved over currently available medicines.

Access

Accelerating Access for Patients

In the year since the first regulatory approval for a three-drug, six-month, all-oral regimen to treat highly resistant TB, TB Alliance and partners have worked to accelerate the global approval and accessibility of this new tool to appropriate patients in the fight against TB. Highlights in the effort to expand global access to pretomanid over the past year include:

- Listing in the Stop TB Partnership's Global Drug Facility (GDF) ensured availability in 150 low- and middle-income countries.
- The WHO issued new guidelines recommending the regimen under operational research conditions.
- Enrollment was completed in TB Alliance's Phase 3 ZeNix and SimpliciTB clinical trials evaluating new combination regimens.
- Received approval from the Drug Controller General of India (DCGI) for conditional access under the National Tuberculosis Elimination Program.
- Received marketing authorization from the European Commission.
- The LIFT-TB (Leveraging Innovation for Faster Treatment of Tuberculosis) initiative was launched to broaden adoption of the regimen, targeting seven countries across Southeast and Central Asia.
- Ukraine and Tajikistan provided access to the new treatment regimen through operational research conditions for highly-resistant TB patients.
- Funded by the United States Agency for International Development (USAID), a new clinical access program will enroll 400 people in South Africa for treatment with the three-drug, six-month, all-oral regimen.

Realizing Global Accessibility through Patient Access Program

In May 2020, TB Alliance's commercialization partner Viatris (formerly called Mylan) launched a Named Patient Access Program (NPAP) to provide access to pretomanid for use as part of a three-drug, all-oral regimen and to help ensure that physicians can consider the drug as a viable treatment option for patients, regardless of where they live. With national registrations underway around the world, the NPAP is designed for patients in countries where regulatory approval or other access mechanisms are not yet available. To learn more about this program or to apply, please visit: www.accesspretomanid.com.

Ensuring Availability through Partnerships

Within five months of receiving approval for a TB treatment, TB Alliance had secured commercialization agreements with three partners to ensure that the regimen is accessible and available around the world. The partners include: Viatris (formerly Mylan), Macleods, and Hongqi Pharma. Multiple manufacturing partnerships will help facilitate global coverage of TB markets and further promote competitive and sustainable pricing. In addition to these agreements, the Stop TB Partnership's Global Drug Facility included the new treatment in its product catalog, helping to ensure global access to those in need.

Research to BENEFIT Kids

It is estimated that about 2 million children are infected with DR-TB and more than 30,000 become sick with active DR-TB each year. While TB Alliance led the introduction of child-friendly medicines available to treat drug-susceptible TB, there remain critical gaps in the availability of medicines designed for children with DR-TB. This results in suboptimal treatment options, putting children at risk for substantially preventable morbidity and mortality. Stellenbosch University has organized a comprehensive network of partners to help address these availability gaps in key second-line medicines for children under the BENEFIT Kids Project (Better Evidence and Formulations for Improved MDR-TB Treatment for Children), funded by Unitaid. TB Alliance is contributing to the BENEFIT Kids project by stimulating progress, partnering with generic manufacturers, and ensuring development of novel child-friendly medicines or optimized formulations suitable for administering to children.

Spotlight: LIFT-TB

TB Alliance, in partnership with ITRC, KOICA, and KNCV, announced an initiative to broaden adoption and scale-up of new TB treatment regimens. This initiative, known as LIFT-TB, will also seek to increase treatment completion rates for drug-resistant forms of TB in some of the countries most affected by this form of TB across the Southeast and Central Asian regions, namely Indonesia, Myanmar, the Philippines, Vietnam, Kyrgyzstan, Ukraine, and Uzbekistan.

Partnerships

Fighting Pandemics

In July 2020, leading voices in global health innovation and pandemic preparedness and response shared insight into enabling the rapid innovation and collaboration required to tackle the world's most threatening pandemics, including COVID-19, TB, HIV/AIDS, and malaria. These discussions took place during *Fighting Pandemics | 2020 and Beyond*, hosted by TB Alliance.

The virtual event was moderated by *The Wall Street Journal* Senior Writer, Betsy McKay and featured Dr. Anthony Fauci, M.D., Director, National Institute of Allergy and Infectious Diseases; Dr. Soumya Swaminathan, M.D., Chief Scientist, World Health Organization; and Dr. Ariel Pablos-Méndez, Founding Board Member, TB Alliance and Professor of Medicine, Columbia University.

Throughout the discussion, the experts noted that funding and political will are significant determinants of the pace of progress against pandemics – both new and old. Dr. Fauci pointed to the importance of consistent commitments that extend beyond individual actors, noting that "the fundamental principle of having a unified approach so that the political leadership supports the public health approach is obviously optimal." The speakers also discussed the experiences, progress, and obstacles relating to global health product development, delving into concerns about efforts against COVID-19.

