

A Quest for Disruptive Innovations to Address Tuberculosis and Other Respiratory Infections in India

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By



In partnership with



TATA TRUSTS



The Global Fund
To Fight AIDS, Tuberculosis and Malaria

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Stop TB Partnership



The Union

International Union Against
Tuberculosis and Lung Disease
Health solutions for the poor

About India Health Fund

India Health Fund (IHF), incorporated as Confluence for Health Action and Transformation Foundation (under Section 8 of the Companies Act, 2013), is seeded by Tata Trusts in association with The Global Fund to Fight AIDS, Tuberculosis and Malaria, to leverage the power of collective impact to catalyze India's fight to end **tuberculosis** by 2025 and **malaria** by 2030. India Health Fund aims to strengthen the health ecosystem by bridging the gap between lab to last mile population.

Mission

India Health Fund envisages itself as an aggregator of resources from the private and public sector, global philanthropic foundations and aid agencies to ensure efficient allocations towards the scaling up of innovative solutions that can catalyze India's mission to eliminate tuberculosis by 2025 and malaria by 2030.

The Journey So Far

IHF has been conducting structured calls for innovations based on specific problem areas and has a growing portfolio on tuberculosis and malaria. IHF is also expanding its scope to include other infectious diseases, such as other vector borne diseases, and responses to public health emergencies like the current COVID-19 pandemic.

Currently, IHF has partnerships with the government, innovators from the private sector, technical institutions, researchers, not-for-profit entities, and philanthropic organizations.

I. Background and Mandate of the Quest

The current global health crisis is an important reminder that the world must continuously focus on emerging and existing infectious diseases to truly ensure health for all. One such infectious disease that has affected humans for centuries and continues to claim hundreds of lives even today is tuberculosis (TB). The COVID-19 pandemic is a reminder that besides managing the challenges posed by known infectious agents, it is crucial to track and control novel and emergent diseases. To stay ahead of the curve and address unmet and emerging healthcare needs, identification of ground-breaking innovations becomes imperative.

Globally, TB is the leading cause of death from a single infectious agent. In 2018, 10 million TB cases were estimated globally, and 1.5 million fatalities were attributed to TB. With an estimated 2.69 million cases of TB and 4,40,000 deaths during 2018, India accounts for the largest TB burden worldwide¹. During the same year, 2.15 million cases were notified to the National TB Elimination Program (NTEP), formerly RNTCP². Co-morbidities with TB are well reported, and in context to the current global health crisis, early evidence in limited settings suggests that latent or active TB may, in fact, be a factor that increases susceptibility to COVID-19^{3,4}.

The National Strategic Plan 2017-2025 (NSP) aims to achieve TB elimination by 2025. NSP's targets include reduction of TB incidence and mortality by 80% and 90%, respectively, and no TB-related catastrophic expenditure to any patient. However, India's current decline rate of TB is slow. To achieve the requisite decline rate of 10-15% annually, it will be critical to identify, support, and deploy novel approaches and innovations that potentiate a non-linear impact in the cascade of TB care.

To compliment national efforts, IHF has been supporting innovations that aim to challenge the status quo across TB care by fostering transformative change through aggregation of resources and promotion of disruptive innovations. IHF's Quest 2020 is a nationwide search for innovators in alignment with this objective. Given the current public health exigencies of the COVID-19 pandemic, it is essential that the scope of innovations be expanded and applied to include other respiratory infections. We, therefore, hope to utilize this Quest as a critical opportunity to seek solutions for TB that have cross-cutting potential and are applicable for responding to COVID-19 and other respiratory infections.

¹ *Global TB Report, 2019*

² *RNTCP, Annual Report, 2019*

³ *Liu et al. 2020*

⁴ <https://www.who.int/tb/areas-of-work/treatment/risk-factors/en/>

II. Quest for Innovations towards eliminating TB

The Quest is envisioned as a means to fast-track adoption and scale-up of innovative platforms or practices, which have received prior validation. These innovations will have strong potential to strengthen and transform key aspects of the TB care ecosystem in a non-linear and disruptive manner.

The Quest aims to catalyze solutions by:

1. Enabling funding support to innovative products or processes
2. Connecting resources for accelerated on-ground adoption, and
3. Engaging stakeholders for sustainability of these efforts

The following activities may be considered for support to facilitate their scale-up in states at block, district and state level.

Product Innovation

- ✓ Beta prototyping
- ✓ Feasibility studies for integration into the healthcare system
- ✓ Clinical validation

(*additional conditions may apply for this type of investigation/intervention)

Process Innovation

- ✓ Process validation
- ✓ Feasibility studies for integration into the healthcare system

Readiness levels of Proposals can be ascertained from the stages given below:

1. Technology Readiness Level (TRL)
 - a. **TRL 9:** Technology has been applied in its final form and is operational
 - b. **TRL 8:** Technology is proven and developed but not yet operational or applied anywhere
 - c. **TRL 7:** Actual system prototype is near completion or ready and has been demonstrated in an operational environment or is at pilot level
 - d. **TRL 6:** Prototype is being tested in simulated operational environment or in a high-fidelity laboratory environment

- e. **TRL 5:** Technology has been put together and can be tested in a simulated environment
- f. **TRL 4:** Basic technological components have been integrated to establish that they work together
- g. **TRL 3:** Proof of Concept stage / Active R&D has been initiated. This includes analytical studies and laboratory studies to physically validate the analytical predictions of separate elements of the technology
- h. **TRL 2:** Technology concept / application formulated
- i. **TRL 1:** There are paper studies to support the technology's basic properties.

