RePORT INDIA

2024 ANNUAL JOINT LEADERSHIP MEETING

HOSTED BY
National Institute of Immunology
New Delhi
April 3 – 5, 2024

Participating Institutions

- Bhagwan Mahavir Medical Research Center (BMMRC)
- Byramjee Jeejeebhoy Government Medical College (BJGMC)
- Byramjee Jeejeebhoy Government Medical College (BJGMC)-Johns Hopkins University (JHU) Clinical Research Site (BJGMC-JHU CRS)
- Boston University/Boston Medical Center (BU/BMC)
- Christian Medical College, Vellore (CMC)
- Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER)
- Johns Hopkins University (JHU)
- Prof. M. Viswanathan Diabetes Research Centre (MVDRC)
- National Institute for Research In Tuberculosis (NIRT)
- National Institute for Research In Tuberculosis (NIRT) – International Centers for Excellence in Research (ICER)
- North Eastern Indira Gandhi Regional Institute of Health & Medical Sciences (NEIGRIHMS)
- P.D. Hinduja National Hospital and Medical Research Centre (Hinduja)
- Postgraduate Institute of Medical Education and Research (PGI), Chandigarh
- Rutgers University
- St. Louis University School of Medicine (SLU)
- University of California—San Francisco (UCSF)
- University of Massachusetts (UMass)

Specialized Labs & Collaborators

- All Indian Institute of Medical Sciences (AIIMS), New Delhi, India
- Cornell University, New York, USA
- Emory University, Georgia, USA
- Fundação Oswaldo Cruz (FIOCRUZ), Bahia, Brazil
- Indian Institute of Science (IISc), Bengaluru, India
- Indian Institute of Science and Education (IISER), Pune, India
- Indian Institute of Technology Bombay (IIT-B) – Proteomics Core, Mumbai, India
- Medgenome, Bengaluru, India
- National Center for Functional Glycomics, Massachusetts, USA
- Office of Cyber Infrastructure and Computational Biology (NIAID), Maryland, USA
- South African TB Vaccine Initiative (SATVI), Cape Town, South Africa
- theraCUES Innovation Pvt Ltd, Bengaluru, India
- Translational Health Science and Technology Institute (THSTI), Faridabad, India

Sponsors

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INDO-US VACCINE ACTION PROGRAM

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SO LOVELY

To see you again

RePORT India 2023 Annual Meeting in New Delhi

RePORT INDIA

By the numbers

25 Papers published in 2023

36 Substudies

73 Grants & Supplemental Awards

164 Papers Published Since 2015

RePORT INDIA

Overview

CMC-Vellore

MVDRC

BMMRC

Background

RePORT (Regional Prospective Observational Research for Tuberculosis) India is a bilateral, multi-organizational, collaborative research effort established in 2013 under the Indo-US Vaccine Action Program (VAP). RePORT India is now the largest of six regional consortia—China, Brazil, Indonesia, Philippines, and South Africa are also undertaking multi-organizational tuberculosis (TB) research efforts. Each RePORT consortium is designed to support local, in-country, TB-specific data and specimen biorepositories and associated research. Taken together, the anticipated results include greater global clinical research capacity in high-burden settings and increased local access to quality data and specimens for members of each consortia and their domestic and international collaborators. Leveraging the data, specimens, infrastructure, and scientific partnerships established by RePORT India in Phase 1, the consortium has now launched Phase II.

Mission

RePORT India is charged with:

1. Advancing regional TB science in India, towards fulfilling the TB strategic goals of the country;
2. Strengthening TB research capacity and infrastructure; and
3. Fostering research collaboration within India and with other countries focused on research that can lead to clinically important biomarkers, vaccines, drugs, and diagnostics.

