

SECURING A TUBERCULOSIS-FREE FUTURE



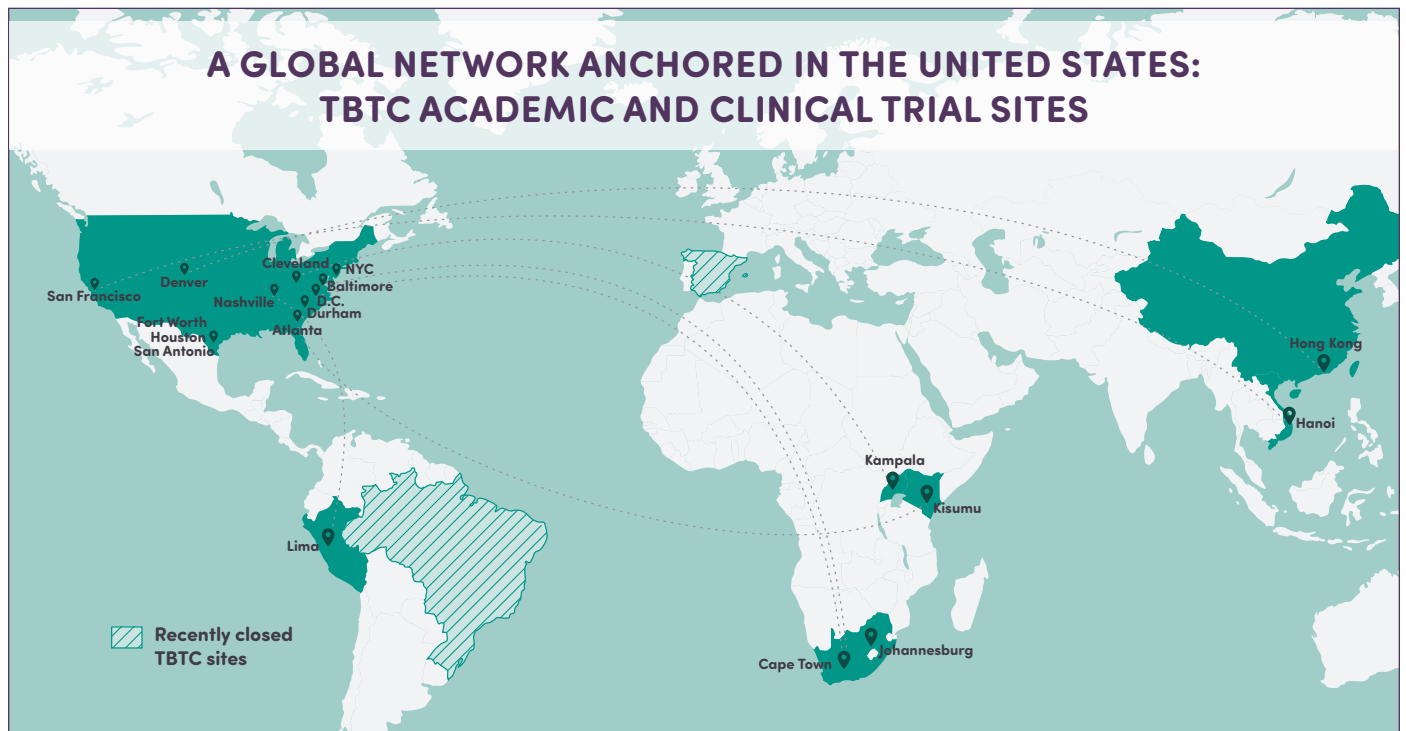
through the Visionary Research of the CDC's Tuberculosis Trials Consortium

The United States is a global leader in research and development (R&D) for better tools to prevent, diagnose, and treat tuberculosis (TB), the world's leading infectious killer. This leadership is thanks in large part to the ambitious research agenda of the TB Trials Consortium (TBTC). Housed within the Centers for Disease Control and Prevention (CDC) Division of TB Elimination (DTBE), the TBTC conducts clinical research of high public health relevance and is key to strengthening domestic and global campaigns to eliminate TB. Since 1995, TBTC clinical trials have enrolled over 16,000 participants across the United States and globally and have led to a breakthrough TB prevention option with the potential to save millions of lives and dollars in averted treatment costs.^{1,2}