(Note: IHF would ideally consider TRL 6 and above)

2. Process Readiness Level (PRL)

- a. **PRL 6:** PI (Process Innovation) has been applied in its final form and is operational on limited scale in real life setting (non-project). It is ready to be tested on a large scale at a sub-district level or district level or larger
- b. **PRL 5:** PI has been proven and deployed in experimental setting (in a few project villages or in a healthcare facility setting) but not applied outside the special project setting
- c. **PRL 4:** PI has been initiated in experimental setting (in a few project villages or in a healthcare facility setting) but not applied outside the special project setting
- d. **PRL 3:** PI is developed and being tested in formative studies in the community or healthcare facility and it works but not yet ready for field trial or deployment
- e. **PRL 2:** PI package has been put together but needs to be tested in small scale in limited environment – few villages or ward of a city
- f. **PRL 1:** PI components have been identified based on theory or practical experience or literature. And the package seems workable and synergistic. But not yet tested anywhere

(Note: IHF would ideally consider PRL 4 and above)

III. Purpose

The purpose of this Quest is to identify and support innovative products and processes that have demonstrated potential in making a significant difference in the areas mentioned below pertaining to TB elimination and other respiratory infections.

The innovations can address any of the following:

1. **Prevention:** *Fast tracking infection control measures to curtail the transmission of tuberculosis and other respiratory infections*
2. **Detection:** *Screening and diagnosis of Paediatric TB, Extrapulmonary TB, Pulmonary TB, and Latent TB infection*
3. **Treatment:** *Predicting and preventing adverse drug reactions in patients undergoing treatment for TB*

Funding will be provided to support high-potential innovations that can be leveraged by mainstream operations that ensure scale-up in the public (district/state/national level) and private sector. Awards will be announced after review by an expert panel, followed by extensive technical/operational/financial due diligence.

Program Offerings

1. Milestone-based funding support
2. Collective engagement with public/private stakeholders and providing access to the healthcare ecosystem working towards TB elimination
3. Providing opportunities to present innovations to National Tuberculosis Elimination Program (NTEP), state government, and private sector entities to enable seamless integration
4. Need-based mentoring by a panel of experts for guidance on study design and methodology, deployment, understanding regulatory landscape, patent law, market analyses, and current policies.
5. Potential opportunity to explore support through IHF's network in raising subsequent rounds of funding.

IV. Problem Statements

Problem Statement #1

Prevention: Fast tracking infection control measures to curtail the transmission of tuberculosis and other respiratory infections

Patients with TB of the lungs may release several tiny particles (1-5 micrometer) called droplet nuclei into the air when coughing or sneezing. Anyone who is exposed to this air is at risk of contracting TB. Undiagnosed patients with active pulmonary TB contribute to the transmission of the infecting bacteria before they begin anti-TB treatment. Till they are detected and put on treatment, they may visit multiple public and private spaces since the onset of active TB, causing the infection to spread. Droplet nuclei can remain airborne in air in a room for a long period of time, unless removed by interventional procedures or natural/mechanical ventilation⁵. The most infectious cases are those with sputum smear-positive disease. The closer the contact is to the infected individual, the higher the exposure and greater the risk of contracting TB⁶. The mode of transmission is similar in other respiratory illnesses that are transmitted by droplet infection, including SARS and COVID-19. Infection control solutions focused on TB may have cross-applicability and prevent transmission of these or other respiratory infections.

Systematic infection control in healthcare settings include:

Administrative controls: At a facility level, administrative controls play a major role in reducing the risk of TB transmission and are essential for the implementation of other controls (i.e. environmental controls and personal protective equipment). These controls include, but are not limited to, patient segregation and fast-tracking the investigations of patients visiting the clinics.

Environmental controls: Ventilation and interventional procedures should be prioritized to reduce the number of infectious particles in the air.

Personal protective equipment (PPE): PPE (e.g. particulate respirators certified as N95 or FFP2) should be mandatorily available as required in high-risk situations, especially drug-resistant tuberculosis, and during high-risk aerosol-generating procedures such as bronchoscopy or sputum induction. PPE is also vital in community settings outside the healthcare facilities.

⁵ <https://apps.who.int/iris/bitstream/handle/10665/311259/9789241550512-eng.pdf?ua=1>

⁶ *Guidelines on Airborne Infection Control in Healthcare and Other Settings. Directorate General of Health Services (2010)*

Scope for Innovation

Innovations to prevent droplet infection transmission could be at different levels:

1. **Prediction:** Identifying infection sites is crucial for breaking chains of transmission in tuberculosis-endemic areas and where respiratory infections are prevalent. Broad-based health systems innovations that are transformative in nature are essential for reducing infection transmission for hotspot mapping:
 - a. Concepts of spatial scan statistics, tracking travel, activity space (a place where patients spend most of their waking hours), residential statuses and environmental features have been used to detect hotspots⁷
 - b. Drug sale/consumption pattern monitoring across private & public facilities
 - c. Use of open access databases, public/social media etc. for data mining & analysis⁸
 - d. Other non-pharmaceutical modelling methods⁹
2. **Prevention:** Creating conditions that help reduce the bacterial and viral load in the environment in congregate settings, healthcare facilities, means of transport and households would be useful. These include both bacteriostatic and bactericidal technologies which significantly reduce infection risks. Following similar approaches for respiratory diseases caused by viruses will be critical. These should be able to operate in most climatic conditions across different patient-care settings, easy to maintain, and cost-effective.
 - a. Safe, replicable, and affordable designs of air filtration units for sterilizing and ventilating homes, congregate settings like slum rehabilitation authority buildings, slum areas, densely populated areas, and areas with high footfall.
 - b. Affordable and acceptable PPE, such as nasal filters, respirators and masks that can be used by close contacts or healthcare workers in close and continuous proximity to infected patients.
 - c. Use of affordable PPE by patients with pulmonary TB can prevent spread of infection. This equipment should be non-stigmatizing and comfortable for the patient to wear outside of the healthcare facility over long durations.
 - d. Hand hygiene is critical in spread of infectious illnesses. Although a direct relation to spread of TB has not been established, this maybe important to curtail other bacterial and viral infections that weaken the person's immune system or causes acute or chronic lung diseases, thereby making them