Phase I – Parent Protocols

Phase I (2013–18) commenced with six Clinical Research Sites (CRSs) in Western and Southern India that were partnered with five U.S. academic institutions. P.D. Hinduja National Hospital and Medical Research Centre was subsequently added as the seventh Indian site. Initially, each site had its own "Parent Protocol" with distinct research topics. Clinical, behavioral, radiological and biological samples were collected from the enrollees, including sputum, blood, urine etc. The specimens were stored at the ICMR-NIRT biobank for scientific analysis. TB patients and their household contacts were followed for a period of two years.

Cohort A: Participants who have active TB disease. Studies involving this cohort of patients focused on TB diagnosis and treatment outcomes.

- 2455 patients enrolled with TB inside the lungs (including 133 with drug-resistant TB)
- 588 patients enrolled with TB outside the lungs
- 207 children enrolled with TB

Cohort B: Participants who are household contacts (HHCs) of an active case of TB. Studies involving this cohort of participants focused on risk of infection and progression to TB disease after exposure.

- 3766 HHCs of coughing adult patients with TB inside the lungs enrolled

Phase I – Parent Protocol Achievements

- 106 scientific publications to advance TB science and public health
- 64 new projects utilizing the collected and stored samples for new biomarkers
- 245 presentations to showcase the work done in the RePORT Consortium
- New child TB diagnosis and treatment response gene-signatures unique for India
- New Transcriptomic, Lipidomic and Metabolomic signatures as blood biomarkers
- New vaccine trials to prevent TB relapse, Clinical biomarkers of TB death and relapse
- Key public health finding that informed the country's National TB Elimination Program guideline policies and more public health findings in the list with potential to guide further.

Phase I – Common Protocol

Based on the tremendous productivity of RePORT India's Phase I identifying new blood-based, sputum-based and urine-based biomarkers that can diagnose TB, or predict TB patients treatment success or failure or death, and for assessing new vaccines to prevent getting TB again (relapse) for those starting TB treatment, the governments of India and the US bilaterally funded the extension of Phase I in to a "Common Protocol" in 2017. The Common Protocol allowed for standardized data elements and harmonized procedures for enrollment across all sites to 1) identify newer, more accurate biomarkers and 2) confirm the utility of previously discovered biomarkers by validating them on samples stored in the ICMR-NIRT sample bank. The Common Protocol enrolled and followed TB patients and their HHCs for a period of two years.

Cohort A: Participants who have active TB disease.

- 724 adult patients enrolled with TB inside the lungs

Cohort B: Participants who are household contacts (HHCs) of an active case of TB.

- 898 household contacts of coughing adult patients with TB inside the lungs enrolled

BMMRC & SLU

- **Topic of Study:** Immunologic Markers of Persons at Highest Risk of Progression of Latent TB Infection to TB
- **India PI:** Dr. Vijaya Valluri, Bhagawan Mahavir Medical Research Centre (BMMRC), Hyderabad, India
- **U.S. PI:** Dr. Krishna Vankayalapati, St Louis University School of Medicine, St. Louis, MO, USA
- **Participating Patient Cohort:** Cohort B

BJGMC, NIRT, & JHU

- **Topic of Study:** Host and Microbial Factors Associated with Poor Treatment Response and Progression to Active TB (C-TRIUMPH)
- **India PIs:** Drs. Sanjay Gaikwad, Aarti Kinikar and Shashikala Sangle, Byramjee Jeejeebhoy Government Medical College (BJGMC), Pune, India; Dr. Vidya Mave, BJGMC-JHU CRS, Pune, India; Drs. Padma Chandrasekaran and Bhavani PK, National Institute for Research in TB (NIRT), Chennai, India
- **U.S. PI:** Dr. Amita Gupta, Johns Hopkins University, Baltimore, MD, USA
- **Participating Patient Cohorts:** Cohort A (Adult Pulmonary TB, Pediatric TB, and Extrapulmonary TB) and Cohort B

