

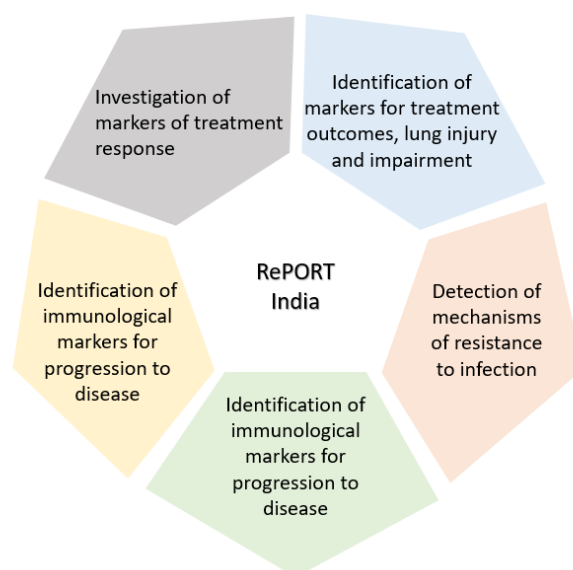
Regional Prospective Observational Research in Tuberculosis (RePORT) India

Tuberculosis (TB) is one of the top ten causes of death worldwide and is the leading cause from a single infectious agent, according to the World Health Organization (WHO). In India, TB is a major public health problem, with the nation harbouring the largest number of TB cases in the world; over a quarter of the global TB and multidrug-resistant TB (MDR-TB) patients are in India.

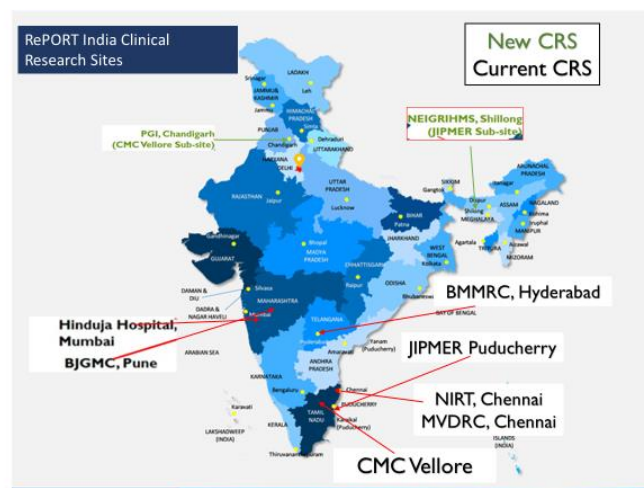
Taking cognizance of the same, the RePORT India Initiative was conceived to promote collaborative scientific efforts, within India and with US, to foster critically important TB research that will ultimately lead to enhanced interventions to tackle the TB challenge. The RePORT India initiative is being implemented by the Department of Biotechnology (DBT) under the auspices of the Indo-US Vaccine Action Programme (VAP).

Mandate: RePORT India is focused on establishing a TB consortium with PAN India representation involving long-term longitudinal cohorts of TB patients in India. Basic and applied research for development of newer diagnostics and identification of novel improved biomarkers for targeted therapy is being conducted under the RePORT India initiative. These efforts are hoped to strengthen TB research capacity and infrastructure, and foster research collaboration within India and with other countries.

Overall objectives: Confirming to the WHO framework for global TB control and in line with the Sustainable Development Goals of the United Nations (UN), RePORT India is focusing on the 3rd pillar of ‘**Intensified research and innovation**’. RePORT India supports various aspects of tuberculosis research as depicted below:



Current status: RePORT India was the first consortium to be established as part of the six current global RePORT International networks of TB consortia across the world. It is a multi-institutional clinical and translational research consortium in India, facilitating high quality human subjects' research on TB. At present, a network of nine Indian Institutions and five US Universities constitute the RePORT India Consortium with the co-ordination hub currently located at JIPMER, Puducherry.