⁷ Tiwari et. Al., Investigation of Geo-Spatial Hotspots for the Occurrence of Tuberculosis in Almora District, India, Using GIS and Spatial Scan Statistic. *International Journal of Health Geographics* (2006)

⁸ Generous et. Al., Global Disease Monitoring and Forecasting with Wikipedia. *PLOS Comp Bio* (2014)

⁹ Peak et. Al., Comparing nonpharmaceutical interventions for containing emerging epidemics. *PNAS* (2017)

susceptible to the onset of active TB and other respiratory infections, especially in those who might already be latently infected or are in close contact with an infected patient.

- e. Respiratory diseases due to droplet infections spread from infected surfaces as the bacteria or viruses may remain viable outside the patient's body for a substantial period of time. Disinfecting these surfaces is crucial to prevent further spread.

Problem Statement #2

Detection: Screening and diagnosis of Paediatric TB, Extrapulmonary TB, Pulmonary TB, and Latent TB

Rapid and accurate diagnosis is critical for timely initiation of anti-tubercular treatment (ATT) and is an essential component of TB control. TB remains undetected in several individuals for a long period of time; late detection leads to increased transmission, poor health outcomes, distress to the patients, and economic hardship. Early diagnosis can accelerate the progress in controlling TB and alleviate the consequences associated with this deadly disease¹⁰. Several unmet needs exist with regard to TB diagnosis, including the necessity for accuracy, rapidity, affordability, simplicity and a point - of - care (POC) format¹¹. Globally, there exists a large gap between the number of reported TB cases (7.0 million) and the estimated 10.0 million cases in 2018. In 2018, 2.69 million cases of TB were estimated to occur in India¹². A total of 2.15 million cases were notified to the NTEP (formerly RNTCP)¹³. Gaps between the number of estimated and reported TB cases could be partly attributed to underdiagnosis, i.e. individuals with TB do not access health care or are not diagnosed when they do¹⁴. Novel products and processes that address the challenges associated with diagnosing TB could reduce morbidity and mortality as a result of early detection and treatment.

Innovations targeted towards development of platform solutions or multi-disease diagnostic platforms that enable detection of TB and other respiratory infections including COVID-19 would be desirable. Adaptation and applicability to more than one airborne and respiratory infections are current needs. Routine recording and reporting pertaining to respiratory diseases of infectious origin, particularly tuberculosis, would be beneficial and help prevent discrepancies among the number of estimated and reported cases. Here, we focus on four domains within TB that could benefit from innovations catered towards diagnosis and screening.

1. Paediatric TB

Paediatric TB (TB among the population aged less than 15 years of age) is a major cause of childhood morbidity and mortality globally. In 2018, of the 10 million annual TB cases occurring globally, about 11% occur in children (aged <15 years). Out of the total TB incidence in India, it was estimated that 0.2 million of the cases occurred in the 0-14 years age group. In 2017, 0.1 million childhood TB cases were notified in India, and 250,000 children died of TB (including children with HIV-associated TB)^{15,16,17}. The most common age of children presenting with TB is between 1-4 years¹⁸. The diagnosis of paediatric TB is

¹⁰ <https://www.who.int/tb/areas-of-work/laboratory/en/>

¹¹ Dheda et al. 2012

¹² Global TB Report, 2019

¹³ RNTCP, Annual Report, 2019

¹⁴ Global TB report 2019

¹⁵ India TB Report 2019, RNTCP, India

¹⁶ Diagnosing Childhood Tuberculosis in India, FIND, 2018

¹⁷ Global TB Report, 2019

¹⁸ National Guidelines on Management of Tuberculosis in Children, 2013, Division of Leprosy, Tuberculosis, and Lung Disease

challenging due to the absence of appropriate sample collection methods and detection protocols. It is considerably more difficult to diagnose paediatric TB in resource constrained settings with poor laboratory and X-ray services. EPTB is common in children and diagnosing extrapulmonary TB is more challenging than pulmonary TB^{19,20}.

Scope for innovation

1. Identifying children with sub-clinical disease who are thought to be at higher risk of developing clinically apparent disease: an intuitive algorithm or process to identify these children would be useful.
2. Algorithms based on image analyses to identify active TB in paediatric patients is imperative.
3. Novel assays that are rapid, utilize easy to obtain samples, do not rely on sputum sampling, are minimally invasive and point-of-care would be useful.
4. A test that can distinguish TB from other respiratory diseases that are common in childhood
5. Evaluation of symptom-based screening tools of child TB contacts (HIV-positive and -negative)
6. Models for predictive analysis and efficient screening can enable prompt treatment decision in children with presumptive TB

2. Extrapulmonary tuberculosis (EPTB)

Bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs is defined as EPTB²¹. Pulmonary TB (PTB) is the most common presentation of TB, however, EPTB is also a critical clinical problem²². TB of the lymph nodes and of the pleura are the most common manifestations of EPTB²³. Diagnosis of patients with EPTB is particularly challenging, and data paucity exists²⁴. Worldwide, EPTB represented 15% of the 7.0 million incident cases that were notified in 2018²⁵. EPTB accounts for more than 50% of TB cases in HIV-positive individuals²⁶. Current data from reliable sources regarding the precise prevalence of EPTB among the Indian population is lacking. In 2014, 16.5% of cases in India were new EPTB cases²⁷. Additionally, EPTB is common in children²⁸. Absence of a gold standard diagnostic test, varied clinical manifestations, need for invasive procedures to secure appropriate samples, paucibacillary nature of the disease, lack of laboratory facilities in resource-limited settings are factors that contribute to difficulty to diagnosis²⁹. Biomarkers may be used to diagnose EPTB, but since analyses are at preliminary stages, validation would be necessary.