CMC Vellore & U of Wash/U of Cambridge

- **Topic of Study:** Host Determinants in the Eicosanoid Pathway that Modulate the Inflammatory Response, Disease Outcome, and Treatment Responsiveness in TB
- **India PI:** Drs. DJ Christopher and Balamugesh Thangakunam, Christian Medical College (CMC), Vellore, India
- **U.S. PI:** Dr. Lalitha Ramakrishnan, University of Washington/University of Cambridge, UK
- **Participating Patient Cohort:** Cohort A (Adult Pulmonary TB and TB Meningitis)

Hinduja & JHU

- **Topic of Study:** MDR-TB Treatment Outcomes, Adverse Effects, Mtb Genotyping, and Pharmacokinetic Testing
- **India PIs:** Drs. Zarir F. Udwadia, Tester F. Ashavaid, and Camilla Rodrigues; P.D. Hinduja National Hospital and Medical Research Centre, Mumbai, India
- **U.S. PIs:** Drs. Amita Gupta and Jeffrey Tornheim, Johns Hopkins University (JHU), Baltimore, MD, USA
- **Participating Patient Cohorts:** Cohort A (Adult/Adolescent MDR-TB) and Cohort B

JIPMER, BU/BMC, & Rutgers

- **Topic of Study:** Biomarkers for Risk of TB and for TB Treatment Failure and Relapse
- **India PIs:** Drs. Gautam Roy and Sonali Sarkar, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India
- **U.S. PIs:** Drs. Jerrold Ellner and Padmini Salgame, Rutgers University, Newark, NJ, USA; Dr. Robert Horsburgh, Boston University (BU), Boston, MA, USA; Dr. Natasha Hochberg, Boston Medical College (BMC), Boston, MA, USA
- **Participating Patient Cohorts:** Cohort A (Adult Pulmonary TB and Pediatric TB) and Cohort B

