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August 2020

TB Research Investments Provide Returns in Combating Both TB and COVID-19:

Sustained and Expanded Financing Is Needed to Safeguard Tuberculosis Research Against COVID-19–Related Disruptions and Improve Global Epidemic Preparedness

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INTRODUCTION

Since its appearance in December 2019, COVID-19 has spread rapidly around the globe and caused a staggering loss of life. As the world turns its urgent attention and commits unprecedented resources to tackling this novel disease, governments and donors must ensure that research and development (R&D) efforts for tuberculosis (TB) are maintained and strengthened.

> *Modeling estimates that disruptions of TB services due to COVID-19 could lead to an additional 6.3 million TB cases and 1.4 million TB deaths between 2020 and 2025, setting back global gains in combating TB by five years.*

Despite its long history, TB remains an urgent health crisis and the leading cause of death by an infectious disease. Around 10 million people develop TB disease and 1.5 million people die from TB every year.[1] Modeling estimates that disruptions of TB services due to COVID-19 could lead to an additional 6.3 million TB cases and 1.4 million TB deaths between 2020 and 2025, setting back global gains in combating TB by five years.[2]

New diagnostic, treatment, and prevention tools for TB are urgently needed to put the world on track to meet the United Nations (UN) Sustainable Development Goals to end the TB epidemic by 2030.[3] However, COVID-19 and responses to it are complicating and disrupting critical TB research efforts underway. Sustained and expanded investment in TB R&D is urgently needed to fortify TB research efforts against COVID-19–related complications and disruptions and to deliver game-changing new public health tools to aid the fight against TB.

In addition to combating TB disease and deaths, investment in TB R&D can deliver broad global health benefits, advance infectious disease research, and strengthen global epidemic preparedness. Cross-disease benefits harnessed from TB R&D are already evident for COVID-19. Tools, concepts, capacity, and infrastructure stemming from TB R&D investments have informed, assisted, and jumpstarted COVID-19 research and responses.

Shoring up investments in TB R&D may therefore not only deliver new tools for TB but also advance efforts to tackle the novel coronavirus and improve our preparedness to confront future pandemic threats.

INCREASED FINANCING IS NEEDED TO SUSTAIN CRITICAL TB R&D ACTIVITIES DURING THE COVID-19 PANDEMIC

While financing for TB R&D reached an all-time high in 2018, it remained at less than half of the $2 billion funding target needed to develop new tools to end TB by 2030.[4] Despite the considerable funding gaps facing TB research, expanded political will and increased investment to combat TB in recent years have bolstered research efforts and ushered in promising new scientific advances. With sustained and increased investment, these advances may lead to the delivery of game-changing new tools to prevent, diagnose, and treat TB. However, COVID-19 and responses to it are complicating and threatening ongoing and prospective TB research efforts (see table 1). Supporting TB research has tremendous benefits for efforts to curb COVID-19 (see table 2), especially given similarities in the transmission and public health response to both diseases (table 3, appendix).

As governments and funders scale up financing commitments for COVID-19, they must ensure that prospective funding is not diverted away from TB R&D and that ongoing research funding commitments for TB R&D continue uninterrupted. This is particularly important given the overlap between key funders of TB and COVID-19 R&D and the critical role of public financing in advancing research for both diseases.

Public financing accounts for more than two-thirds of overall funding for TB R&D. The United States is the largest funder of TB R&D (investing over 60% of public sector funding in 2018), followed by the United Kingdom. In 2018, only three countries (South Africa, the Philippines, and the United Kingdom) met their 'fair share' targets by investing at least 0.1% of their total R&D expenditure in TB, as called for by civil society to close the funding gap.[5]

Funding for TB R&D must be sustained and expanded throughout and after the COVID-19 pandemic to advance promising research and implement new TB medicines, diagnostics, and vaccines (see table 4, appendix). Unless governments and other donors shore up TB R&D against the COVID-19 pandemic, we put at risk existing investments in ongoing studies and stand to lose out on the potential to deliver new tools and approaches to end TB in our lifetimes.

