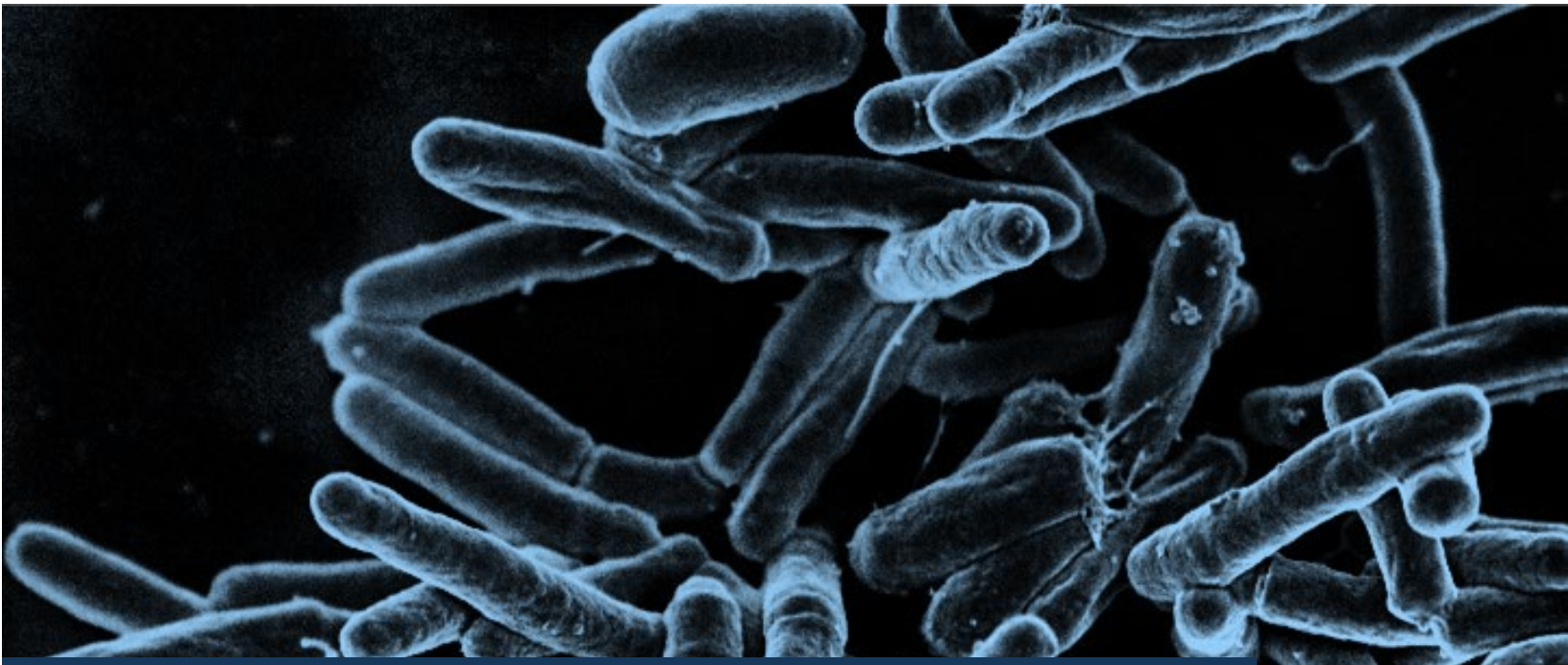
National Institute of Allergy and Infectious Diseases



NIAID Strategic Plan for Tuberculosis Research

2024 Update

March 2024

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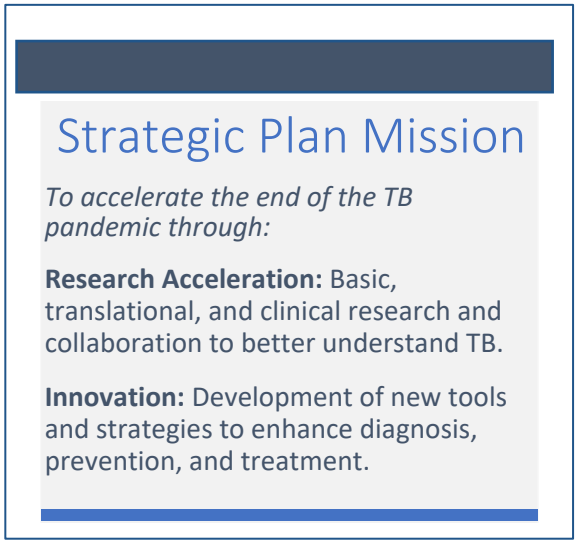
EXECUTIVE SUMMARY

Tuberculosis (TB) is the second leading cause of death from infectious disease in the world after COVID-19. In 2022, TB caused nearly twice as many deaths as HIV. In the United States (U.S.), up to 13 million people are living with latent TB infection and have a 5-10% chance throughout their lives of developing active TB.

Over the past decade, multiple global and domestic efforts have been established to accelerate the development of prevention strategies and treatments for TB. In 2015, the World Health Organization (WHO) established an End TB Strategy with a goal of a 90% reduction in TB incidence by 2035. Domestically, the U.S. government's Global TB Strategy and the National Action Plan for Combating Multidrug-resistant TB have outlined respective paths to end the TB pandemic.



The COVID-19 pandemic impacted all facets of biomedical research and healthcare activities, including TB research and control programs. The resulting interruptions in TB diagnosis and treatment lead to abrupt global reversals in what had been a trend of decreasing TB cases and deaths before 2020. As the world continues to emerge from the COVID-19 pandemic, efforts to combat the longstanding TB pandemic need to be revisited and enhanced to end the global impact of this deadly disease.

The National Institute of Allergy and Infectious Diseases (NIAID) released its first Strategic Plan for Tuberculosis Research in 2018, which was highlighted at the United Nations General Assembly High-level Meeting on TB in September 2018. This **2024 NIAID Strategic Plan for Tuberculosis Research Update** reaffirms the commitment of NIAID to accelerate basic and preclinical, translational, and clinical research and expedite the development of innovative tools and strategies to improve diagnosis, prevention, and treatment of TB. The updated plan is structured around four strategic priorities that are critical to the development and evaluation of the knowledge and tools needed to end TB globally (Figure 1):

1. **Improve Fundamental Knowledge of TB**
2. **Advance Research to Improve the Diagnosis of TB**
3. **Accelerate Research to Improve TB Vaccine Development**
4. **Support Research to Advance Therapeutic Strategies to Treat and Prevent TB**

To accelerate research relevant to these four strategic priorities, NIAID will continue to leverage current resources and global collaborations, including existing NIAID-supported clinical trials networks (Appendix 2). NIAID continues to promote a multidisciplinary approach to TB research, drawing on expertise from fields within and outside of TB research to facilitate studies of complex biological questions and encourage the application of state-of-the-art technologies. Efforts that connect the U.S. government to global health researchers and stakeholders have the potential to result in new and improved global TB prevention and control strategies that advance efforts to end the TB pandemic.

Figure 1: The NIAID Strategic Plan for TB Research Update proposes to advance four TB research priorities: 1) improving fundamental knowledge, 2) advancing research to improve diagnostics, 3) advancing research to improve vaccine development, and 4) supporting research to advance therapeutic strategies. Collectively, these priorities serve as primary approaches to achieve the overall mission of this plan.

INTRODUCTION

Despite ongoing efforts to develop safe and effective countermeasures, tuberculosis (TB) remains the second deadliest infectious disease in the world after COVID-19. In 2023, the World Health Organization (WHO) estimated that TB claimed the lives of 1.3 million people in the previous year, including 167,000 people co-infected with HIV. The causative agent of TB, *Mycobacterium tuberculosis* (*Mtb)*, is transmitted through the air and primarily infects the lungs (Figure 2). *Mtb* infection can result in a spectrum of outcomes: elimination or clearance of infection, latent TB infection, subclinical or asymptomatic TB disease, or active disease.

Disease Manifestations

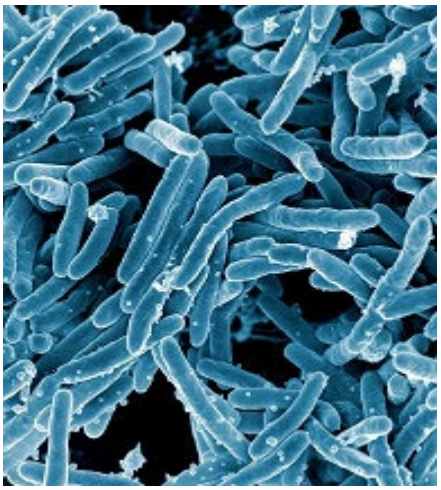


Figure 2: Scanning electron micrograph of Mycobacterium tuberculosis, the bacterium that causes TB. Image credit: NIAID.