¹⁹ Ilker Devrim, 2014.

²⁰ TB in Children, TB FACTS.ORG

²¹ Mbuh et al. 2019

²² Sabu et al. 2019

²³ Sharma S.K. and Mohan, 2004

²⁴ Mbuh et al. 2019

²⁵ Global TB report 2019

²⁶ Index TB guidelines-Guidelines on extra-pulmonary tuberculosis for India

²⁷ Tuberculosis control in the South-East Asia Region: Annual Report 2016

²⁸ TB CAB Extrapulmonary TB; <http://www.tbonline.info/posts/2016/3/31/extrapulmonary-tb/>

²⁹ Purohit and Mustafa 2015

Scope for innovation³⁰

A more accurate test to diagnose various forms of EPTB that can easily be incorporated in the routine TB control program and decentralized specimen collection mechanisms would contribute significantly towards improving EPTB case-detection³¹.

1. Non-invasive and cost-effective tests that have a rapid turnaround time would be beneficial. Diagnostic assays employing easy to obtain samples that can be safely transported would be preferred.
2. A diagnostic testing algorithm to enable easier detection of EPTB
3. Algorithms based on organ-specific imaging can be used for screening and assessment of the affected site
4. Developing interventions to improve diagnosis in children with presumptive EPTB would be useful.
5. Identifying and validating biomarkers in the diagnosis of EPTB, including organ-specific biomarkers, would be critical.

3. Pulmonary TB (PTB)

According to the Global TB report 2019, 2.69 million cases of TB and 4,40,000 deaths (HIV-negative TB mortality) were estimated to occur in India during 2018³². A total of 2.15 million cases were notified to the Revised National Tuberculosis Control Program³³. TB primarily affects the lungs (PTB) but can also affect other sites³⁴. Absence of reliable and sensitive POC diagnostics for TB leads to false negatives and delay in detection. Transfer and storage of sputum samples is challenging since there is a likelihood of contamination and uninterrupted refrigeration is required to maintain sample integrity. Furthermore, there exists a lack of uniformity regarding the protocols being followed to diagnose TB within the private sector. Lastly, in the current scenario, multi-drug resistant TB case identification can take weeks.

Scope for innovation

1. Rapid and portable options for community screening would be useful.
2. Sample collection, storage and transport: Diagnostic assays that utilize simple and safe sample collection procedures, have a lower requirement for sample volume, and are reliant on samples that are safe to store and transport, would be beneficial
3. Prior to initiation of ATT, an accurate and prompt diagnosis needs to be ensured, preferably at POC using field-friendly tools. *Optimal characteristics for a future POC test:*

³⁰ Index TB guidelines-Guidelines on extra-pulmonary tuberculosis for India

³¹ Purohit and Mustafa 2015

³² Global TB Report, 2019

³³ RNTCP, Annual Report, 2019

³⁴ Global TB Report, 2019

higher sensitivity and specificity than existing systems; user friendly (can be used by any healthcare worker, requires minimal training); rapid turnaround time; robust (shelf - life >24 months, stable in high temperature and humidity, battery powered, easy and environmentally friendly waste disposal, minimal maintenance); affordable; accessible; safe for healthcare workers (no cross-contamination or requires minimal biosafety facilities); ability to process various types of biological samples; easy to read; should be capable to screen for drug resistance³⁵

4. Latent TB infection (LTBI)

About one-third of the global population is estimated to be infected with *Mycobacterium tuberculosis* (*M. tb*). Approximately 5-10% of the infected individuals will develop active TB disease during their lifetime³⁶. Nearly 40% of the Indian population is infected with TB³⁷. Among the 30% exposed population that becomes infected, approximately 95% individuals contain the infection that causes the disease to become latent. However, some of the *M. tb* bacilli continue to remain viable, possess the capability to reactivate, and cause active TB disease. LTBI is defined as a state of persistent immune response to *M. tb* without evidence of clinically manifested active TB³⁸. There exists no gold standard test for diagnosing LTBI³⁹.

Scope for innovation

1. Active case finding (ACF) aims to identify cases of active TB amongst high-risk groups. Similarly, intensive case finding can be used to identify people with LTBI; HIV-positive individuals and household contacts of TB patients are two high priority groups for intervention.
2. Designing improved LTBI screening algorithms for the inclusion of high-risk groups
3. Mechanisms that enable identification of individuals with LTBI who are most likely to progress to active TB disease. Predictive biomarkers such as LAM would be useful⁴⁰.
4. Diagnostic assays that enable stage identification within the spectrum of *M.tb* infection would be beneficial.
5. Developing efficient multi-disease diagnostic tests/platforms (LTBI, HIV, diabetes, malaria) with higher accuracy, sensitivity, specificity and cost-effectiveness in TB endemic areas will be beneficial. Developing POC assays for LTBI detection will be crucial (biosensing technologies in conjunction with nanotechnology, Lab-on-Chip technology etc.)⁴¹.