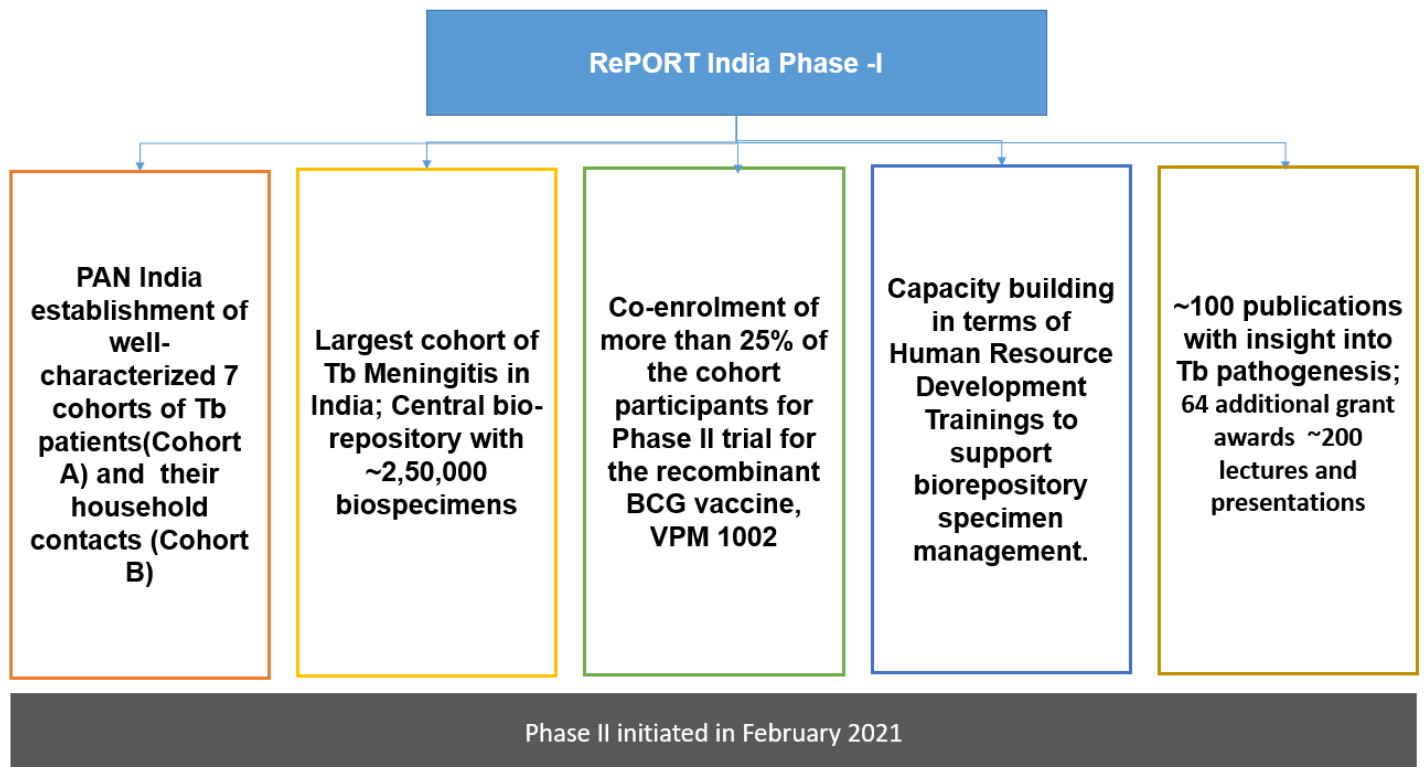
Phase I of RePORT India consortium was initiated in 2013, as part of which, initially, seven Indian institutions collaborated with five Universities from the US to establish cohorts of TB cases and their household contacts.

Initially, each site or Institution had its unique objective or 'Parent Protocol'. In 2017, the RePORT India Common Protocol was initiated with an aim to collect specimens and make them available for biomarker researchers and collaborators so as to gain better understanding of prognosis of TB disease and pathogenesis of progression from TB exposure to disease.

As part of Phase I, a central biorepository has been supported at NIRT, Chennai and central data management centre was set up at SAS-CHRD, New Delhi.

The total enrolment of cohort A is ~3500 individuals and cohort B is ~4500 individuals across all the Clinical Research Units (CRUs). The total number of bio-specimens archived is ~1,25,000 (Cohort A) and ~96,000 (Cohort B).