The most common outcome of infection is latency, which results from a balance between immunological control and bacterial persistence. Historically, the *Mtb* infection paradigm has been a binary one: individuals are either infected with *Mtb* but have a latent infection or individuals are actively sick from infection and are transmitting *Mtb*. The reality is a more nuanced spectrum of disease pathology that encompasses previously unrecognized disease states that were likely lumped into the 'latent' categorization.

Asymptomatic or **subclinical** TB disease refers to active infection with *Mtb* but with no or minimal clinical symptoms. These categorizations present with abnormalities that can be detected using existing radiologic or microbiologic assays. **Incipient** TB is used to define cases of infection with *Mtb* that is likely to progress to active disease without treatment and may also be associated with no or few clinical symptoms. **Latent** TB refers to cases with immunological evidence of exposure to TB, for example, by a positive interferon-gamma release assay (IGRA) or Tuberculin Skin Test (TST), but without symptoms and without detection of the organism using radiologic or microbiologic assays. Individuals who are latently infected with *Mtb* have a 5 - 10% risk of developing active TB at some point in their lives.

Pulmonary TB is the most contagious active form of the disease and is characterized by an array of symptoms including cough, fever, weight loss, and night sweats. Left untreated, severe complications can develop that lead to death in about half of patients. *Mtb* can also cause extrapulmonary TB wherein disease affects organs outside of the lungs (e.g., heart, abdomen, skeletal, genito-urinary, and central nervous systems). Roughly 15 - 25% of overall cases are classified as extrapulmonary TB, and many of these *Mtb* infections cause high mortality. It is unclear why *Mtb* infection leads to such varying outcomes in individuals. To reach the WHO End TB goal of reducing TB incidence by 90% and TB deaths by 95% by 2035, a better understanding of the spectrum of pathology from *Mtb* infection must be achieved.

Challenges with TB Infection

One of the challenges in addressing the TB pandemic is that an estimated 30% of individuals with active TB disease (approximately 3 million people) are not diagnosed, and thus are neither reported to public health authorities nor receiving treatment. Undiagnosed and untreated individuals account for a significant portion of TB deaths and continue to fuel the TB pandemic by acting as a reservoir for the pathogen. The development of rapid, accurate, cost-effective, and easy-to-use diagnostics for TB and drug resistant TB (DR-TB) remains a research priority and will help identify and facilitate prompt, effective treatment of TB patients.

People living with HIV (PLWH) and *Mtb* experience additional challenges because they are 16 – 18 times more likely to develop TB disease than people without HIV. While HIV positive individuals with low CD4 T cell counts have the highest risk and higher rates of extrapulmonary TB, those with viral suppression and high CD4 T cell counts maintain TB risk that is higher than the general population. Additionally, TB drug regimens need to be compatible with HIV antiretroviral therapy (ART) and vice versa, which further complicates treatment. Despite significant efforts to improve the care of patients, TB continues to be the leading cause of death in PLWH worldwide.

Need for Improved Vaccines and Therapies

To change the trajectory of the TB pandemic, the development of a safe and effective preventive vaccine remains the most pivotal milestone. Although not employed for TB prevention in the U.S., the Bacillus Calmette–Guérin (BCG) vaccine is used in many countries with a high prevalence of TB to help prevent childhood TB, including TB meningitis (inflammation of the brain and spinal cord) and miliary TB (disseminated disease through the circulatory system). The BCG vaccine does not sufficiently protect adults and adolescents from disease, however. Therefore, ongoing research is needed to accelerate the development of additional safe and effective TB vaccines.

While significant strides have been made towards improved, shorter course regimens to treat TB disease, availability of these new regimens remains limited. Currently, curative therapy for drug-sensitive TB (DS-TB) typically requires a challenging six-month, four-drug regimen in most settings. In addition, large, dedicated public health programs are required to assure drug access and daily adherence to treatment to avoid recurrence or the development of drug resistance. In 2021, a collaboration supported by NIAID and the Centers for Disease Control and Prevention (CDC) reported that a new regimen of rifapentine (RPT), isoniazid (INH), pyrazinamide (PZA), and moxifloxacin (Mfx) cured patients with DS-TB within four months of treatment. This accomplishment has demonstrated that shorter therapy for TB is possible and resulted in endorsement of the regimen by the WHO.

CDC has provided guidance for the use of bedaquiline, pretomanid, and linezolid (BPaL) to treat DR-TB. Multidrug-resistant TB (MDR-TB) occurs when *Mtb* becomes resistant to the two most effective anti-TB drugs, rifampin (RIF) and INH, and is much more difficult to treat than DS-TB. Traditional treatment of MDR-TB can take more than 2 years, sometimes including daily injections for 6 months, and is prohibitively expensive. Extensively drug-resistant TB (XDR-TB) is resistant to at least four of the core TB drugs. XDR-TB therapy is even more complex than MDR-TB therapy and often fails. Some of these treatments may also result in long-lasting or permanent side effects (e.g., deafness). The continued challenge of effectively and affordably treating DS-, MDR- and XDR-TB underpins the critical need for

shorter, safer, and more effective drug regimens that are well tolerated and can be delivered to patients in all care settings.

Updated Research Priorities for TB

In 2020 and 2021, the COVID-19 pandemic impacted all aspects of global biomedical research and patient care. Shutdowns, quarantines, and the global effort to contain the pandemic resulted in limited access to medical providers, interruptions in the supply chain, and temporary refocus of resources and research from other infectious agents of concern to SARS-CoV-2. Due to the effects of the COVID-19 pandemic across the world, there was an 18% drop in the number of people newly diagnosed with TB and reported in 2020. Simultaneously, there was an increase in reported deaths from TB in 2021. Despite the global impact on biomedical research, the lessons learned and technological advances from the COVID-19 response, including the importance of understanding and addressing health disparities and social determinants, can be leveraged to bolster and enhance efforts to combat TB.

In 2018, the NIAID TB Working Group developed a series of strategic priorities to advance research on TB and address the ongoing challenges of developing safe and effective countermeasures to TB. These priorities were described in the NIAID Strategic Plan for TB research. In 2023, the working group reconvened to update the plan. This effort included outlining critical research areas of focus and the solicitation of public input through a Request for Information (RFI). The updated plan emphasizes four strategic priorities that support basic and preclinical, translational, and clinical research focused on enhancing the fundamental knowledge, diagnosis, prevention, and treatment of TB. Advances guided by the four strategic priorities are expected to be interdependent and complementary. NIAID anticipates that this updated plan will serve as a foundation for its future research investments and guide comprehensive efforts toward the successful development of diagnostic, prevention, and treatment tools necessary to end the TB pandemic.

STRATEGIC PRIORITY 1: Improve Fundamental Knowledge of TB

Mtb has evolved in parallel with the human immune system for millennia. Thus, *Mtb* is extraordinarily well-adapted to evade and exploit host immune responses to complete the cycle of infection establishment, replication, persistence, and, ultimately, transmission to uninfected individuals. Advancing efforts in basic TB bacteriology and immunology are central to our understanding of the *Mtb* infection cycle and possible disease progression and outcomes. Identification of basic elements of *Mtb* biology are interwoven into efforts to identify intervention strategies. Areas where continued research is needed to advance our fundamental knowledge of TB include *Mtb* virulence mechanisms; induction and maintenance of latency; and immune mechanisms associated with *Mtb* clearance, containment, and disease pathogenesis.

STRATEGIC PRIORITY 1: IMPROVE FUNDAMENTAL KNOWLEDGE OF TB
Objective 1.1: Enhance Understanding of *Mycobacterium tuberculosis* (*Mtb*) to Improve Options for Intervention
Objective 1.2: Characterize Immune Responses and Host Factors that Contribute to TB Progression and Pathology
Objective 1.3: Understand the Critical Drivers of TB Transmission
Objective 1.4: Improve and Develop Animal and non-Animal Models of TB Disease

Objective 1.1 Enhance Understanding of *Mycobacterium tuberculosis* (*Mtb*) to Improve Options for Intervention

One of the major features of *Mtb* physiology is the presence of a unique lipid-dense cell envelope. The lipids organized between the inner and outer components of the *Mtb* cell envelope present a barrier to drugs and serve as a fundamental constituent of virulence. The bacterium also secretes virulence factors that can manipulate host cell proteins to make the environment more hospitable to *Mtb* by improving nutrient availability and modulating the immune response. Further characterization of such virulence mechanisms is critical to understanding how *Mtb* survives and evades the immune system. In addition, these secreted factors are potential targets for both anti-bacterial treatments and host directed therapies (HDTs) and may be utilized as diagnostic markers.