³⁵ Dheda et al. 2012

³⁶ Global TB Report, 2019

³⁷ RNTCP, Annual Report, 2019

³⁸ Sharma, 2019

³⁹ Madhukar Pai, 2015

⁴⁰ Margarida Correia-Neves, 2019

⁴¹ Shagun Gupta, 2018

6. Developing assays that are simple, rapid, and utilize less volume of blood to identify latent TB, particularly among paediatric patients, are required.
7. Digital tools for assessing adherence to TB preventive therapy and long-term follow up to detect onset of active disease may be explored.

Advances in digital technologies and data science offer a considerable scope for innovation across the screening and diagnostic landscape of TB and other respiratory infections.

The following may enable better patient care:

1. Handheld or handsfree fever/symptom detectors or other non-invasive detection mechanisms for simultaneous use in large population settings.
 2. Scanners using artificial intelligence, big data and/or facial recognition tools to assess a person's health status in congregate settings or in areas (e.g., workspaces, construction sites, mines etc.) with high migratory population or high footfall (e.g.; bus terminals, railway stations and markets)
 3. Easy to use patch sensors or dipstick tests to assess indirect indicators of active tuberculosis or other respiratory disease in patients using low volume non-invasive samples, including sweat, saliva, sputum or urine, to assess physiological parameters, bio-chemical parameters or secretory biomolecules.
 4. Latest developments in wireless communication and IoT devices offer multiple opportunities for utilizing wearable technologies in health care settings for patient monitoring and reporting.
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Problem Statement#3

Treatment: Predicting and preventing adverse drug reactions in patients undergoing treatment for TB

According to WHO, adverse drug reaction (ADR) is a response to a drug which is noxious and unintended, and that occurs at doses normally used in human for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. Most of the ADRs associated with anti-TB drugs are minor and can be managed without discontinuation of treatment, however, some can be serious and life-threatening leading to hospitalization, significant disability, congenital anomaly or even mortality if timely intervention is not provided⁴².

Pharmacological, physiological and co-morbid status can affect the manifestation of ADRs. The prevalence of ADRs observed in various studies conducted worldwide ranged from 8% -85%, these vast variations are due to non-uniform standards of reporting an adverse event. There was also difference in whether all ADRs were reported or only the most severe ones. The overall prevalence of ADRs with first-line anti-tuberculosis drugs (FLDs) is estimated to vary from 2.3%-17% in various Indian studies.

Ototoxicity has been reported in 12%-70%, tinnitus in 5%-45% patients, and deafness in 6.7%-33% patients. Ototoxicity is predominantly associated with kanamycin although there is possibility of additive effects due to other potentially ototoxic drugs, such as ofloxacin and cycloserine, used in the regimen. Gastrointestinal disturbances, hepatotoxicity, peripheral neuropathy, psychiatric disorders, optic neuritis, nephrotoxicity, cardiotoxicity, immunological and haematological disorders, musculoskeletal effects (arthralgias and myalgias), dermatological reactions, and severe drug reactions are other ADRs. These drug-related toxicities tend to challenge the benefits of treatment when administered over prolonged durations. Several studies have highlighted these ADRs to be major reasons of treatment interruption in 19%-60% of multi-drug resistant TB patients, and in people on prophylactic treatment, especially children.

Scope for innovation:

1. Host factors like genetic make-up, physiological condition (malnutrition etc.), pathological state (co-morbidities like HIV infection, diabetes etc.), psychological state (stress etc.) and behaviour (alcohol, abuse, smoking etc.) maybe associated with ADRs and have been studied extensively⁴³. At a large scale, these factors can be analysed simultaneously to enable predictive scoring & development of intuitive algorithms that enable segregation of patients who are likely to develop ADRs at initiation of treatment.
2. Recently, the role of pharmacogenomics in the context of disease management and ADRs has been explored in relation to many diseases.

⁴² Prasad et. Al., Adverse drug reactions in tuberculosis and management. *IJT* (2019)

⁴³ Sahu et. Al., Adverse Drug Reaction to anti-tuberculosis drugs: Pharmacogenomics Perspective for Identification of Host Genetic Markers. *CDM* (2015)

Profiling these markers at the clinic may reveal the genomic signature of the individual, and a personalized drug dosing approach may be formulated for efficient treatment

3. Data on factors that directly or indirectly cause ADRs (pharmacological, immunological, physiological, ethnic, age, gender, social factors etc.) can effectively be analysed for descriptive and predictive purposes by advanced methods of statistics, machine learning, and data mining. This information, along with ongoing efforts to assure patient adherence, can be more focused and individualized with intuitive algorithms⁴⁴
4. Innovations ensuring data access pertaining to prevalence of TB-related ADRs would be beneficial. Mechanisms that enable healthcare workers to efficiently track TB-related ADRs would facilitate treatment adherence.
5. Drug pressure on infecting microbe (bacteria or virus) causes decline of the drug-sensitive variants but is ineffective against the drug-resistant variant, if present, that often remains undetected. This is one reason for disease resurgence. If the drug-resistance pattern is detected early and treated appropriately, the patient will benefit from a more focused treatment regimen

⁴⁴ Ho et. Al., *Data-driven Approach to Detect and Predict Adverse Drug Reactions. Current Pharmaceutical design* (2016)

V. Outcome indicators and potential impact

Keeping relevant performance measures (i.e. indicators) in mind would be important to ensure that the proposed project meets its desired objectives and is successful. The table below mentions outcome indicators and potential impact that would be useful for monitoring and evaluation of the proposed innovation. However, assessments need not be necessarily limited to outcome indicators mentioned here, and applicants are encouraged to propose additional indicators that pertain to their thematic focus.