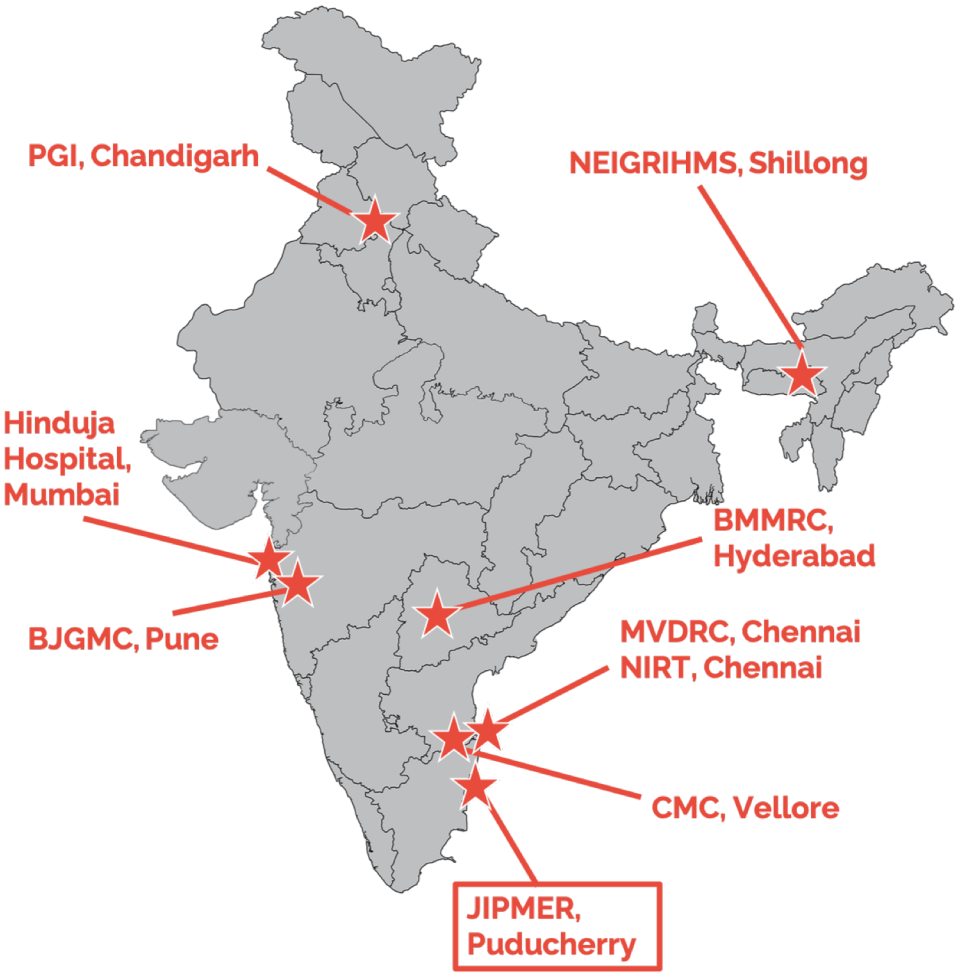
MVDRC, NIRT-ICER, & UMass

- **Topic of Study:** Effects of Diabetes and Prediabetes on TB Severity
- **India PIs:** Dr. Vijay Viswanathan, MV Diabetes Research Centre (MVDRC), Chennai, India; Dr. Subash Babu, National Institute for Research In Tuberculosis (NIRT) – International Centers for Excellence in Research (ICER), Chennai, India
- **U.S. PI:** Dr. Hardy Kornfeld, University of Massachusetts (UMass) Medical School, Boston, USA
- **Participating Patient Cohort:** Cohort A (Adult Pulmonary TB)