Mtb may also respond to stressful environments and activate dormancy survival factors with important implications for immune evasion and persistence during treatment. A better understanding of this initial host-pathogen interaction may provide new insights into *Mtb* pathogenesis. Fundamental knowledge of *Mtb* metabolic systems is required to identify potential new drug targets. Thus, more research is needed on *Mtb* pathways for metabolism, catabolism, sequestration, and energy production and how these pathways change in response to host environments.

As basic elements of *Mtb* biology continue to be elucidated, further characterization and understanding of the impact of genetic variation within the different lineages of the organism may inform strategies to diagnose, prevent, and treat TB. For example, genetic variation, which depends on numerous factors, such as the ancestral lineage, fitness, and numerous host and environmental factors, can impact virulence of DR strains. In the last several years, studies have shed light on bacterial molecular

mechanisms, host genetic predispositions underlying treatment failures, and emergence of drug resistance and tolerance.

Another challenge to effectively control or eliminate TB disease is a subpopulation of *Mtb* organisms, referred to as bacterial persisters, that exhibit tolerance during exposure to therapeutic doses of antibiotics. Persisters are thought to contribute to the long treatment duration required for TB, but precisely how these persisters evolve is not clearly understood.

NIAID will continue to leverage research activities and resources to expand the fundamental knowledge of circulating strains of *Mtb* and disease characteristics. Technological and methodological advances, such as CRISPR-based genetics and single cell RNA sequencing (scRNAseq), will facilitate interrogating the *Mtb* genome for relevant targets for therapeutic intervention. NIAID will continue to promote the development and use of state-of-the-art tools, including imaging technologies, multidisciplinary systems biology, computational modeling, and -omics approaches, to evaluate the dynamics of *Mtb* evolution, TB pathology, and the complicated interplay of pathogen with host factors that contribute to disease.

Objective 1.2 Characterize Immune Responses and Host Factors that Contribute to TB Progression and Pathology

Upon infection with *Mtb*, the human host mounts a series of innate and adaptive immune responses. However, the specific nature and interplay of the immune mechanisms required to limit disease progression remain unclear. There is evidence that immune mediators can contribute to pathology and, subsequently, to disease progression and post TB sequelae. In determining the underlying mechanisms of infection and immune responses, researchers may identify differences in those who become infected with *Mtb* but clear the infection, those who become latently infected, and those who develop active TB. It is also important to understand how co-morbidities in the host may impact these immune mechanisms.

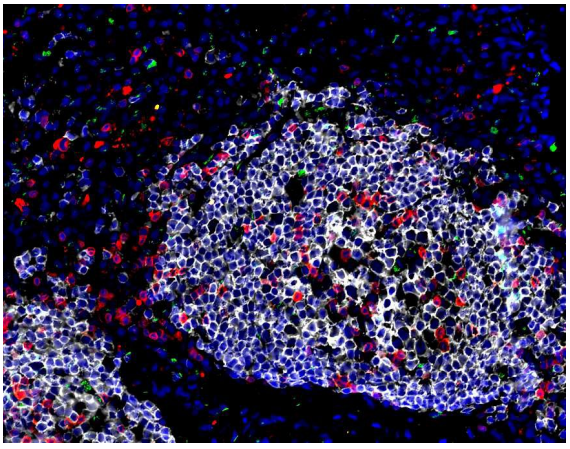


Figure 3: Innate lymphoid cells (green) near and within a small area of inflammation, or granuloma, in a non-human primate infected with Mtb. Image credit: NIAID

Following inhalation, *Mtb* infects innate immune cells, which subsequently stimulate the adaptive immune response by priming antigen-specific T cells. These T cells then migrate to the site of infection to control *Mtb* and prevent dissemination. The adaptive immune response takes some time to ramp up and is instrumental in the formation of granulomas (Figure 3). A granuloma is a structure consisting of an aggregation of immune cells that both limit growth of *Mtb*, but also provide a cache of sequestered, live *Mtb* that can perpetuate the infection cycle. Imaging technologies, such as positron emission tomography/computed tomography (PET/CT) are providing insights into the diversity of granuloma and disease dynamics (Figure 4).

Each immune cell type involved in infection provides an opportunity for potential intervention—either to enhance protective mechanisms or prevent inflammation-induced pathology. However, mechanisms that prevent *Mtb* infection or lead to active disease are not fully understood. Efforts are underway using animal model systems to assess host factors that play a role in prevention of infection or disease

progression. Major strides in analytical approaches offer new platforms to dissect such mechanisms on a cellular level in an experimental environment. This allows for the assessment of tissue and single cell transcriptional changes in specific cell types resulting from changes in host, environment, or microbial variables.

NIAID will continue to support research aimed at understanding host immune responses to *Mtb* infection and identifying immune pathways that may be dysregulated and/or contribute to immune evasion and pathogenesis. The identification of pathways that can be targeted by HDTs may augment antibiotic interventions, contribute to further efficiencies in therapy and vaccine development, and reduce lung inflammation and fibrosis that impairs lung function following treatment. To accomplish this task, NIAID will continue to prioritize research to further define the contribution of innate and adaptive immune cells in regulating host responses to *Mtb*. This effort will include more comprehensive evaluations of immune responses from individuals with active disease including extrapulmonary disease, subclinical disease, or latent infection. Additionally, NIAID supports fundamental research grants and specialized programs such as the Tuberculosis Research Units Network (TBRU-N) , a multidisciplinary, collaborative effort focusing on understanding *Mtb*-host interactions.

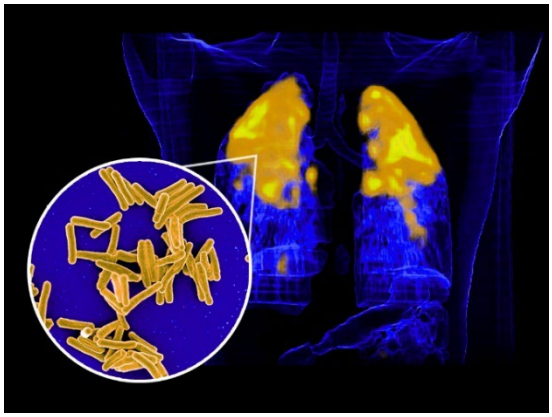


Figure 4: Scanning electron micrograph of Mtb bacteria (circular foreground image; bacteria are colorized gold) and a PET/CT scan showing TB infection (gold and yellow) in a patient's lungs (background image). Image credit: NIAID.

Objective 1.3 Understand the Critical Drivers of TB Transmission

Mtb is highly contagious, and the TB transmission cycle is extremely complex with multiple contributing biological factors including host, pathogen, and micro-environments, as well as a broad array of socioeconomic and demographic factors. For example, TB incidence among historically marginalized communities is high, and these communities often have higher levels of risk factors for progression to TB disease. Recent evidence suggests that community spread may be as important as spread through household contacts. To better characterize factors that drive TB transmission, NIAID will support the development of tools for predictive modelling and advanced real-time mapping of infection clusters that can be used to identify key sites of transmission. These tools can be used to identify variables contributing to transmission and to improve community- and population-based strategies for prevention and active case finding. NAID also will continue to support research to characterize TB transmission, particularly within high-burden settings and high-risk populations. This may identify underlying pathogen and host factors that affect transmission and progression to disease.

The previously understood model was that *Mtb* transmitted primarily by coughing. However, recent evidence suggests that *Mtb* may be transmitted through regular breath exhalations (tidal breathing) wherein *Mtb* is aerosolized and can be inhaled by nearby individuals. This model is particularly problematic given that prevalence studies demonstrate that many people with microbiologically confirmed TB have asymptomatic or subclinical TB infections. With that awareness, there is a need to understand what role people with asymptomatic or subclinical disease may have in TB transmission and

how to clinically manage these people most effectively. NIAID will support research to understand the dynamics of all TB disease manifestations and how they impact *Mtb* transmission. Other areas of research that are of high priority to NIAID are the impact of the immune response on TB transmission and how HIV infection (including viral suppression with ART) may affect intra-host *Mtb* burden, the likelihood of transmission, and the resulting population dynamics of TB among PLWH.