COVID-19 IS THREATENING CRITICAL ONGOING AND PROSPECTIVE TB RESEARCH

COVID-19 and responses to it are complicating TB research efforts and threatening the delivery of timeous and meaningful research results. Disruptions of ongoing TB research will delay and impede the development of urgently needed new tools to combat TB.

TB research studies and networks from around the world have reported challenges due to COVID-19 and are adapting their research efforts and protocols to enable the continuation of critical research. Study responses to COVID-19 will have budgetary implications, and additional funding will be required to cover extended timelines and unforeseen expenses (table 1).

Governments and donors must ensure the availability of funding to continue and complete critical TB research, as well as to deliver meaningful study results to guide TB responses.

Table 1. COVID-19–related challenges for TB R&D and study responses[6]

Trial enrollment	TB trials and sites around the globe have paused enrollment due to concerns regarding the safety of trial participants and staff. A decline in routine TB services due to health facility avoidance and COVID-19–related barriers to movement further impedes enrollment efforts. In some locations, study site infrastructure and staff have been diverted to support COVID-19 responses. Postponed enrollment in TB trials will delay critical research necessary to inform TB responses and introduce new TB tools. Further, some studies may need to close before reaching their intended sample sizes due to costs associated with extending trial timelines, which would threaten the significance of trial results and their value in informing TB responses.
Patient monitoring and support	TB trials worldwide have reported efforts to limit in-person health facility visits during the COVID-19 outbreak to protect the health of trial participants while ensuring that critical safety monitoring and adherence support continues. To limit health facility visits, many ongoing trials are now using phone and video calls and/or conducting home visits for patient monitoring and follow-up. Private transportation has also been provided to participants requiring health facility visits and check-ups, as well as to staff conducting home visits. In some cases, TB trials have been able to continue operations during country lockdowns, as they provide essential health care services to patients with TB.

Continuity of treatment	Efforts to limit health facility visits, as well as challenges faced by participants in accessing study sites due to lockdown and stay-at-home orders, have complicated the ongoing provision of treatment to trial participants. Several sites have developed alternative methods to deliver medications typically provided during routine health facility visits. The strategies include home delivery of medications, staggering medicine collection at designated sites, and increasing supplies of medication provided to participants. The United States has also used mail delivery of medications.
Supply chain disruptions	Supply chain disruptions and unexpected export bans have created challenges for ensuring the continuity of treatment and availability of trial drugs. While no studies have reported treatment interruptions among participants to date, some studies have experienced 'close calls' due to COVID-19–related transport restrictions that have delayed the importation of trial medication. Manufacturing disruptions in India and China (where most TB medicines and their ingredients are produced), as well as the threat of an export restriction in India, could further hamper access to medicines for trials.
Collection of samples	Research sites have reported that maintaining continuity of sputum and blood sample collection for safety monitoring has been a key challenge. While most sites have developed alternative approaches to collect samples, including during limited facility visits or through home collection, some sites have reported that the collection of samples has been indefinitely interrupted. The interruption of sample collection raises critical concerns regarding patient safety monitoring and the integrity and quality of trial data and results. It also threatens to undermine biomarker discovery, which relies on stored specimens from clinical trials. Lack of access to COVID-19 test materials has also been a challenge for research sites seeking to identify and record COVID-19 infection as an adverse event in trial data and to ensure that trial participants with COVID-19 receive proper diagnosis and care.
Export of samples	Studies that use centralized laboratories to conduct safety and microbiology testing have reported challenges in transporting samples to these labs due to COVID-19–related export restrictions and transport disruptions. Some sites are now amending study procedures to use local laboratories instead. Other sites have arranged charter flights to transport samples to centralized labs, adding to study costs.
Appropriate laboratory infrastructure and staff	Laboratories meeting biosafety level-3 (BSL-3) and animal biosafety level- 3 (ABSL-3) requirements, which are necessary for studying potentially lethal agents that can be transmitted in the air (such as tuberculosis and COVID-19), as well as laboratory staff with experience working in these labs, are being diverted for or overwhelmed by the COVID-19 response. The diversion of these key resources impedes ongoing TB research and responses.
Engagement with regulatory authorities and ethics bodies	Given changes to research procedures and study protocols as a result of COVID-19, studies must engage with and receive guidance from regulatory authorities and ethics bodies (i.e., IRBs). Rapid guidance from regulatory authorities and IRBs on acceptable protocol deviations and changes due to COVID-19 has facilitated the continuation of research in some locations. Conversely, where regulatory and IRB activities have been suspended or delayed, research activities have been impeded.
Community engagement	Community engagement structures enable studies to identify and respond to COVID-19–related challenges. These structures also facilitate critical engagement with communities regarding the potential impacts of trial changes and disruptions on patient safety and trial results. However, in some sites, critical community engagement activities have been disrupted due to COVID-19.