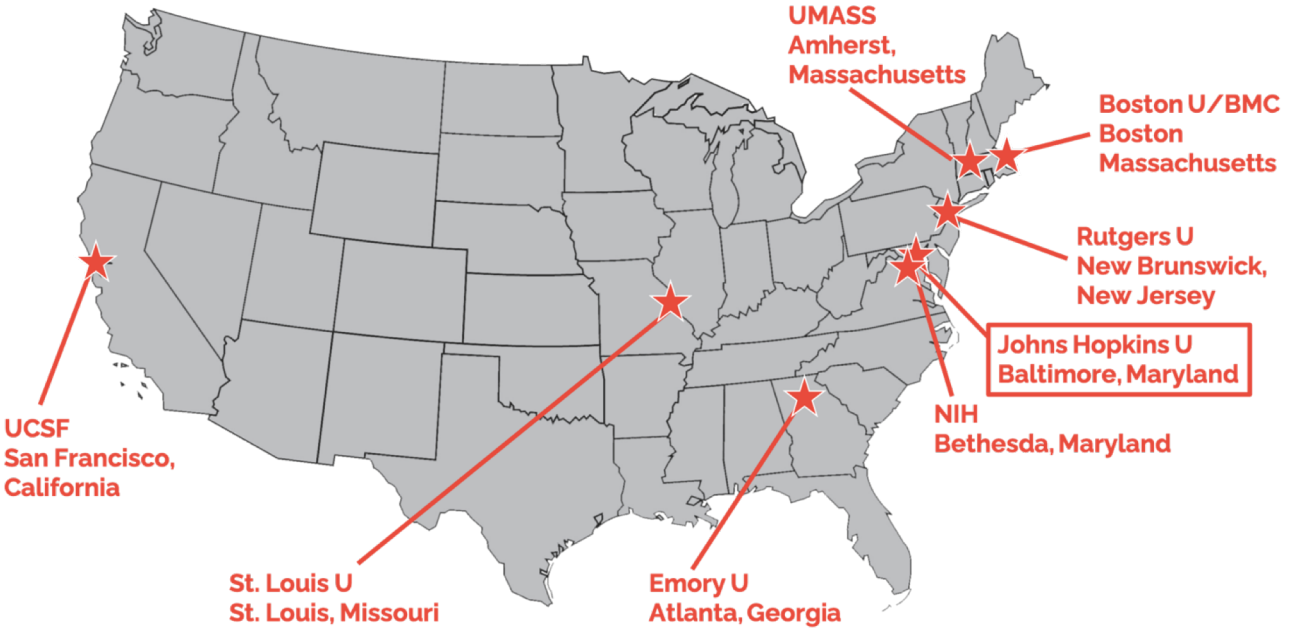
Phase II – Common Protocol

Both Indo-US governments have further supported the scientific research goals of RePORT India by expanding the number of sites represented across the country, especially by involving scientists and participants from the Northern and North-eastern parts of the country. In addition to the existing group of TB patients and their household contacts across nine Indian sites in the RePORT India Phase II Common Protocol, the consortium plans to support the enrollment of 1500 adult and child patients who are suspected of having TB outside the lungs, 588 adult patients with TB inside the lungs, and 794 household contacts of adult patients with TB inside the lungs. On the following pages, the Phase II CRSs and their study focus areas are outlined.

RePORT India Phase II



Under a Phase II Common Protocol, we are pursuing five specific scientific aims including the following cohorts: Diagnostic (New TB suspects), Cohort A (Active TB disease), and Cohort B (HHCs). Samples collected under this protocol will be curated, stored, and managed at the RePORT India Central Biorepository at NIRT where Phase I Common Protocol samples are currently stored. A data management center is being established at JIPMER in Puducherry and PPD will continue to provide technical support. The Phase II Common Protocol Co-Chairs are: Drs. Kamakshi Prudhula Devalraju (BMMRC) and Robert Bollinger (JHU). The consortium has now been expanded to include two new CRSs in Northern India.



Phase II Scientific Aims

AIM 1. DIAGNOSTICS

Evaluate Novel Diagnostics & Biomarkers of Diverse States of Mtb Infection

Participating Patient Cohort: Diagnostic (New TB suspects)
Leads: Dr. Sonali Sarkar (JIPMER) and Dr. Jerry Ellner (Rutgers)

Participating Patient Cohort: Cohort B (XDR HHCs)
Leads: Dr. Tester Ashavaid (Hinduja) and Dr. Jeff Tornheim (JHU)

AIM 2. MARKERS OF TREATMENT RESPONSE

Participating Patient Cohort: Cohort A (Active TB disease)

2.A: Identify TB Treatment Response Biomarkers
Leads: Dr. Vijay Viswanathan (MVDRC) and Dr. Hardy Kornfeld (UMass)

2.B: Investigate Host-Related Mechanisms of Treatment Failure
Leads: Dr. Vidya Mave (BJGMC-JHU CRS) and Dr. Natasha Hochberg (BMC)

2.C: Investigate Pathogen-related Mechanisms & Predictors of Recurrence
Lead: Dr. David Alland (Rutgers)

AIM 3. LUNG INJURY & IMPAIRMENT

Identify Markers of Lung Injury Associated with Unfavorable TB Treatment Outcomes

Participating Patient Cohort: Cohort A (Active TB disease)

Leads: Dr. DJ Christopher (CMC Vellore), Dr. Ashutosh Aggarwal (PGI Chandigarh), and Dr. Akshay Gupte (BU)

AIM 4. RESISTANCE TO INFECTION

Mechanisms of Protection against TB in Exposed Persons

Participating Patient Cohort: Cohort B (Phase I HHCs)

4.A: Examine Host Antimicrobial Pathways in Inducing their infection resistant (IR) Phenotype in HHC

4.B: Test if IR & Plasma Differ in Modulating Macrophage-Mediated Restriction of Mtb Growth & Evaluate AB Repertoires of Plasma from the IR and infection susceptible (IS) Cohorts

Leads: Dr. Padmini Salgame (Rutgers), Dr. Subash Babu (NIRT-ICER), and Dr. Kamakshi Prudhula Devalraju (BMMRC)

AIM 5. PROGRESSION TO DISEASE

Identify Immunologic Markers of Persons at Highest Risk of Progress of Latent TB Infection to TB