There may be genetic factors present in the pathogen that promote transmission, including genes that induce host responses to *Mtb* infection with characteristics that increase transmissibility. Some responses that may be stimulated by *Mtb* include development of granulomas, production of higher bacterial burden in sputum, or increased coughing. Understanding the genetic, epigenetic, and microbial characteristics that help *Mtb* survive stressful conditions during transmission may also provide unique targets for interventions that can prevent TB transmission.

Objective 1.4 Improve and Develop Animal and non-Animal Models of TB Disease

Currently, no models of TB disease exist that completely recapitulate all aspects of human *Mtb* infection and disease. Animal models, however, offer the most predictive information. The most common animal models used in TB research continue to be mice, guinea pigs, and non-human primates (NHPs), with rabbits and zebrafish being used less often. Mouse models are useful for the analysis of fundamental immunological studies and are valuable to examine basic mechanistic studies. Other small mammals, such as the guinea pig and the rabbit, adequately model some disease features, but their use is constrained by the limited availability of immunological tools and reagents. NHPs may offer additional insights into complex biological questions that are not accessible in small animals. It is still unknown how well any animal model mimics the dynamics of human host-pathogen interactions, pathology, and responses to vaccines and therapeutics. As a result, small and large animal models need further refinement and must be analyzed in parallel and iteratively with human clinical studies to validate hypotheses and endpoints and for testing new drug and vaccine candidates and regimen combinations.

NIAID continues efforts to develop models that can replicate and/or predict findings in specific human target populations. *In silico* models, or computational models, and *ex vivo* models, including 3D lung models and organ-on-a-chip technologies, may serve as tools to bridge the results obtained in different animal models and humans. As part of this effort, NIAID will prioritize the harmonization of these models and standardization of approaches, including the establishment of benchmarks to allow for comparisons between these models and to determine their ability to predict outcomes in human clinical trials.

STRATEGIC PRIORITY 2: Advance Research to Improve Diagnosis of TB

The development and optimization of sensitive, specific, and rapid diagnostics for *Mtb* infection is critical to ensure that individuals with TB receive proper and timely treatment. Currently, acid fast smear – microscopic analysis of sputum – is still used in many low resource settings, but it has poor sensitivity and may miss cases, especially paucibacillary TB (TB disease with low levels of detectable *Mtb* bacteria). Culture, where *Mtb* is grown in a laboratory, is the gold-standard; however, because *Mtb* is slow growing, results from culture can take weeks to months. Ideally, newly developed or improved nucleic acid amplification-based technologies (NAAT) and other molecular based technologies, including Next-Generation Sequencing (NGS), culture-based platforms, and other new diagnostic technologies would allow testing directly on patient samples with minimal or no sample processing. These assays should be low complexity to allow minimal operator expertise, yield results in a short time frame, and accommodate easy to obtain samples. A diagnostic with these characteristics may even allow for strategies to be developed for an at home or self-administered test to be integrated into TB control programs. Although ideal TB diagnostics with the highest sensitivity and specificity should be made available for all settings and for all people, a less sensitive test with greater accessibility could have a significant impact on the overall TB pandemic and would allow more people to be diagnosed and referred for treatment. Bringing TB diagnosis closer to the point of care (POC) and the patient may allow more populations to be reached and increase the overall yield of cases identified and treated.

STRATEGIC PRIORITY 2: ADVANCE RESEARCH TO IMPROVE DIAGNOSIS OF TB
Objective 2.1: Develop and Improve Accurate and Rapid Diagnostics, Including Point of Care (POC) Diagnostics
Objective 2.2: Discover and Validate Novel TB Biomarkers or Biosignatures

Objective 2.1 Develop and Improve Accurate and Rapid Diagnostics, Including Point of Care (POC) Diagnostics

There has been significant progress in developing molecular diagnostics that detect the presence of *Mtb*. Some examples of these diagnostics include GeneXpert MTB/Rif Ultra and MolBio TrueNat. The latter is both portable and battery-powered, which makes it more amenable to a POC setting. Molecular-based tests are recommended and preferred by the WHO; however, the currently available tests have limitations, particularly in low- and middle-income countries due to cost, required human resources, and infrastructure. Improved molecular-based tests for *Mtb* diagnosis and *Mtb* drug susceptibility testing (DST) are in development, including many that are suitable for POC or near POC use. The NIAID Feasibility of Novel Diagnostics for TB in Endemic Countries (FEND for TB) program supports the evaluation of early-stage diagnostics and novel diagnostic strategies for TB in endemic countries to address an urgent need for improved TB diagnostics.

Most of the currently used diagnostics for active TB disease utilize sputum samples that can be difficult to obtain, particularly from young children and PLWH. These patients may also have low concentrations of *Mtb* in their sputum or may have paucibacillary disease wherein the sputum test will be negative, although samples from these individuals would be positive when analyzed via *Mtb* culture. Further, extra-pulmonary forms of TB cannot be detected in diagnostic tests that are based on sputum samples.

Mtb diagnostic development areas should focus on the development of tests utilizing easy to obtain specimens and tests that are rapid, sensitive, and inexpensive (Figure 5). Innovative molecular based test development, including improved NAATs, NGS, and CRISPR, is underway. Additionally, there are continual advancements in developing tests that are breath-based or that utilize urine, blood/serum, or stool as these samples are often easier to obtain than sputum samples. Urine Lipoarabinomannan (uLAM), is a promising non-sputum based test which is low-cost, has high specificity, and can be used at the POC. The sensitivity of the currently available uLAM test is low, however, and is only recommended by the WHO as part of the diagnostic toolkit for PLWH with very low CD4 T cell counts. There is significant effort in the field to increase the sensitivity of uLAM assays for use in broader patient populations, as well as efforts to develop other urine based diagnostic assays.

Other innovative diagnostic technologies include artificial intelligence (AI)-based tools to analyze images including chest X-ray (CXR) and computed tomography (CT) and AI-based tools for analysis of cough and lung sounds. Computer-aided detection software for automated interpretation of CXR is a useful tool that can assist in rapid and consistent CXR interpretation. CT is often only available in high-resource settings but can improve diagnosis of TB in more complex cases. Automated interpretation tools may expedite research, allow for more consistency between researchers, and enable comparisons of data between different research groups.

Additionally, there is a need for improved DST, including DST for newly approved TB drugs. Current DST is used to determine which drugs are effective against *Mtb* and are performed when the patient is first found to have a positive *Mtb* culture. DST ensures that treatment can be initiated with the appropriate therapy. It is critical to develop the diagnostics for determining resistance to newly developed drugs as rapidly as new drugs are developed. This will ensure that as new drugs are rolled out, the tools are available to effectively use these drugs and reduce emergence of resistance. Ideally DST is molecular-based and drug-specific; however, phenotypic DST that is fast and accurate would be useful as new drugs are developed. Further, tests should be suitable to detect drug susceptibility in people with paucibacillary disease, children, and HIV seronegative and seropositive populations.

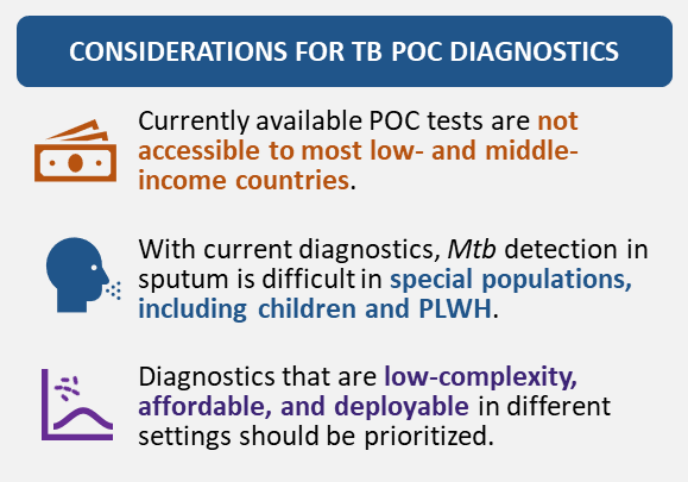


Figure 5: Considerations for developing novel point of care (POC) diagnostics for TB. Currently, available tests are not widely accessible in most low- and middle-income countries and detection is difficult in children and people living with HIV (PLWH). New diagnostics should be low-complexity, affordable, and deployable in all settings.