Dr. Swaminathan further called for the world to avoid ignoring preexisting pandemics, such as tuberculosis, HIV/AIDS, and malaria in the face of COVID-19. She said that the world has seen "tremendous scientific collaboration in this pandemic and willingness to share data, knowledge, and experiences. If that same philosophy and that same collaboration could go into developing drugs and vaccines for tuberculosis [and other neglected diseases], I think we could make a lot of progress."

20 Years of Impact

Amid a global resurgence of TB in the year 2000, a diverse group of organizations gathered in Cape Town, South Africa. On February 8th of that year, these partners issued the Cape Town Declaration, describing the increasing TB burden as "a blot on the consciousness of human kind." From this declaration came the call for the establishment of TB Alliance, a nonprofit product development partnership that would be dedicated to discovering, developing, and delivering faster, better TB cures.

When TB Alliance began this journey in 2000, the vision was clear: a world where no one dies of TB. Over the past 20 years, we've advanced toward this goal, and with help from partners and the global TB community, we continue to strive to make this vision a reality.

Spotlight: Dr. Ariel Pablos-Méndez

Dr. Ariel Pablos-Méndez founded the TB Alliance in 2000 and, today, serves as a member of the Board of Directors. He has dedicated much of his professional career in medicine to eradicating TB, with a particular focus on multidrug-resistant TB. In July 2020, Dr. Pablos-Méndez participated in the *Fighting Pandemics | 2020 and Beyond* webinar, where he urged the global health community to "continue to work on the science and technology of new tools," and to "go beyond current paradigms" to achieve progress. He is currently a Professor of Medicine at Columbia University Irving Medical Center and had previously worked as Director of Knowledge Management at the World Health Organization and Managing Director for Global Health at The Rockefeller Foundation. In 2011, Dr. Pablos-Méndez was appointed by President Obama (with U.S. Senate consent) to lead USAID's bureau for Global Health.

Financials

Leveraging Resources

TB Alliance relies on support from our donors and we are indebted to them for their support. None of the accomplishments of the past year would have been possible without their continued commitment. TB Alliance makes every effort to ensure donor money contributes optimally to developing and enabling widespread access to impactful and affordable new TB therapies.

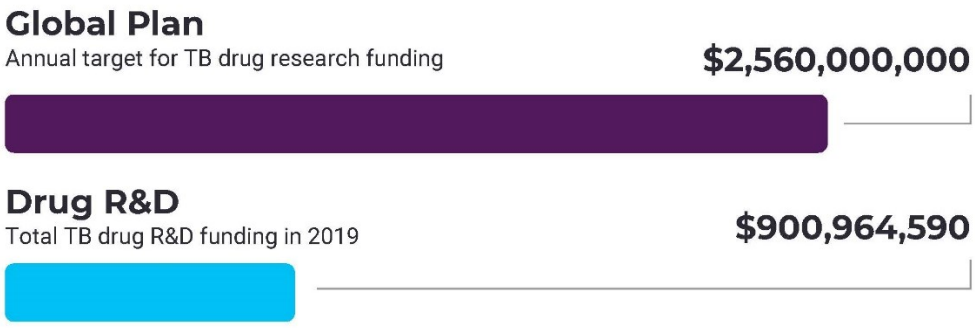
Download our audited 2019 financial statement

Fighting a Pandemic through New Challenges

The WHO's Global Tuberculosis (TB) Report 2020 confirms that efforts to track and treat TB worldwide continued to trend in a positive direction during 2019. However, it also notes the more than $1 billion annual shortfall in funding targets for TB research persists. Full funding of a robust portfolio of new TB treatments, vaccines, and diagnostics – as well as investment in ensuring widespread access to those technologies – is needed to realize rapid and effective TB prevention, diagnosis, and therapy for all.

While 2019 progress was moderately encouraging, hard-won gains against TB are at risk. The report estimates that the number of people developing TB could increase by more than 1 million per year between 2020–2025 due to COVID-19.

The emergence of the COVID-19 pandemic renders the pursuit of funding for TB research and control more competitive than ever before, while illustrating what is possible when stakeholders around the world mobilize against a health threat with urgency and willingness to invest. Like COVID-19, any attempt to eradicate TB requires a tremendous global financial commitment to discover and develop new technological modalities, including vaccines, therapeutics, and diagnostics. The TB field remains far from realizing those resources.



TB Alliance is indebted to its partners, especially all participants in our clinical trials, for the progress seen in 2020.