THE TBTC'S HISTORY: FORMATION IN RESPONSE TO A COMPLEX EPIDEMIC

Once a leading cause of death in the United States, the impact of TB started to wane in the second half of the 20th century due to better living standards as well as improved methods of TB prevention and treatment spearheaded by the groundbreaking research of the U.S. Public Health Service (USPHS). In 1960, the USPHS transferred ongoing TB research to the CDC. As TB numbers declined, resources for TB research began to drop dramatically in the 1970s—but this success proved short-lived.

TB resurged in the mid-1980s following the rise of the HIV epidemic, the dismantling of public health infrastructure, and more than a decade of scientific inattention. The TB epidemic of these years proved more challenging to confront than in the past given the spread of deadlier, more drug-resistant forms of TB, high rates of HIV-TB co-infection, outbreaks among vulnerable communities, and the reliance of public health programs on outdated tools. In 1992, Congress provided crucial funds to help the CDC halt the TB resurgence. The CDC DTBE devoted some of the increased funding to conduct a series of clinical trials, which led to the formation of the TBTC in 1999.⁴



ADVANCES IN TB CARE FROM TBTC STUDIES

<i>Examples</i>	<i>Impact</i>
<i>Improving the patient experience</i>	
<ul style="list-style-type: none"> • A landmark phase III clinical trial conducted by the TBTC in partnership with the U.S. National Institutes of Health (NIH) AIDS Clinical Trials Group significantly shortened treatment for latent tuberculosis infection from 9 months of daily medication to 12 once-weekly doses (the “3HP” regimen). • The TBTC is now studying regimens with potential to shorten treatment of active TB by a third and simplify drug-resistant TB treatment. • One of the earliest TBTC studies led to understanding how low body weight is correlated with increased risk of relapse after treatment. 	<ul style="list-style-type: none"> • The shorter TB prevention regimen is easier for patients to complete, with a lower risk of causing the liver toxicity associated with the older approach to treatment. • Practitioners can identify patients vulnerable to poor treatment outcomes and tailor nutrition during the course of treatment to minimize risk.
<i>Designing smarter clinical trials</i>	
<ul style="list-style-type: none"> • The TBTC has been a pioneer of pharmacokinetic/pharmacodynamic (PK/PD) studies to achieve the best possible drug dosing that maximizes effectiveness and minimizes side effects. 	<ul style="list-style-type: none"> • Better dosing information supports smarter implementation by ensuring that patients receive the optimal drug dose most likely to lead to a successful treatment outcome.
<i>Prioritizing research for populations vulnerable to TB</i>	
<ul style="list-style-type: none"> • TBTC studies have included and even prioritized vulnerable communities that are often excluded from clinical trials, such as people who are homeless, people living with HIV, and children and adolescents. 	<ul style="list-style-type: none"> • Evidence generated by TBTC studies is critical in ensuring that clinical guidance to health practitioners addresses how to best prevent TB and care for the most vulnerable.
<i>Supporting U.S. research leadership in global TB</i>	
<ul style="list-style-type: none"> • With clinical trial sites throughout the United States and U.S. sites mentoring select sites around the world, the TBTC builds the capacity of a talented cohort of researchers responding to TB domestically and globally. 	<ul style="list-style-type: none"> • The TBTC ensures the next generation is prepared to tackle the important questions remaining in TB and prevent another resurgence in the United States. • The TBTC creates jobs and supports American research institutions in eight cities.
<i>Leveraging private sector investment</i>	
<ul style="list-style-type: none"> • The TBTC partners with private sector companies such as Sanofi and Cepheid, ensuring that compounds or products with the potential to improve the TB response are developed and taken up. 	<ul style="list-style-type: none"> • The TBTC keeps the private sector engaged in TB R&D, an area without much commercial interest. • The TBTC leverages public investments to gain in private sector expertise and resources.