NIAID will continue to support research on inexpensive screening diagnostics that can be paired with other more sophisticated technologies or can stand on their own and allow for cost-effective integration of these tools into TB control programs. These new diagnostics should be rapid, sensitive, and specific, useful at the POC or near care, cost-effective and employ easy to obtain samples. NIAID will also continue to support the development of DST, especially for newly developed TB treatment drugs.

Objective 2.2 Discover and Validate Novel TB Biomarkers and Biosignatures

Research efforts prioritize the identification of novel biomarkers or biosignatures, which may be able to identify recent infection, detect risk of disease progression from latent to active TB, monitor response to therapy, and predict disease relapse. Biomarkers may identify aspects of *Mtb* infection that precede active pulmonary disease or may be able to detect paucibacillary disease. Some approaches for studying early events in *Mtb* infection include the use of imaging probes and *Mtb* strains suitable for imaging studies *in vivo*, including tracking the presence, growth, and distribution of *Mtb* from infection through disease progression and treatment. Other comprehensive approaches such as multi-omics based studies are being advanced to identify biomarker signatures of clinical relevance. Omics based biomarkers that would be successful for diagnosing and managing TB in pediatric populations, PLWH, and for extrapulmonary TB are of particular interest. These biomarkers or biosignatures then need to be integrated into suitable technologies to provide accurate, reliable, and actionable information to clinicians.

There are TB diagnostic assays currently in use that measure host biomarkers for *Mtb* infection or exposure, including the TST and IGRA, but these approaches only indicate prior infection or exposure to *Mtb* and cannot distinguish individuals with an immune memory of a prior infection from those with active TB disease and cannot predict those who may develop TB disease in the future. Further, the TST will test positive for those who received the BCG vaccination, whereas the IGRA will not. Improved diagnostics that can distinguish between people with TB disease and people with prior exposure to *Mtb* or BCG vaccination would be useful clinically. NIAID supports the identification and development of novel biomarkers or biosignatures to improve TB diagnostics, including biomarkers detectable in easy to obtain samples (e.g., urine, blood, serum, breath, or stool).

STRATEGIC PRIORITY 3: Advance Research to Support TB Vaccine Development

Safe and effective preventive vaccine(s) and related vaccination strategies remain critical development milestones to combat the TB pandemic. The WHO End TB targets emphasize that a new vaccine effective for pre- and post- *Mtb* exposure is a critical piece of the effort to lower TB incidence. Studies have predicted that a TB vaccine targeting adolescents and adults could have a major beneficial impact on the epidemic. Although several vaccine candidates are in clinical development, ongoing research is needed to accelerate the development of additional safe and effective TB vaccines that prevent infection and disease. Identifying correlates of immune protection (COP) from *Mtb* disease/infection continues to be a research priority that would enable more efficient testing and advancement of TB vaccine candidates. In addition, given the significant burden of disease and risk of progression to active TB disease, it is crucial that the safety and performance of TB vaccines be evaluated in people with HIV and other co-morbidities.

STRATEGIC PRIORITY 3: ADVANCE RESEARCH TO SUPPORT TB VACCINE DEVELOPMENT

Objective 3.1: Identify Immune Correlates of Protection (COP)

Objective 3.2: Support Design and Development of Vaccine Candidates for Prevention of Infection and Prevention of Disease

Objective 3.1 Identify Immune Correlates of Protection (COP)

A COP is an immune marker that can substitute for a clinical end point and can be used to reliably predict vaccine efficacy. Although progress has been made in understanding the nature of *Mtb*-specific immune responses, mechanisms that prevent *Mtb* infection or disease progression are not fully understood. Identifying and assessing COP for TB will require building on *in vitro* studies, *ex vivo* or explant systems, and *in silico* modeling combined with animal model studies to characterize immune responses that predict a successful vaccine candidate. These findings will need to be corroborated by vaccine efficacy trials to demonstrate a positive correlate.

NIAID has made investments in supporting research to gain an understanding of the immune responses and correlates required to prevent initial infection with *Mtb*, establishment of latent infection, and transition to active TB disease. Multidisciplinary research teams, supported by the IMPAc-TB program, are conducting immunological analyses of tissue-specific and systemic responses in small animals, NHPs, and humans to identify key correlates needed for protection against *Mtb*. These studies will also identify immunologic targets that can be used to improve TB vaccine strategies and determine the impact of HIV and nontuberculous mycobacteria infections on relevant immune responses to *Mtb* infection or TB vaccines. NIAID has supported intravenous BCG vaccination studies in NHPs, which demonstrated a significant level of protection against *Mtb* infection and enabled the study of COP.

Another potential way to identify COP is through the use of Controlled Human Infection Models (CHIM). CHIMs are studies that utilize healthy adult volunteers who are intentionally exposed to pathogens (or attenuated forms of a pathogen) in a controlled environment to more closely study an infectious organism. In addition to providing insight into COP, CHIMs can be used to better understand host-pathogen interactions, determine host factors that contribute to infection, and accelerate the

development and testing of vaccines. The information gained from CHIMs can be compared to results from preclinical models and clinical trial results allowing for validation of model systems.

NIAID is committed to continue studies to identify immune COP through comparative immunological analyses of tissue-specific and systemic responses in relevant animal models and clinical samples. Furthermore, immunological characterization of individuals with latent TB infection who do or do not progress to active disease will help researchers better understand the factors that impact progression to active disease vs. containment or resolution of infection. Similarly, a more thorough characterization of markers from individuals who resist *Mtb* infection (remain IGRA negative) despite high exposure will help researchers investigate the factors that determine the outcome of an infectious event. Learning about the immune responses of those individuals who resist infection with *Mtb* could be useful in the development of prophylactic vaccines or other protective treatments.

Objective 3.2 Support Design and Development of Vaccine Candidates for Prevention of Infection and Prevention of Disease

NIAID supports the discovery of new immunogens and immunogen/adjuvant combinations that can be tested in diverse vaccine expression and delivery platforms. Two NIAID initiatives, Innovation for Tuberculosis Vaccine Discovery and Advancing Vaccine Adjuvant Research for Tuberculosis (AVAR-T), support the design of novel TB vaccine candidates that exploit innovative approaches and the development of side-by-side comparisons of adjuvants in combination with *Mtb* immunogens, respectively. Additional areas of support focus on the design and development of vaccine candidates against both initial acquisition of *Mtb* infection (prevention of infection) and against the transition from latent TB infection to active TB disease (prevention of disease), as well as in the context of PLWH. Other investigations include trials of therapeutic TB vaccines (prevention of recurrence), administered to persons during or after treatment for active TB, with the objective to accelerate resolution and prevent recurrence.

Currently, there are few TB vaccines candidates in early-stage clinical development. Given that, NIAID is committed to supporting preclinical and clinical development of novel TB vaccine approaches. To accomplish this goal, additional studies are needed to evaluate novel vaccine platforms, test different delivery routes, and support product development and manufacturing activities. Furthermore, given the different vaccine needs and epidemiologic patterns in key study populations, NIAID supports studies across the life span (infants, children, adolescents, adults) and in people living with co-morbidities such as HIV.

STRATEGIC PRIORITY 4: Support Research to Advance Strategies to Treat and Prevent TB

The development of novel treatments and safe drug combinations, for both treatment and prevention, is an important part of the strategy to end the TB pandemic. NIAID supports basic, preclinical, and clinical research investigations into therapeutic treatments for pulmonary and extrapulmonary disease caused by *Mtb*. These investigations include the use of *in vivo*, *in vitro*, or *in silico* model systems and clinical trials. Many clinical trials investigate the safety and effectiveness of new therapeutics often in combinations with existing medications. The two-pronged approach: basic and preclinical research paired with clinical trials is an important bridge from bench to bedside.