TB RESEARCH AND INFRASTRUCTURE HAS SUPPORTED COVID-19 RESPONSES

Beyond delivering game-changing new tools for TB, investment in TB R&D can advance infectious disease research and improve global epidemic preparedness. Investments in TB R&D have already provided significant cross-disease benefits for COVID-19 research and responses. Global TB research infrastructure and capacity are being activated in response to COVID-19, and tools and techniques developed for TB are being utilized in COVID-19 research and responses.

Shoring up global investments in TB R&D may therefore deliver not only new tools to end TB in our lifetimes but also cross-disease benefits that may be leveraged in combating COVID-19 and future pandemic threats.

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Table 2. Cross-disease benefits for COVID-19 from TB R&D

Transmission dynamics and aerobiology research	• Aerobiology research investigates how airborne biologic components, such as virus- or bacteria-containing respiratory droplets, move through the air and impact human health. • Aerobiology research related to TB has contributed to the development of air sampling techniques and technologies that may be useful in learning about how COVID-19 is transmitted and how transmission can be prevented.[7,8] • Modeling methods developed to research subclinical TB (asymptomatic active TB disease) and its contribution to TB transmission have been applied to investigate asymptomatic transmission of COVID-19.[9]
Artificial intelligence	• Artificial intelligence or deep-learning methods developed to review chest radiographs and identify TB-related lung changes are now being adapted for COVID-19. • Rapid identification of COVID-19 lung changes can aid in the triage and diagnosis of people with symptoms of COVID-19 in the absence of sputum results, as well as in poorly resourced and remote locations where access to radiologists is limited. • This technology can also provide medical workers with useful 'second opinions' in diagnosing COVID-19 and has been used in New York and other locations.[10,11]
Diagnostic tools	• Diagnostic technologies developed to enable rapid diagnosis of TB and detect drug resistance are now being used for the diagnosis of COVID-19. • Cepheid's GeneXpert multi-disease PCR testing platform is used for rapid diagnosis of TB and detection of rifampicin resistance, and developed with substantial investment from the U.S. government[12] and philanthropic donors. With support from BARDA[13], Cepheid has now developed a COVID-19 test that can be used on the 23,000 GeneXpert diagnostics machines already present worldwide. • Diagnostics manufacturer Molbio recently received a positive review from the World Health Organization for the TB and rifampicin resistance diagnostic tests it developed for use on its Truenat multi-disease PCR testing platforms.[14] Molbio has now received approval from India's regulatory authority for a Truenat COVID-19 test, expanding the number of existing diagnostics platforms that can be repurposed for the current pandemic.[15] • Immunoassay platforms (technologies used to identify and characterize immune responses) that were developed for TB are being applied in immunology research for COVID-19.[16]