5.A: Stored Samples: Validation of PREDICT29 in Progressors & Nonprogressors from RePORT Sites
Participating Patient Cohort: Cohort B (Phase I HHCs)
Leads: Dr. Padmini Salgame (Rutgers) and Dr. Luke Elizabeth Hanna (NIRT)

5.B: Immune & Hormone Studies in Freshly Collected Samples
Participating Patient Cohort: Cohort B (Phase II HHCs)
Leads: Dr. Vijaya Valluri (BMMRC) and Dr. Ramakrishna Vankayalapati (SLU)

In addition to these five aims, we will assess cross-cutting epidemiologic and COVID-19 related aims.

Administration

RePORT India has established a collaborative governance structure composed of: 1) an Executive Committee led by two Chairs and two Co-chairs from India and the U.S.; 2) an Indo-U.S. Coordinating Hub; 3) three Scientific Working Groups (Basic Science, Clinical Epidemiology, Behavioral Science); 4) five Operational Working Groups (Common Protocol Leadership, Study Coordination, Publications Committee, Laboratory Management, and Data Management); and 5) a Data Coordinating Hub (JIPMER).The EC's mission is to set research priorities, guide scientific activities, and offer administration and logistics in support of research priorities.

The consortium is currently led by:

- Chairs: Dr. Sonali Sarkar (JIPMER, Clinical Epi) and Dr. Amita Gupta (JHU, Clinical Epi)
- Co-Chairs: Dr. Vijaya Valluri (BMMRC, Basic Science) and Dr. Padmini Salgame (Rutgers, Basic Science)

Funding

The RePORT India Consortium is supported with bilateral funding from the Government of India's (GOI) Department of Biotechnology (DBT) and the U.S. National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS), and Office of AIDS Research (OAR). CRDF Global administers and oversees the funding from the U.S. government.

MVDRC

JIPMER

RePORT INDIA

Junior Investigator Abstracts

BJGMC

NIRT

Hinduja

Junior Investigator Abstracts

TITLE	INVESTIGATORS
Toward understanding the molecular signature of T cells in drug resistant and drug sensitive TB in India: Report of preliminary findings	**Himanshu Tripathi, Visista Adiga**, Asma Ahmed, Saptak Bannerjee, Plamena Naydenova, Natarajan Alangudi Palaniappan, Mohan Natrajan, Dina Nair, Sridhar Rathinam, Vinod Kumar V, Soumya Swaminathan, Eoin F Mckinney, Annapurna Vyakarnam
Hyperglycemia induced metabolic changes enhance necroptosis in type 2 diabetes mellitus mice infected with *Mycobacterium tuberculosis*	**Rajesh Kumar Radhakrishnan**, Abhinav Vankayalapati, Olamipejo Durojaye, Padmaja Paidipally, Bismark Owusu-Afriyie, Tanmoy Mukherjee, Ramakrishna Vankayalapati, Rajesh Kumar Radhakrishnan
Differential cytokine profiles in tuberculous meningitis: Unveiling distinctive markers for definite diagnosis	**Arul Nancy P**, Nathella Pavan Kumar, Deepa Shankar, Rajasekar Sekar, T Balamugesh, D. J. Christopher, Subash Babu
Do high Treg cells and low CD14+ monocytes render children susceptible to TB?	**Kamakshi Prudhula Devalraju**, Venkata Sanjeev Kumar Neela, Rajesh Radhakrishnan, Anvesh Kumar Bogam, Varalakshmi Mallidi, Mohammad Soheb Ansari, Sindhu Joshi, Ramakrishna Vankayalapati, Vijaya Lakshmi Valluri
Prevalence of helminth infection and its modulation of cytokine and chemokine immune response in latent TB infected household contact of pulmonary TB patients	**Abilasha Narayanan,** Abilasha Sathishkumar, Komal Jain, Chelsie Clinton, Madolyn Dauphinais, Senbagavalli Prakash Babu, Sonali Sarkar, Natasha Hochberg, Padmini Salgame, Pranay Sinha, Subitha Laksminarayanan, Prakash Babu Narasimhan