STRATEGIC PRIORITY 4: SUPPORT RESEARCH TO ADVANCE STRATEGIES TO TREAT AND
Objective 4.1: Discover and Develop New TB Drug Targets and Interventions
Objective 4.2: Develop and Improve TB Preventive Treatments (TPT) Interventions
Objective 4.3: Develop and Evaluate Shorter and/or Safer TB Treatment Regimens for All Patient Populations and Forms of TB

Objective 4.1 Discover and Develop New TB Drug Targets and Interventions

Research to develop more effective, shorter, and safer treatments and preventative treatment strategies for TB disease is a high priority. Discovery of new drug targets is crucial for developing innovative strategies for these priorities. New drug targets could include essential metabolic pathways, virulence factors, or components involved in drug resistance mechanisms (Figure 6). One approach that could be applied to TB includes using induced proximity therapeutics, a rapidly growing field featuring small molecules that bring two proteins together thereby speeding up or instigating a molecular reaction. One example of this technology is Targeted Protein Degradation (TPD). TPD induces breakdown of a specific, or targeted, protein. PROteolysis TArgeting Chimeras (PROTAC) is a promising TPD; clinical trials of oncology therapeutics based on PROTAC approaches are ongoing, and its use has expanded to other therapeutic areas. Another innovative approach involves the use of bacteriophages – viruses that infect and kill bacteria. For example, *Mtb*-targeting bacteriophages can be combined with antibiotics as an entirely new type of therapeutic intervention.

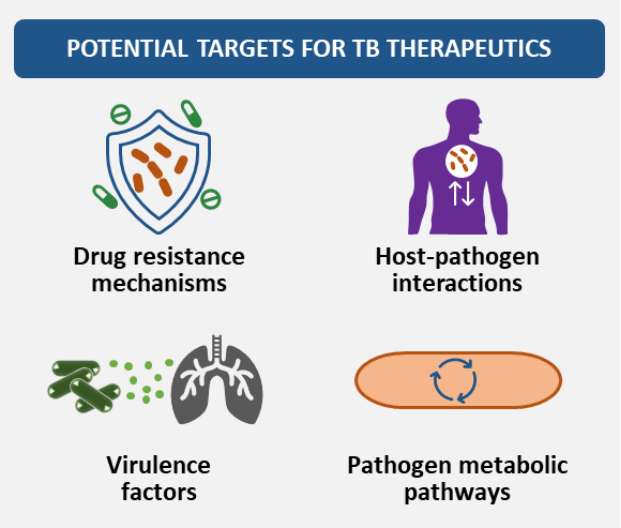


Figure 6: Therapeutic targets could include components involved in drug resistance mechanisms, host-pathogen interactions, virulence factors, and metabolic pathways.

Targeting specific host-pathogen interactions or exploiting the immune response or other host metabolic pathways offer alternative avenues for HDTs that may help protect the lungs, improve

long term survival, and shorten treatment duration. Innovative research to identify new targets for HDTs and to evaluate novel immune modulating treatments, and therapeutic vaccines are needed to improve the effectiveness of immune responses to *Mtb*. Novel treatments should also aim to reduce tissue destruction caused by *Mtb* infection. Basic and preclinical research is required to identify these host-pathogen interactions for further refinement and testing. The preclinical work supported by NIAID is foundational for the eventual development of novel drugs to treat pulmonary and extrapulmonary *Mtb* infections.

Some existing TB drugs are associated with adverse events such as myelosuppression, anemia, neuropathy, hearing loss, and kidney damage that can present during the long treatment period necessary for MDR- and XDR-TB. Safer therapeutics with less severe adverse events during treatment are needed. Additionally, research is needed to determine the mechanisms of TB drug toxicities and to develop improved methods to detect these toxicities earlier in treatment.

Objective 4.2 Develop and Improve TB Preventative Treatment (TPT) Interventions

Significant strides have been made in developing improved TB Preventative Treatment (TPT) strategies. For example, a 2019 study showed that a TPT strategy that included a 1-month treatment of RPT and INH can effectively prevent progression from latent to active TB infection among adult PLWH. The efficacy of this regimen is being evaluated further in children and in people not infected with HIV. Another TPT trial, the Protecting Households on Exposure to Newly Diagnosed Index Multidrug-resistant Tuberculosis Patients (PHOENIx), co-funded by NIAID and the National Institute of Child Health and Human Development (NICHD), is investigating the ability of a new TB drug (delamanid) to prevent TB disease among household contacts of individuals with MDR-TB. This trial represents a collaboration between the Advancing Clinical Therapeutics Globally for HIV and other Infections (ACTG) Network and the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network.

With advances in formulation technologies and the discovery of more potent drugs with activity against *Mtb*, it is possible to further simplify TPT regimens into shorter, safer, and more effective courses. As research in these diverse fields advances, NIAID will continue to support platforms to integrate these efforts into combined interventions so maximal benefit is achieved at individual and population levels.

Objective 4.3 Develop and Evaluate Shorter and/or Safer TB Treatment Regimens for All Patient Populations and Forms of TB

As TB treatments are advanced through the research and development pipeline, they must be evaluated for their interactions with other TB treatment regimens, in various disease states, and in persons with co-infections or co-morbidities. The anticipated result is that new regimens will enable patients to adhere to TB treatment more easily, ensure better patient outcomes, and reduce forward transmission (Figure 7). As such, NIAID is prioritizing rational design of new TB drug regimens. New drug combinations may result in improved efficacy and shorter treatment schedules, thereby improving implementation of these regimens in various settings. Importantly, safety and tolerability of new treatments are important characteristics for new regimen development.

NIAID supports TB research tools such as the TB Portals, a collaborative and open access platform to provide clinical investigators with outcome data on a global scale. Other translational work and clinical

trials investigate potential therapeutics for treating TB in combination with drugs for co-morbidities, particularly PLWH.

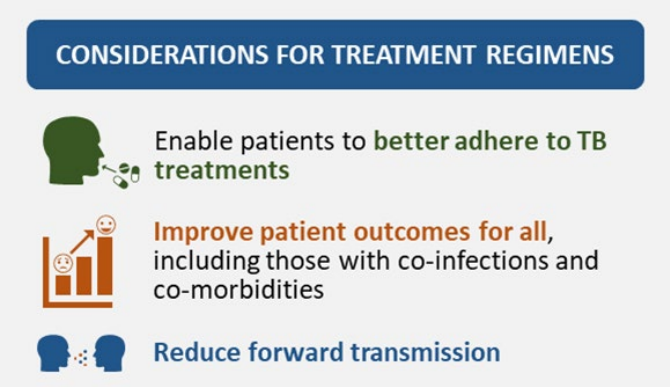


Figure 7: Continued development of novel treatment regimens for TB can lead to shorter treatment times that can enable better patient adherence; improved outcomes for all, including those with co-infections or co-morbidities; and decreased transmission.

The development of quantitative measures of *Mtb* burden in all populations, as well as microbiologic studies to characterize the sterilizing activity of existing drugs, will contribute to advancing novel drug candidates. Continued investigation of the impact of HIV infection on TB disease and treatment outcomes should be prioritized to ensure that PLWH benefit from advances in TB treatments. Clinical evaluations of promising regimens must consider the spectrum of populations affected by TB including pregnant women, pediatric populations, and those with disease modifying co-morbidities. NIAID will continue to support development and evaluation of treatment regimens against both DS and DR TB as improved TB therapeutic interventions are critical to enhancing efficacy, shortening treatment duration, overcoming drug resistance, and ultimately reducing the global burden of TB.

As part of this effort to develop and test promising drug candidates, NIAID will build on existing investments in clinical research infrastructure and resources (Appendix 2). These efforts will be directed both within and outside of the U.S. where TB is endemic to facilitate the development of therapeutics for people with TB, including PLWH and in people with other co-morbidities (e.g., diabetes, cardiovascular disease, and other lung conditions).

Extrapulmonary TB, especially TB meningitis, continues to exact a substantial toll in morbidity and mortality. Thus, improvements in therapies to treat these conditions are greatly needed. Research has shown that treatments that work well for pulmonary TB may not have the same level of efficacy for TB meningitis due to several factors, including limited penetration through the blood-brain-barrier. Research to fully understand the factors impacting treatment efficacy in TB meningitis and development of improved strategies should be prioritized.

In addition to HIV, it is known that other co-morbidities, including diabetes, hypertension, malnutrition, and tobacco smoking, are risk factors for TB and for poor TB treatment outcomes. Co-morbidities complicate patient health status by affecting local or systemic immune responses, drug metabolism, hormonal balances, or nutrient malabsorption. It is therefore important to understand how co-morbidities impact TB progression to improve co-management and treatment strategies. Collaborative research conducted in TB-endemic countries provides novel insights into the impact of co-infections and co-morbidities on *Mtb* infection. To begin to address these issues, NIAID created the Regional Prospective Observational Research in Tuberculosis (RePORT) International program to foster collaborations between bench and clinical researchers. Each international cohort is designed to support local, in-country, TB and TB/HIV-specific data and specimen biorepositories and associated research and NIAID will continue to support building global clinical research capacity in high burden settings and share common protocols and data and specimen collection to address research needs.