Key achievements of the Phase I of RePORT India



Critical insights into TB pathogenesis by RePORT India Investigators

MVDRC & University of Massachusetts Medical School - Effects of Diabetes On Tuberculosis Severity [EDOTS]

- Very high (>50%) prevalence of Diabetes Mellitus (DM) in adult pulmonary TB patients in Chennai as well as high prevalence of multiple TB risk factors in TB/DM patients (under nutrition, smoking, alcohol).
- Identified Visceral Adiposity Index as a biomarker for adverse treatment outcomes.
- Elucidated activation of diabetic complication pathway with implications for associated NCD viz Epigenetic regulation, Oxidative stress, DNA damage, Cellular senescence, Platelet activation, RAGE signalling, CVD biomarkers.
- Poor glycaemic control in TB/DM patients and distinct and prolonged pattern of increased inflammatory cytokine protein expression in TB/DM.

National Institute for Research in Tuberculosis, Byramjee Jeejeebhoy Government Medical College and Johns Hopkins University - Cohort for TB Research with Indo-US Medical Partnerships (CTRIUMPh)

- Identified a 71-gene TB diagnostic signature and a 25-gene TB treatment response signature for pediatric TB in India.
- Identified pre-treatment IL-6 as a biomarker for unfavorable tuberculosis treatment outcomes.
- Found that Hair levels of INH and its metabolite may predict TB treatment outcomes.
- Identified 3 metabolites among paediatric TB that correctly identified TB status at distinct times during treatment: N-acetylneuraminate, Quinolinate and pyridoxate.
- Identified a lipid signature with prognostic accuracy for TB treatment failure.

Bhagwan Mahavir Medical Research Center and Univeristy of Texas at Tyler

- Young adult HHCs (Healthy House-hold Contacts) of the TB patients exhibiting decreased production of the thyroid hormones and IL-1 α and increased numbers of the CD16+CD56+ cells and Tregs at baseline, are at the highest risk for developing active TB disease.
- Increased levels of specific metabolites can regulate innate resistance against Mtb infection in HHCs of TB patients who never develop LTBI or active TB.

CMC, Vellore & University of Cambridge:

- Established the largest clinical cohort of TB Meningitis in India which is also one of the largest globally.
- Latent TB infection among healthy undergraduate medical students has been described in detail for the first time.
- Thoracoscopic pleural biopsy improved yield of Xpert MTB/RIF for diagnosis of pleural tuberculosis.
- Xpert ultra provided superior yield when compared to Xpert, for pleural and other extrapulmonary samples.

JIPMER, BU & Rutgers:

- Successfully completed phase IIb of a multicenter double-blind randomized placebo-controlled study to evaluate the efficacy and safety of recombinant TB vaccine candidate VPM1002. Screening, 2nd week, 2nd month and 6 months follow up for all the participants has been completed and the site is ready for the next phase of the trial.
- Developed a computational profiling platform of TB signature gene sets and found that existing gene sets for TB differentiate active TB from LTBI effectively in the setting of malnutrition.
- Our studies on Transcriptional profile indicate that classifiers generated from different ethnic populations can accurately discriminate active and latent TB.
- Population attributable fraction of malnutrition for TB was 57.4% in males and 61.5% in females - demonstrating the importance of undernutrition in propelling the TB epidemic.

P. D Hinduja Hospital & John Hopkins University:

- Established a cohort of Multi-Drug Resistant Tuberculosis (MDR-TB) in India and Household Contacts (HHC) Cohort for MDR-TB Participants to evaluate the risk exposure.
- Developed and validated pharmacokinetics and pharmacodynamic assessments for all second line TB drugs in collaboration with Perinatal HIV Research Unit, South Africa and University of Cape Town, South Africa.
- Currently evaluating Whole Genome Sequencing and correlation of phenotypic and genotypic assessments for MTB isolates.

Way forward: Building on the success of Phase I, implementation of Phase II of RePORT India has been initiated in February 2021, whereby, two additional sites at Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh and North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), Shillong have been included for enrolling cohorts from North and North-Eastern India.

SOPs have been developed for implementation of externally funded studies as sub-studies under RePORT India initiative. A Data Coordination Center is being set-up at JIPMER and data sharing SOPs are being developed.

RePORT India Phase II aims at the utilization of harmonized data elements and specimen collection SOPs for gaining insight into TB pathogenesis, generate newer diagnostics and identification of novel improved biomarkers for targeted therapy.