Focus (Problem statements)	Outcome Indicator (Intermediary or end of the project)	Impact (Long-term)
I. Prevention: Infection control		
	<ul style="list-style-type: none"> ➤ Reduced transmission of TB and other respiratory infections among healthcare workers, patients, and their contacts <p style="text-align: center;">Well proven and validated novel solution ready for adoption by public or private health care systems</p>	<ul style="list-style-type: none"> ➤ Reduced morbidity among healthcare workers, in patients, and their contacts <p style="text-align: center;">Reduced mortality among healthcare workforce, in patients, and their contacts</p>
II. Detection: Screening and diagnosis		

<p>A. Identifying innovative diagnostic techniques in the domain of paediatric tuberculosis</p>	<ul style="list-style-type: none"> ➤ Well proven and validated novel diagnostic solution ready for entry into the public or private healthcare system ➤ Increase in percentage of new and relapse paediatric TB patients identified using the novel diagnostic assay ➤ Increase in paediatric TB case notification 	<ul style="list-style-type: none"> ➤ Increased availability of tests for the paediatric population ➤ Increase in paediatric TB patients initiated on ATT ➤ Reduced morbidity ➤ Reduced mortality
<p>B. Identifying innovative diagnostic techniques in the domain of extra-pulmonary tuberculosis (EPTB)</p>	<ul style="list-style-type: none"> ➤ A well proven and validated novel diagnostic solution ready for entry into the public or private healthcare system ➤ Increase in percentage of new and relapse EPTB patients identified using the novel diagnostic assay ➤ Increase in EPTB case and notification 	<ul style="list-style-type: none"> ➤ Increased access to testing ➤ EPTB patients initiated on ATT ➤ Increased access to ATT ➤ Reduced morbidity

<p>C. Identifying innovative diagnostic techniques in the domain of pulmonary tuberculosis (PTB)</p>	<ul style="list-style-type: none"> ➤ A well proven and validated novel diagnostic solution ready for entry into the public or private health care system ➤ Increase in percentage of new and relapse PTB patients identified using the novel diagnostic assay ➤ Increase in PTB case notification 	<ul style="list-style-type: none"> ➤ Increased access to testing ➤ PTB patients initiated on ATT ➤ Reduced morbidity ➤ Reduced mortality
<p>D. Detecting latent tuberculosis cases among immunosuppressed</p>	<ul style="list-style-type: none"> ➤ A validated novel diagnostic solution ready for regulatory approval and entry into market and health care system ➤ Percentage of latent TB cases identified 	<ul style="list-style-type: none"> ➤ Increased availability of latent TB testing ➤ Increased number of latent TB positive individuals eligible for prophylaxis ➤
<p>III. Treatment: Adverse Drug Reaction</p>		

	<ul style="list-style-type: none"> ➤ Identifying the proportion of patients completing treatment among those who started drug-sensitive and drug-resistant TB treatment ➤ Identifying the proportion of patients who were lost to follow-up among those who initiated drug-sensitive TB and drug-resistant TB treatment 	<ul style="list-style-type: none"> ➤ Increase in number of patients who successfully completed ATT <p>Increase in number of patients cured as evident by microbiological tests</p>
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Note: Outcome and impact indicators must be developed suitably for any proposed innovation that is deemed adaptable to address COVID-19.

VI. Qualifications of an Applicant

Applicants can include:

1. Companies incorporated in India
2. Registered Indian non-profit or non-governmental organizations
3. Government aided private/semi-private/deemed institutions and universities
4. Autonomous or semi-autonomous institutions
5. Consortiums

VII. Selection Criteria

The Quest invites applications that propose an innovative product or process for addressing any of the problem statements.

Eligibility

1. Applications must be submitted by registered and incorporated entities in India.
2. The proposal is relevant and aligned to problems statements.

3. The innovation should have completed the proof-of-concept stage and pilot stage.
4. Validation data should be readily available for justifying support for next stage.
5. The innovation should be superior than the currently available solutions or approaches in terms of sensitivity, specificity, accuracy, safety, turnaround time, usability, unit pricing, etc.
6. An innovation that is cross-applicable to various respiratory infections
7. The innovation should have potential for scale-up across diverse settings.
8. Transparency in furnishing relevant data in support of the proposed innovation should be agreeable by the applicant.

Co-funding could be considered for supplementing parts of a proposal. However, the applicant should make sure to disclose in case the proposal has been submitted, is under review, or being funded, in part or full, by another donor agency.

The following fall outside the scope of the Quest and will not be supported by IHF:

1. Basic science research
2. Epidemiological studies/surveys/disease burden analysis.
3. Proposals focused on service delivery
4. Innovations in the ideation / proof-of-concept stage/ formative studies
5. Incomplete or poorly articulated proposals
6. Applications which propose incremental solutions without a clear innovative element in their proposal
7. No alignment with National Goals of Government
8. No alignment with Sustainability Development Goals (SDGs) in health care

The Quest is a voluntary and discretionary measure in addressing the public health problem of Tuberculosis and other infectious respiratory diseases in India. Therefore, India Health Fund reserves the right to the following:

1. Disqualify proposals that do not fall within the thematic focus areas stated below.
2. Disqualify proposals that plagiarizes works by other innovators/ institutions/ organizations.
3. Select or reject proposals strictly based on eligibility criteria.

4. Modify and refine proposals before final selection.
5. Modify budgets based on rationale and justification.
6. Not provide or justify reasons or feedback on rejection of proposals.
7. Verify any information provided by application through different sources.
8. Nullify the Quest at any time owing to any reason.