CONCLUSION

This updated 2024 NIAID Strategic Plan for TB Research builds on the momentum generated from high-profile, international reports and meetings, including the WHO End TB Strategy, 1st WHO Global Ministerial Conference on TB, and UN General Assembly High-Level Meeting on Ending TB. The updated plan also aligns with the global goals and supports the objectives delineated in the U.S. Government Global TB Strategy and the National Action Plan for Combating Multidrug-resistant TB. These reports and meetings highlight the importance of biomedical research as a critical component of a global strategy to end TB and underscore the need to continue efforts to improve knowledge and tools to prevent, diagnose, and treat TB. NIAID aims to address these needs through a comprehensive scientific agenda and infrastructure expansion that are geared towards strengthening TB research.

To continue the advancement of efforts to end the TB pandemic, it is important to continue recruiting experienced, as well as new investigators to the field of TB research and increase collaborative, multidisciplinary research that includes researchers from all backgrounds. In 2022, NIAID established new TB Research Advancement Centers (TRACs) to promote these goals and support mentoring and funding of new investigators and researchers new to TB. NIAID will draw on expertise from diverse disciplines, including but not limited to virology, immunology, microbiology data science, genetics, and epidemiology, to drive the research that will increase fundamental knowledge and the development of new diagnostics, preventative measures, and treatments.

NIAID continues to leverage its existing portfolio of resources and investments in biomedical research to expand and modernize its TB research program. These efforts are expected to reinvigorate TB research and accelerate the development and evaluation of new and improved methods to diagnose, prevent, and treat TB. By advancing fundamental TB research, resource development, and training of the next generation of researchers, NIAID will accelerate the development of a comprehensive toolkit to end TB.

APPENDICES

Appendix 1: NIAID TB Working Group Members

Last Name	First Name	Position
Azeez	Olumayowa	Health Science Policy Analyst; Policy, Planning and Evaluation Branch, OD
Boggiano	Cesar	Chief; Preclinical Research and Development Branch, DAIDS
Boyce	Jim	Program Officer, Tuberculosis and Other Mycobacterial Diseases Section, DMID
Bushar	Nicholas	Branch Chief; Policy, Planning and Evaluation Branch, OD
Dang	Que	Program Officer; Preclinical Research and Development Branch, DAIDS
Darrah	Patricia	Staff Scientist; Cellular Immunology Section, VRC
Deckhut	Alison	Branch Chief; Basic Immunology Branch, DAIT
Deschamps	Anne	Senior Health Science Policy Analyst; Policy, Planning and Evaluation Branch, OD
Drew	Jessi	Scientific Policy Analyst (Contractor); Policy, Planning and Evaluation Branch, OD
Eichelberg	Katrin	Program Officer; Tuberculosis and Other Mycobacterial Diseases Section, DMID
Grace	Beth	Senior Financial Analyst, DCR
Hutter	Julia	Medical Officer; Vaccine Clinical Research Branch, DAIDS
Kim	Peter	Director; Therapeutics Research Program, DAIDS
Lacourciere	Karen	Program Officer; Tuberculosis and Other Mycobacterial Diseases Section, DMID
Laughon	Barbara	Program Officer; Tuberculosis and Other Mycobacterial Diseases Section, DMID
Leitner	Wolfgang	Section Chief; Innate Immunity Section, DAIT
Mendez	Susana	Program Officer; Tuberculosis and Other Mycobacterial Diseases Section, DMID
Miers	Sarah	Program Analyst, Office of Scientific Coordination and Program Operations, DMID
Ramachandra	Lakshmi	Section Chief; Tuberculosis and Other Mycobacterial Diseases Section, DMID
Robinson	Richard	Program Officer; Tuberculosis and Other Mycobacterial Diseases Section, DMID
Read	Sarah	Deputy Director; DAIDS
Schmit	Ginny	Health Science Policy Analyst; Policy, Planning and Evaluation Branch, OD
Shaffer	Meredith	Scientific Program Specialist; DIR
Vázquez-Maldonado	Nancy	Program Officer; Innate Immunity Section, DAIT
Vernon	Andrew	Branch Chief; Tuberculosis Clinical Research Branch, DAIDS

Appendix 2: NIH-Supported TB Research Resources

Resource Name	Description
Adjuvant Development Program	The goal of the adjuvant development program is to establish and expand the availability of novel vaccine adjuvants that researchers can use for preclinical vaccine development in infectious and immune mediated diseases.
Adjuvant Discovery Program	NIAID plays a leading role in the discovery, development, and characterization of new vaccine adjuvants that may be used to: improve the efficacy of current vaccines; design new or improved vaccines for existing and emerging infectious diseases; and develop vaccines to treat allergies, autoimmune diseases, and cancer.
AIDS Reagent Program	Acquires, develops, and produces state of the art reagents and provides these reagents at no cost to qualified investigators throughout the world.
Advancing Vaccine Adjuvant Research for Tuberculosis (AVAR-T)	The AVAR-T program will provide support to further the development of preventive, including post-exposure, TB vaccines through side-by-side comparisons of adjuvants in combination with *Mtb* immunogens and to establish immunological profiles of adjuvants that work through different mechanisms.
Bacterial and Viral Bioinformatics Resource Center (BV-BRC)	Information system that integrates bacterial pathogen information with rich data and analysis tools to support work on infectious diseases.
BEI Resources Repository	Central repository that supplies organisms and reagents to the broad community of microbiology and infectious diseases researchers.
Bioinformatics Resource Centers	Collects, archives, updates, and integrates research data with user-friendly interfaces and computational analysis tools.
Centers for Research on Structural Biology of Infectious Diseases (CRSTAL-ID)	Applies state-of-the-art technologies/methodologies to characterize 3-D atomic structures of molecules to support infectious disease research.
Clinical Genomics Program	Provides centralized resources to be used for genomics and related research.
Cooperative Centers on Human Immunology	Translates immunology research into clinical applications in infectious disease.
Early Phase Clinical Trial Units	Supports design, development, implementation, and conduct of Phase I clinical trials against viral (other than HIV), bacterial, parasitic, and fungal pathogens.

Resource Name	Description
Finding TB Cases Actively, Separating safely and Treating - effectively (FAST-TB)	FAST-TB is an approach to preventing TB spread in congregate settings. The acronym FAST focuses on effective treatment which is the most important TB transmission intervention.
Feasibility of Novel Diagnostics for TB in Endemic Countries (FEND for TB)	The FEND for TB program supports the evaluation of early-stage diagnostics and novel diagnostic strategies for TB in TB endemic countries to address an urgent need for improved TB diagnostics.
Genomic Centers for Infectious Disease (GCID) Resources	Provides innovative application of genomic technologies and rapid, cost-efficient production of high-quality genome sequences for pathogens and hosts.
HIV/AIDS Clinical Trials Network	Group of clinical trials networks addressing HIV scientific priorities including vaccines and therapeutics for co-infection.
HIV, Opportunistic Infection and TB Therapeutics Database (ChemDB)	Extracts from the scientific literature structure / activity information on compounds tested against HIV, opportunistic infections, and TB.
Human Immunology Project Consortium (HIPC)	Uses modern tools to examine the human immune system before / after infection, vaccination, or adjuvant treatment.
Infectious Disease Clinical Research Consortium	A clinical trials research consortium that prioritizes vaccines, diagnostics, and other interventions to test in clinical trials.
International Epidemiology Databases to Evaluate AIDS (IeDEA) Cohort Consortium	Generates large, harmonized HIV/AIDS datasets from seven international regional data centers to help address high priority research questions.
In-Vitro Assessment for Antimicrobial Activity Program	Tests for antimicrobial activity of products against microbial pathogens and vectors. Strains and panels include those derived from clinical specimens.
ImmPort	Platform to share and analyze immunology data generated from human and animal models.
Immune Epitope Database (IEDB) and Analysis Resource	Database with detailed information for more than 1,000,000 unique immune epitopes (antibody/B cell and T cell) related to infectious and immune mediated diseases.
Immune Mechanisms of Protection Against Mycobacterium tuberculosis Centers (IMPAc-TB)	The IMPAc-TB program is an initiative established by NIAID in 2019 to elucidate the immune responses needed to protect against infection with *Mtb*. The program will lead to a better understanding of TB immunology which is critical to guide the design and development of new and improved TB vaccines.
ImmuneSpace	Powerful data management and analysis engine for the HIPC program that enables integrative analyses and visualization of human immunological data.