Vaccine platforms	• Vaccine platforms developed and undergoing research for TB are being investigated as possible vaccine candidates and platforms for COVID-19. • Studies of the 'off target' effects of the bacillus Calmette-Guérin (BCG) vaccine have helped elucidate a new area of human immunology known as 'trained innate immunity'. As a result, BCG, currently in use to combat childhood TB, is being evaluated for its potential to protect high-risk populations, such as COVID-19 healthcare workers, through its off-target effects. • Further investment is needed to confirm the possible protective effect of BCG against COVID-19, as well as its mechanism of action (i.e., whether BCG can train the innate immune system to respond to pathogens other than TB, including SARS-CoV-2).[17] • The novel TB vaccine candidate VPM1002 is being investigated for efficacy against COVID-19 as part of worldwide efforts to develop a vaccine against the new pandemic.[18] • Other COVID-19 vaccine candidates are making use of vaccine strategies previously studied for TB.[19,20]
Research infrastructure and capacity	• Infrastructure and capacity developed for TB research, including trial networks, laboratory facilities, research and clinical expertise, and community advisory boards, are being activated for COVID-19 research and responses. • TB researchers and research sites have supported COVID-19 responses through a range of activities, including training medical workers on the use of personal protective equipment, guiding and assisting contact tracing efforts, providing epidemiologic and modeling support, and even researching COVID-19 interventions.[21,22] • Community advisory boards (CABs) established to enable community engagement and input on TB research are being consulted regarding proposed research for COVID-19.
Laboratory biosafety	• TB R&D investments in laboratory capacity have enabled COVID-19 diagnosis and research globally, as key elements of COVID-19 diagnosis and research must be conducted in labs with appropriate infrastructure and procedures in place for the safe handling and study of potentially lethal airborne infections. • The establishment and maintenance of BSL-3 labs around the world has, to a large extent, been driven by the need for BSL-3 infrastructure and procedures to diagnose and study drug-resistant TB.[23] • In particular, large investments made to establish ABSL-3 facilities for conducting nonhuman primate research as part of TB vaccine discovery are now being used to accelerate the development of COVID-19 vaccines.

"TB clinical trials carry inherent challenges at the best of times. Locations with the highest TB burden often have less resilient regulatory infrastructure, complex operational environments and more limited clinical trial experience. During an unexpected and large-scale disruption like COVID-19, the impact of these weaknesses becomes more magnified."

– ID Rusen, Trop Med Infect Dis, June 2020

KEY MESSAGES AND RECOMMENDATIONS

1. **All governments and donors should recognize that investing in TB research will not only accelerate progress toward ending TB, which remains the world's leading infectious killer, but also deliver broad benefits through scientific breakthroughs and capacities that can be harnessed to respond to COVID-19 and future pandemic threats.** Airborne respiratory pathogens, in particular, pose significant risks to health, society, and the economy given their ability to spread rapidly at large scale. Investment in TB R&D has considerably improved scientific knowledge regarding airborne pathogens and interventions to curb their spread.

2. **Governments must increase their TB R&D investments to meet or exceed 'fair share' targets**, defined as 0.1% of their total R&D expenditure, to achieve the global goal of $2 billion in annual financing for TB R&D, shore up TB research investments against COVID-19, and deliver game-changing new technologies.

3. **As governments and other donors commit financing to combat COVID-19, they must not shift or divert funding away from critical TB R&D.** TB remains an urgent global health crisis requiring investment, attention, and prioritization throughout and after the COVID-19 pandemic.

4. **COVID-19 has revealed the importance of building local research capacities, so that when major unanticipated disruptions to research do occur, researchers can more nimbly mitigate negative consequences.** Building critical laboratory infrastructures and maintaining networks of clinical trial sites in diverse locations reduces the need to find workarounds for exporting clinical trial samples to central labs for analysis and validation. Local research capacities also create resiliencies by putting in place scientific expertise and infrastructure that can be quickly leveraged to expedite the initiation of research to understand and address emerging pathogens.

5. **Enhanced international cooperation in science is needed to advance research efforts for both COVID-19 and TB.** Governments should encourage and require collaboration and openness to hasten the development of new knowledge and public health tools and to avoid costly research duplication and silos. Instruments available to governments to advance international cooperation in science include (among others) participating in joint financing instruments and pools; requiring open access to research data and results; participating in pools to share patents and knowledge; prohibiting anti-competitive and restrictive patenting and licensing practices; and requiring broad transparency regarding the pricing, sale, and distribution of health technologies.