VIII. Project Duration

Proposal should have a maximum time duration of up to 2 years (in case of product centric innovations) and this can be extended to a maximum of 3 years (in case of process centric innovations) with adequate rationale and supporting evidence on case to case basis.

IX. Tentative Project Budget

Promising proposals will be supported by the India Health Fund with grants or contracts of Rupees 50 Lakh or above across the entire duration of the project, contingent on milestones achieved at different stages.

X. Co-Funding for Proposals

IHF is a strong believer in co-funding to bring about bigger impact and multiplier effect in the TB ecosystem. The proportion of co-funding and support sought from IHF will be assessed and may vary on a case to case basis.

As an important part of the evaluation process, we request all applicants to keep IHF updated on any co-funding and partnership efforts with reference to the application. We value transparency in the funding process.

XI. Evaluation Criteria

The applications will be evaluated on the following parameters:

1. Provision of preliminary data; data pertaining to parameters, including accuracy, specificity, sensitivity, turnaround time, unit cost, and safety
2. Applicability to other respiratory infections
3. Relevance of the innovation proposed
4. Alignment to government policy goals
5. Receptive to the demands of the prevalent market

6. Existing technical and instrumental validation
7. Transformative value
8. Simplicity and feasibility to scale
9. Financial sustainability
10. Organizational strength
11. Partnership
12. Business sustainability plan

XII. Timeline and Process Flow for Applications

Call for Applications	7th April 2020
The Applicant will be required to submit an online application following registration on https://quest2020.innovatealpha.org/login Only the applications submitted online will be accepted for further evaluation. No e-mail or hard copy will be entertained.	
Application deadline	22nd April 2020
Screening, evaluation, due diligence	April – May 2020
Final Results	Date will be announced on the IHF website

XIII. Frequently Asked Questions

1. What does the Quest support?

The Quest for disruptive innovation on TB and other respiratory diseases in India supports innovative post proof of innovations which have reached TRL-6 or beyond for products; or PRL-4 or beyond for processes. Such innovations should be in any one or more domains addressed by the problem statements.

Products should have crossed proof of concept and reached TRL-5 or beyond (where TRL defines the Technology Readiness Level and TRL 5 describes that the Technology has been put together and can be tested in a simulated environment).

2. Can an applicant submit more than one application for different innovations?

Yes, the applicant can submit multiple applications within the domain framework as mentioned for Q1. Please note that each application is associated with one email address. Therefore, please use different email addresses if you are making more than one application.

3. What should be the grant size of the individual project proposal?

IHF does not suggest any grant size for any project submitted in the TB Quest. The financial ask should be realistic and in alignment with the proposed work. The decision to approve the grant request; the periodicity and the conditions of the disbursements lies wholly with IHF.

4. Can an applicant's proposal address more than one problem statement?

It is possible that the applicant's proposed innovation addresses aspects which are covered in more than one problem statement. In such case the applicant may mention in the application the specific aspects within the problem statements that the application addresses. However, while applying, **ONLY ONE** problem statement should be selected which, according to the applicant, most closely aligns to the proposal.

5. If the proposal fits more than one problem statement, should I make separate submissions of the same proposal?

No, you must submit the proposal only once while selecting the problem statement which most closely aligns to your proposed innovation. However, in the proposal, please mention the other problem statements that your innovation can potentially address.

6. What is the maximum file size of an upload in the online application?

The maximum file size of an upload in the online application is 30Mb.

7. How many projects will be selected for support per problem statement?

IHF does not want to limit the number of applications selected under individual problem statements. Final decision on proposals will be purely assessed on merit.

8. What is TRL 6?

TRL-6 refers to the level when your Prototype is being tested in simulated operational environment or in a high-fidelity laboratory environment.

For more information on the different TRLs, please see below:

- a. **TRL 9:** Technology has been applied in its final form and is operational.
- b. **TRL 8:** Technology is proven and developed but not yet operational or applied anywhere.
- c. **TRL 7:** Actual system prototype is near completion or ready and has been demonstrated in an operational environment or is at pilot level
- d. **TRL 6:** Prototype is being tested in simulated operational environment or in a high-fidelity laboratory environment.
- e. **TRL 5:** Technology has been put together and can be tested in a simulated environment.
- f. **TRL 4:** Basic technological components have been integrated to establish that they work together.
- g. **TRL 3:** Proof of Concept stage / Active R&D has been initiated. This includes analytical studies and laboratory studies to physically validate the analytical predictions of separate elements of the technology.
- h. **TRL 2:** Technology concept / application formulated
- i. **TRL 1:** There are paper studies to support the technology's basic properties.

9. What is PRL 4?

PRL-4 refers to a process innovation which has been initiated in experimental setting but has not been applied outside the special project setting.

- a. **PRL 6:** PI (process Innovation) has been applied in its final form and is

- operational on limited scale in real life setting (non-project). It is ready to be tested on a large scale at a sub-district level or district level or larger
- b. **PRL 5:** PI has been proven and deployed in experimental setting (in a few project villages or in a healthcare facility setting) but not applied outside the special project settings
 - c. **PRL 4:** PI has been initiated in experimental setting (in a few project villages or in a healthcare facility setting) but not applied outside the special project setting
 - d. **PRL 3:** PI is developed and being tested in formative studies in the community or healthcare facility and it works but not yet ready for field trial or deployment
 - e. **PRL 2:** PI package has been put together but needs to be tested in small scale in limited environment – few villages or ward of city
 - f. **PRL 1:** PI components have been identified based on theory or practical experience or literature. And the package seems workable and synergistic. But not yet tested anywhere.