Resource Name	Description
Preclinical Models of Infectious Disease Program	Provides development, screening, and efficacy testing in preclinical infectious diseases models, including traditional lab species, non-human primates, and non-traditional models.
Regional Prospective Observational Research in Tuberculosis (RePORT) International	Supports the establishment of regional RePORT consortia in cooperation with host countries for future combined or comparative data analysis and is a resource to bridge collaborations between bench and clinical researchers.
Tetramer Core Facility	Produces and distributes major histocompatibility complex tetramers and related reagents to the research community.
TB Portals	Advancing TB research through open-access, multi-domain, global TB data and tools.
Tuberculosis Research Units Network (TBRU-N)	The Tuberculosis Research Units operate as a collaborative network designed to improve the understanding of *Mtb* host interactions.
Therapeutic Development Services: Biopharmaceutical Product Development Services	Offers services for biotechnology products, such as planning, product characterization, process development, formulation, Good Manufacturing Practice, and Chemistry, Manufacturing and Control documentation.
Therapeutic Development Services: Interventional Agent Development Services	Facilitates development of therapeutics, including lead identification and development, chemistry and manufacturing, toxicology, and pharmacokinetics.
Tuberculosis Research Advancement Centers (TRACs)	Centers will support the development of a next generation of TB researchers by providing focused mentoring and funding support for new investigators, opportunities for multidisciplinary and collaborative research; and training in laboratory and clinical settings.
Tuberculosis Information for Researchers	Through the information offered here, researchers can learn about the science being conducted at NIAID and by NIAID funded researchers.
Vaccine Adjuvant Compendium	Displays adjuvant characteristics or metadata defined through NIAID-supported adjuvant studies, helps vaccine developers identify suitable adjuvants for vaccine indications.
Vaccine and Treatment Evaluation Units	Supports efforts to develop new and improved vaccines and therapies against infectious diseases.
Vaccine Development Services	Offers services for vaccine and adjuvant development such as assay development, non-clinical immunogenicity and efficacy studies, clinical and non-clinical sample testing and safety and toxicity testing, and for manufacturing. Manufacturing services include gap analysis and product development plan support as well as product optimization and other assistance.

Appendix 3: Analysis of Public Comments to Request for Information (RFI)

NIAID sought input from stakeholders in the scientific research community and the public regarding the proposed priorities for the **NIAID Strategic Plan for Tuberculosis Research Update** through a Request for Information (RFI). The RFI (NOT-AI-23-052) was open for comments from June 13, 2023 to August 22, 2023. Submissions were received through a web-based form or by email. Input was requested on, but was not limited to, the following five topics regarding tuberculosis (TB) research:

- Improving fundamental knowledge of TB
- Advancing research to improve diagnosis of TB
- Accelerating research to improve TB prevention
- Supporting research to advance strategies to treat TB
- Developing tools and resources to advance TB research

NIAID received 16 responses to the RFI, mostly from those in academia and from professional organizations. The submissions largely supported the priorities outlined in the plan, while offering specific input on gaps, resources necessary to advance TB research, and emerging technologies. A summary of themes based on an analysis of the RFI responses is provided.

Specific Themes

TB Biology and Disease

Commenters noted several gaps related to TB biology and disease. Some indicated that more support is necessary to improve the fundamental knowledge of TB, including how microbial physiology and genetics impact disease phenotype. Host factors that are associated with risk of TB infection, progression, transmission, and treatment response must also be better understood. Additionally, there is a need to define sub-phenotypes of TB disease more precisely.

Gaps also remain in understanding the biology of lung tissue damage and repair in TB disease. These gaps extend from mediators of matrix destruction and cavity formation to the subsequent remodeling that occurs in response. Other post-TB sequelae that should be more thoroughly investigated include recurrent infections and long-term co-morbidities.

Tools, Resources, and Models of TB

Respondents noted the need to use natural, minimally cultured patient isolates of *Mtb* rather than the more widely used *in vitro* passaged laboratory strains. Doing so would expand knowledge into the natural biological diversity of TB on both the host and microbe.

Commenters stressed the need for continued development of TB disease models, including animal and non-animal alternatives (e.g., *ex vivo* human tissue models). These models should have increased complexity that allow for mechanistic studies and enable the detection of immune COP. Robust validation strategies must accompany these new models. In addition, a dedicated resource sharing database, widely accepted definitions, and standards as they pertain to complex immunological TB studies are needed. Multimodal and whole-body imaging technologies (PET/CT/MRI) can provide detailed insights regarding the dynamics and pathophysiology of TB disease and can assist in development of novel host-directed therapies, biomarkers, and can provide cross-species analyses.

Surveillance, Screening, and Diagnostics

Many respondents identified a need for TB case-finding and tracking outbreaks, especially among pediatric populations, people living with HIV (PLWH), pregnant women, and migrants. To address better

screening and surveillance activities, more sensitive diagnostic tests are needed. These tests should be suitable for mass screening measures using non-sputum sampling (e.g., exhaled breath, blood, or urine) and should be capable of deployment in remote settings. Commenters also stated that development of point of care diagnostics and home-based testing assays should be prioritized and should leverage successes developed during the COVID-19 pandemic. With that, better diagnostic laboratory capabilities and capacities are also needed.

TB Prevention and Treatment Strategies

Several comments stressed the necessity for advances in host-directed immunomodulatory or immunotherapeutic treatments. Host-directed therapies could improve the efficacy of antibiotic treatment, shorten required treatment durations, reduce pressures driving antibiotic resistance, and enhance immune protection against secondary infection. Continued development of shorter regiments for drug-sensitive and drug-resistant forms of TB, including in children and PLWH, is especially warranted, commenters stated.

Respondents also noted that technology advances can assist in the development of TB therapies. AI or machine learning may be useful in development of TB treatments and could be employed to predict treatment response. Additionally, mobile apps to trace contacts and monitor patients' treatment compliance and response would be a useful area for development.

Cross-cutting Themes

TB Workforce

Support for early career investigators and physician-scientists focused on TB research warrants emphasis, commenters noted. Dedicated funding strategies to support the next generation of early career TB researchers is especially needed. NIH should also encourage innovative and high-risk projects, especially cross-disciplinary collaborations that could bring in expertise from other fields.

U.S. based researchers conducting global health research should have strong ties and collaborations with the partner institutions and communities where the work is based. Comments also indicated that more specialist inputs from TB endemic regions through collaborations between the NIH and other federal agencies would facilitate research. Professional development and training for researchers and clinicians from TB endemic regions through collaborations between the NIH and other federal agencies would also be beneficial.

TB Research Funding and Infrastructure

Respondents noted that a boost in TB research funding, as called for by the Stop TB Partnership, would produce dramatic results in achieving the goal of ending TB. Increased investment in TB Research Advancement Centers (TRAC) could also generate successes in TB research similar to that of the Centers for AIDS Research (CFAR) program. Investment in an NIH core or other funding mechanism for T cell and B cell antigen discovery platforms for infectious disease research, including TB, would be welcomed. Respondents also commented that there is a need for dedicated mechanisms of support for BSL3 facilities, as they are difficult to maintain via typical grant mechanisms.

At-risk Populations

Commenters indicated that TB research should account for social and economic factors that fundamentally drive the epidemic. All populations of patients including pediatric populations, PLWH, pregnant women, migrants, and asylum seekers should be integrated into all aspects of TB research, treatment, and management. Transmission, diagnosis, and treatment can be partially addressed

through effective public health education provided in a linguistically competent manner among minority populations. Investigations into the social determinants of health that drive TB transmission should also be prioritized. Increasing the numbers of trained professionals to support TB prevention and treatment activities in communities at the highest risk for TB would be beneficial to the field and would further positive public health interactions with diverse populations.

Clinical Research

Respondents indicated that research should refocus on the natural history of tuberculosis disease, especially in high-burden countries, by developing large multi-country cohorts. Increased clinical research capacity, particularly for pediatric populations, should also be prioritized. Additionally, advancing TB drug regimens necessitates the development of standardized, patient-centered endpoints incorporated into clinical trials.