> *"[We] commit to mobilize sufficient and sustainable financing, with the aim of increasing overall global investments to 2 billion dollars, [...] ensuring that all countries contribute appropriately to research and development."*
>
> *– Political Declaration of the UN High-Level Meeting on the Fight Against Tuberculosis*

APPENDIX

Table 3. Similarities and differences between COVID-19 and TB

	COVID-19	TB
Pathogen	COVID-19 is caused by the novel virus SARS-CoV-2.	TB is caused by the age-old bacterium *Mycobacterium tuberculosis* (Mtb).
Scale	Over 13 million cases of COVID-19 have been confirmed since the appearance of the novel SARS-CoV-2 virus in December 2019.[24]	Around 10 million people fall ill with TB disease annually, of whom approximately 500,000 have drug-resistant disease.[25]
Mortality	Over half a million COVID-19 deaths were reported in the first seven months of the pandemic.[26]	Around 1.5 million TB deaths occur every year.[27]
R&D financing	The emergence of the novel SARS-CoV-2 virus has been met with unprecedented financing commitments to advance biomedical innovation to combat COVID-19. In May 2020, the European Union hosted a global pledge drive that secured US$8 billion in financing commitments for the development of COVID-19 vaccines and treatments.[28] The United States has also rapidly authorized large funding allocations to accelerate research, development, and production of COVID-19 countermeasures, including almost US$10 billion through stimulus funding packages.[29]	In 2018, UN member states determined that a minimum of US$2 billion dollars in annual financing for TB R&D is needed to put the world on track to meet global targets to end the TB epidemic by 2030.[30] Although global TB R&D financing reached a record high in 2018 at $906 million, it remained halfway short of the UN's financing targets.[31] To address the funding shortfall, civil society has called on governments to contribute their 'fair share' toward the $2 billion financing target by allocating 0.1% of their overall R&D spend to TB research.[32]
Transmission and infection	COVID-19 is mainly spread in respiratory droplets expelled by individuals with COVID-19 infection during coughing, talking, breathing and other activities. COVID-19 is spread in respiratory droplets inhaled by individuals in close contact, as well as through contact with surfaces on which respiratory droplets have landed. There is also evidence that COVID-19 is spread through airborne transmission in microscopic respiratory droplets that remain suspended in the air after being expelled.[33]	TB is spread in respiratory droplets expelled by individuals with active TB disease during coughing, talking, breathing, and other activities. TB-containing respiratory droplets remain suspended in the air for several hours after being expelled, during which they may be inhaled. TB is not spread through contact with surfaces.[34,35]
Incubation	Individuals who fall ill with COVID-19 typically develop symptoms within two- to 14-days after infection.[36]	Individuals who fall sick with TB disease may do so within weeks or years after infection. Around half of individuals who become ill with TB disease do so within two years of Mtb infection.[37]
Symptoms	Symptoms of COVID-19 illness include (among others) cough, fever, difficulty breathing, fatigue, and a new loss of taste or smell.[38] COVID-19 primarily attacks the lungs.	Symptoms of TB disease include (among others) cough, fever, difficulty breathing, fatigue, weight loss, and night sweats.[39] TB primarily attacks the lungs.

Treatment	There is currently no specific treatment recommended for COVID-19, although many treatments are undergoing investigation. Preliminary research has shown that dexamethasone can reduce mortality for critically ill patients.[40]	Tuberculosis is treated using a combination of four medicines taken daily (typically in a fixed dose combination) for six months. Drug-resistant TB is treated using a combination of three to seven medicines taken daily for between six and 20 months. In addition to its high pill burden and long duration, drug-resistant TB often has difficult side effects and poor treatment outcomes—although expanded uptake and use of new drugs and regimens can reduce side effects and improve outcomes.[41]
Global footprint	COVID-19 has rapidly spread around the globe, and almost all countries have reported cases. High-income countries have accounted for the majority of COVID-19 cases to date, although cases in low- and middle-income countries are rising.[42] (Note: While shortages of COVID-19 test materials are impeding diagnosis globally, this challenge is more acute in low- and middle-income countries.)	Thirty countries with high TB burden account for almost 90% of global TB cases, of which eight countries (India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa) account for two-thirds of cases.[43] While TB predominately occurs in low- and middle-income countries, no country is invulnerable to TB. In the United States, 13 million people are living with asymptomatic, latent TB infection. Anywhere between 650,000 and 1.3 million of these individuals will develop active TB disease in their lifetimes.[44]
Vulnerable populations	While our understanding of populations vulnerable to COVID-19 is rapidly developing, the disease's impact and trajectory to date have yielded important lessons. Older individuals and individuals with certain underlying medical conditions, such as type 2 diabetes, are more likely to develop severe COVID-19 illness following infection. Early data from the United States and United Kingdom demonstrate that racial and ethnic minority groups in these countries are disproportionately affected by COVID-19 and face higher risks of severe illness and death than the general population.[45, 46]	Individuals with weakened immune systems (including HIV-positive individuals) and young children are more vulnerable to TB disease and death than the general population.[47] In the United States racial and ethnic minority groups face disproportionately high risks of TB disease.[48] Globally, key populations that are more vulnerable to TB disease and require dedicated interventions and services include migrants and mobile populations, prisoners and detainees, miners, people who use drugs, and people living with HIV.[49]