10. Can consortiums apply for funding through the Quest?

Yes, consortiums can apply, however, it's important that the roles of the consortium participants are clearly pre-defined. At least one entity, which proposes to receive the grant money, must be registered/incorporated organization in India.

Avoid adding names and details of institutions with whom partnerships have not been formalized, please note that addition of reputed scientists/institutions who are not significant contributors to the proposed innovation will not add value to the application. The application will be based solely on the technical merit of the application.

11. Can an international agency be part of the consortium?

Yes, an international agency can be part of the consortium. However, they cannot be the recipient of funds, all fund disbursements will be done to entities registered in India only. Scientists from these agencies can certainly be scientific contributors to the projects.

12. Can an applicant apply simultaneously for multiple funding for the same project?

The applicant should declare at the time of application and then before receiving the grant if the same application has been submitted for support or is currently receiving support from any other donor. They should also justify why the applicant is seeking

multiple avenues of funding for the same project. Please note that gap funding for covering a shortfall of funds in an existing project will not be provided. Kindly do not apply with proposals of such nature.

13. For what purposes can the funding provided be utilized?

The Quest is meant for post proof-of-concept innovations (at or above TRL-6) that need to be scaled. Funding can, therefore, be utilized for clinical testing study and its outcomes, manpower, consumables, equipment, and project related travel. Additionally, funding can be utilized for publication of project findings. The funding should be solely restricted to work within the focus areas mentioned.

14. Can I edit my application if I want to make changes to my proposal after I've made the submission?

No, you cannot edit your proposal after you have made the submission.

15. What does due diligence entail?

The Due Diligence includes a holistic evaluation of the applicant organization and the proposal. It will cover aspects, including but not limited to, technical and operational feasibility and rationality, progress of clinical study, financial assessment and refinement of business model. It will also include reflecting on the long-term vision, goal and intermediary outcomes envisaged in the proposal, project implementation plan and competence of the applicant.

Due diligence may require multiple iterations between IHF and its expert panel, external independent auditors who may be hired to assist in the process and applicants. Awards will be announced purely on merit basis and after satisfying the rigorous due diligence process. Mere satisfactory completion of due diligence does not entitle an applicant for funding and support

16. Will an applicant be eligible to receive funding from India Health Fund upon selection?

Yes, an applicant will be eligible for funding upon final selection but the final decision on awarding funding will be taken after due diligence as described in Q 15.

17. Can an applicant find other funding partners for additional funding?

Yes, the selected applicants can find other funding partners. However, IHF must be informed about such efforts if it is for the same project.

18. Will the funding provided by IHF be in collaboration with other prevalent government initiatives?

The Quest will complement government initiatives and not duplicate/overlap with them. Further, India Health Fund is independent from ongoing government initiatives.

19. How many applicants are expected to be finalized?

The number of applicants finalized has not been pre-determined.

20. Who will undertake the evaluations?

The evaluations will be undertaken by a panel of experts in the field relevant to the project, and by the IHF team.

21. How can an applicant submit queries?

Please submit queries via email to contact@indiahealthfund.org

22. Why didn't a project idea get accepted?

If a proposal did not fit the problem statements or the applicant did not satisfactorily comply by the eligibility criteria set out by IHF, or for any other conflicting issues etc. then the application maybe rejected. We encourage applicants to apply in subsequent programs aligning proposals with the focus area stated.

23. Where can I get more clarity on the quest and what it entails?

India Health Fund encourages the use of the chatbot for obtaining answers to common queries. This chatbot is available on the application page of the quest. If you have additional queries, then you may send the questions on ***contact@indiahealthfund.org***.

India Health Fund will be organizing multiple webinars as well to further clarify queries that the potential applicant may have. The dates and time will be made available on IHF website as per the schedule mentioned in the timelines. If you have additional queries then you may send the questions on ***contact@indiahealthfund.org*** so that the facilitator may take it up during the course of the webinar. Additional options for live chat/posting queries during the webinar will be shared subsequently.

If you are unable to attend the webinars, you may reach out to us on ***contact@indiahealthfund.org***. Furthermore, post every webinar we will update the FAQs listed on the website.

24. Can an organization which is getting registered soon apply?

Applicant organizations will have to produce relevant supporting documents if they are shortlisted. A shortlisted application will only be processed when all documents that are asked for are submitted. Without these documents, applications will be rejected.

25. Is it possible to apply in languages other than English?

The Quest will be accepting applications only in English. However, if applicable, you can submit supporting documents in a vernacular language while giving us a translated copy in English of the same.

26. Information related to Intellectual Property and Information Access:

IHF works towards saving human lives as its highest priority and this will be the guiding philosophy for promoting solutions towards the achieving the goal. Therefore, IHF encourages applicants to share knowledge, processes and solutions that emerge from the project for benefit of society and accelerate the same in times of crisis.

IHF emphasizes that the project outcomes be published in an open access peer reviewed journal. It is urged that the successful applicant disseminates about development of the solutions and solutions with a wider audience and stakeholders. The ownership of intellectual property will be a discussed post selection between the recipient organization and IHF.

27. What are the characteristics of a good application?

Please note that the quality of the innovation is paramount. This includes demonstrating the following characteristic through the application:

- ✓ Technical quality of the innovation
- ✓ Quality of the scientific data presented in support of the innovation
- ✓ Cross-applicability to other respiratory infections
- ✓ Quality of domain knowledge and data on field applicability of the innovation
- ✓ Sound market/competitive analysis of existing tools and superiority over them
- ✓ Organizational capabilities and relevant sectoral partnerships
- ✓ Clearly written and well-articulated proposals, depicting a theory of change, connecting the problem to proposed strategies (innovations, output, outcome and impact)