BREAKTHROUGHS: IMPACT OF TBTC RESEARCH IN THE FIGHT AGAINST TB

Housing the TBTC within the CDC promotes the seamless exchange of information and knowledge between TB researchers and public health programs. All TBTC clinical trials emphasize programmatically relevant science that can be rapidly translated into practice to strengthen TB programs. In turn, the experiences of TB programs inform the direction of future research. This reciprocal structure ensures programs are up to date, efficient, and evidence based. The TBTC’s overseas sites (see **Map**) make clinical trials more diverse and efficient and ensure that the results are relevant to the global epidemic, which is closely linked to the domestic one.

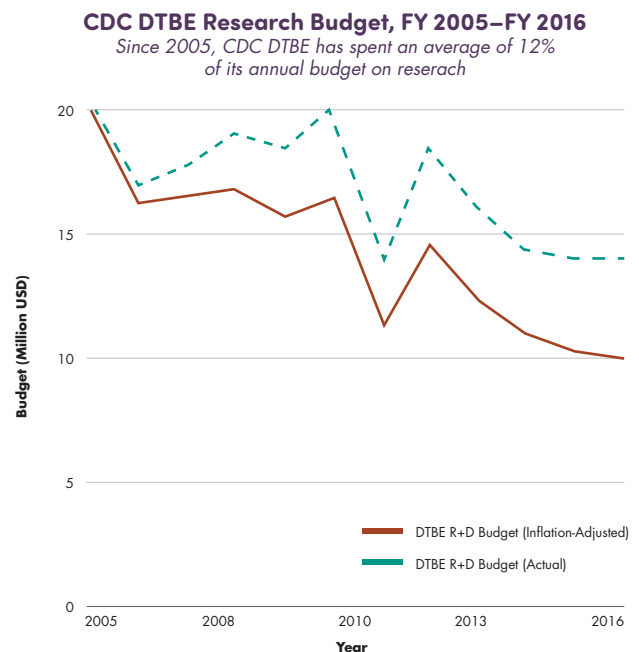
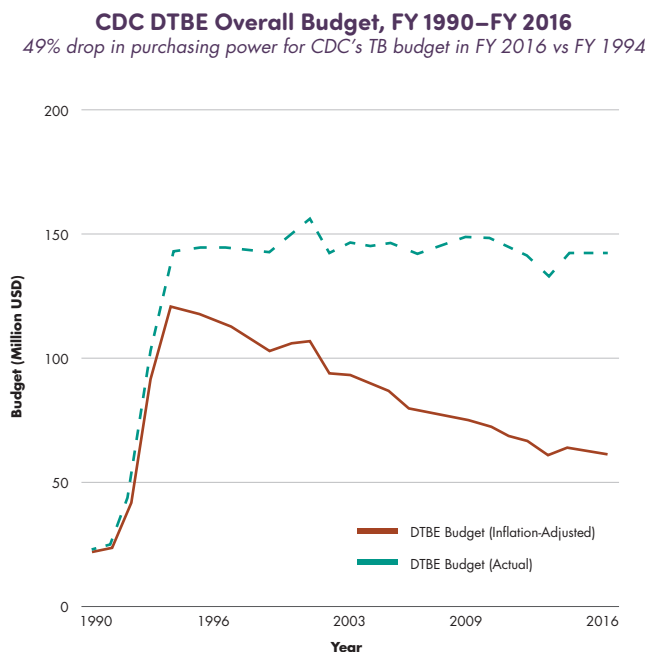
TBTC clinical trials have produced a number of scientific and programmatic breakthroughs (see **Table**). These achievements have also strengthened the United States’ leadership role in promoting science to respond to a range of emerging health security threats. Among TB research networks, the TBTC is notable for prioritizing populations that are especially vulnerable to TB, many of which have been historically excluded from clinical trials.