Table 4. Potentially game-changing TB research that must be bolstered against COVID-19 challenges and disruptions

Research area	Overview
Vaccines	Despite TB's long and deadly history, there is only one vaccine currently licensed for the disease: BCG. The BCG vaccine, which was introduced in 1921, is given to infants and offers protection against TB during infancy and childhood. Research is underway to determine whether revaccination of adolescents and young adults can extend BCG's protective effect. Additionally, after decades of scientific neglect, several novel TB vaccine candidates are at various stages of development. To give one promising example, a vaccine candidate called M72/AS01E is preparing for phase III trials after demonstrating 50% efficacy in preventing TB disease among TB-infected adults in a phase II trial.[50] ➢ *Sustained and expanded financing and support for ongoing and prospective TB vaccine research may lead to the introduction of the first new vaccine against TB in over a century. New vaccines are urgently needed to offer life-long protection against TB infection and disease.*
Drugs and treatment regimens	After more than 40 years of scientific stagnation and inattention, four new TB medicines have been introduced since 2012, and several novel compounds are in early stages of development. However, further research is needed to bring forward new medicines and optimize TB treatment combinations to reduce the duration of TB treatment and improve its efficacy, safety, and tolerability. Treatment of drug-susceptible TB currently involves a six-month course of combination treatment introduced during the 1960s. Treatment regimens for drug-resistant TB can range from six to 20 months, with high pill burdens and difficult side effects.[51] ➢ *Sustained and expanded financing and support for TB research will provide critical data necessary to inform the introduction of shorter, safer, and more tolerable TB treatment regimens and may lead to the introduction of new TB medicines. New medicines developed for TB may also have utility in treating other illnesses, including other antimicrobial-resistant infections.*
Diagnostics	The development and introduction of rapid molecular TB diagnostics in the past decade significantly improved TB diagnosis and detection of drug resistance. However, these and other available TB diagnostic tools have critical shortcomings that continue to impede TB diagnosis. Of the estimated 10 million individuals who develop TB disease every year, 3 million are never diagnosed. Improved diagnostics tools and interventions are urgently needed to identify these 'missing' individuals and link them to appropriate treatment. Most currently available TB diagnostics require sputum samples for testing. However, sputum samples are difficult to collect—particularly from people living with HIV and young children who have difficulty producing sputum—and are not effective for diagnosing extrapulmonary TB. In addition to requiring sputum samples for processing, most currently available TB diagnostics are not suitable for community- or clinic-level use, require hours to weeks for processing, and/or have cost barriers. Several promising research efforts could deliver game-changing new diagnostic tools for TB. Research is underway to: • develop and optimize tools that can diagnose TB using urine and stool samples; • enable TB diagnosis closer to the point of care and reduce costs; • develop comprehensive rapid drug susceptibility tests necessary to inform the treatment of people with drug-resistant TB; and, • identify new TB biomarkers that can inform novel diagnostic approaches.[52] ➢ *Sustained and expanded investment into TB diagnostic development and basic science can lead to a new generation of diagnostic tools that are rapid, accurate, affordable, point-of-care, and rely on easily collectable samples.*

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