BUILDING ON SUCCESS: SUPPORTING THE NEXT 10 YEARS OF TBTC RESEARCH

The need to build on the success of TBTC research is pressing: in 2016, more than 10.4 million people developed TB globally and 1.7 million people died from the disease. In the United States, millions of people are infected with TB, and highly publicized outbreaks from rural Marion, Alabama, to metropolitan Atlanta, Georgia, highlight the need to arm frontline public health workers with the latest tools that only a well-funded research enterprise can provide.

In the face of these global and domestic challenges, TBTC studies are more necessary than ever. The 2015 *National Action Plan for Combatting Multidrug-Resistant Tuberculosis* affirms the need for a robust TB research agenda.⁵ With several promising studies either planned or underway, the TBTC is poised to unlock shorter treatment for active, drug-susceptible TB and shorter, more effective, and safer treatment for drug-resistant TB (DR-TB).

Despite the promise of these studies, the TBTC budget, and overall budget of DTBE, has suffered under years of stagnation (see **Figure**). Flat funding to DTBE has failed to keep pace with inflation, making it increasingly difficult to retain expertise and maintain a high level of scientific activity. U.S. legislators have shown strong bipartisan support for research by increasing the NIH budget, but the TBTC remains neglected. The TBTC and NIH work complementarily to capitalize on the former’s strong link to public health programs and the latter’s strengths in basic discovery and translational science, and each requires robust resourcing.



“TBTC research has made a vital difference to the people with TB disease and infection that my colleagues and I treat in San Antonio, and the findings from TBTC studies have improved treatment throughout the United States. Treatment can be individualized to be as short and safe as possible but still lead to a lasting cure. The shortened treatment regimen to prevent TB developed through TBTC research [3HP] is very effective and replaces a longer, often toxic 9-month regimen that less than 60% of people were able to complete. Treating TB infection prevents transmission of TB in the community and is key to eliminating TB in the United States.”

— Dr. Barbara Seaworth, TB physician and co-chair of the TBTC Community Research Advisors Group, San Antonio, Texas

RECOMMENDATIONS

Given the complexity of the global TB epidemic—marked by deadly DR-TB strains, outdated tools and strategies, and strained resources—the United States is in grave danger of losing ground in the pursuit of TB elimination. The TBTC is an essential partner in achieving the goals outlined in the *National Action Plan for Combatting Multidrug-Resistant Tuberculosis*, with its focus on prevention research as a cost-effective way to combat new infections and prevent the rise of DR-TB. The U.S. government can support the next 10 years of TBTC research by:

- *Strengthening domestic capacity for addressing TB infection to avert future cases:* Addressing the reservoir of TB infection, which affects 13 million people in the United States, is critical to eliminating TB in the country. With the TBTC’s success in shortening treatment for TB infection using the 3HP regimen, we can now curtail progression to active, infectious TB disease and the development of deadlier, drug-resistant forms of TB by implementing 3HP in a robust prevention program. Studies from the TBTC’s equally important sister network, the TB Epidemiological Studies Consortium, are guiding how best to do so. Investing in TB prevention and averting future DR-TB cases can lead to significant savings: a single case of DR-TB costs \$288,888 to treat.⁶
- *Supporting the TBTC in improving international coordination to combat TB globally:* The TBTC fosters important collaboration between U.S. academic institutions and trial sites across the world. This includes centering research within frontline endemic countries. Supporting the TBTC network strengthens global health security and coordination, helping the United States to address all forms of TB.
- *Leveraging U.S. global leadership on TB by accelerating applied R&D at the TBTC:* With growing global political will to address antimicrobial resistance (AMR)—as evidenced by prominent discussions of DR-TB and AMR at recent G20 summits and United Nations General Assembly special sessions^{7,8}—the TBTC’s successful track record puts the United States in a strong position to renew its commitment to TB R&D. The U.S. government should leverage its standing as the global TB R&D leader to accelerate the TBTC’s research agenda at this pivotal moment in the fight against AMR.

END NOTES

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