Junior Investigator Abstracts

Towards understanding the molecular signature of T cells in drug resistant and drug sensitive TB in India: Report of preliminary findings

Submitting Author: Himanshu Tripathi

Co-authors: Visista Adiga, Asma Ahmed, Saptak Bannerjee, Plamena Naydenova, Natarajan Alangudi Palaniappan, Mohan Natrajan, Dina Nair, Sridhar Rathinam, Vinod Kumar V, Soumya Swaminathan, Eoin F Mckinney, Annapurna Vyakarnam

Background: In 2022, the global death toll from TB reached 1.3 million, with India alone accounting for 0.33 million fatalities. Multidrug-resistant TB (MDR-TB) persists as a public health emergency. India recorded approximately 2.82 million new TB cases in 2022, with 110,000 of these being drug-resistant. While sequence-based diagnostics play a crucial role in improving the accuracy of individual patient treatment for multi-drug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB), they typically focus on the genetic makeup of the TB bacteria to guide treatment decisions. Understanding the host immune response through transcriptome profiling of CD4 and CD8 T cells, which are increasingly recognised to play a role in both pathogenesis and immunity, can complement these diagnostics, providing additional insights into disease progression and treatment outcomes.

Aim/Objective: The molecular signature of CD4 and CD8 T cells in drug-resistant vs drug-sensitive *Mycobacterium tuberculosis* infections remain undocumented in India. Our objective was to address this knowledge gap.

Methods: We recruited 50 MDR-TB and 100 drug-sensitive TB patients prior to start of standard anti-TB treatment as per national guidelines, as part of a larger study. Flow cytometry was used to specifically capture a minimum of 100,000 live CD4+ and CD8+ T cells from frozen-thawed PBMC and immediately archived in an RNA stabilisation buffer. RNA was isolated using a Qiagen RNA extraction kit and cDNA synthesis and library preparation was carried out using SMARTer Stranded Total RNA-Seq Kit v2 (Takara). Libraries were then subjected to whole genome RNA Sequencing (RNA-Seq) on the Illumina Platform at 150x2 chemistry to generate 20million paired end reads per sample (outsourced to Genotypic Technology Pvt. Ltd., Bangalore, India). First round analysis of RNA-Seq data of a subset of samples where RNA Sequence data was initially made available was probed: after QC cut-off, sample size was: drug sensitive-CD4 T cells N=10; drug resistant-CD4 T cells N= 22; drug sensitive CD8 T cells N=8; drug resistant CD8 T cells N=20.

Results: Principle component analysis revealed marked difference in gene expression profiles. More than 95% differentially expressed genes (DEGs) (Fold change 1.5, adjusted p-value < 0.05) were under expressed in drug-resistant CD4 and CD8 compared to the drug-sensitive T-cell groups. Pathway enrichment analysis shows that Ribosome and Coronavirus disease pathways (DEGs: Ribosomal protein genes) are down-regulated in both CD4 and CD8 resistant groups while one of the immune related pathway (i.e. IL-17 signalling pathway (DEG: FOSB)) was up-regulated in CD8 T cell drug resistant group.

Interim Conclusion: RNA Sequence analysis confirms gene expression profiles of CD4 and CD8 T cells in subjects with drug- resistant and -sensitive TB to be distinct, prior to initiation of standard anti-TB treatment, with 95% of the DEGs identified being downregulated in drug resistant TB. With recent availability of the wider RNA Sequence data set of paired purified CD4 and CD8 T cells from N=39 drug resistant and N=36 drug sensitive cases, we have initiated data integration of gene expression profile analysis from all samples.

Hyperglycemia induced metabolic changes enhance necroptosis in type 2 diabetes mellitus mice infected with *Mycobacterium tuberculosis*

Submitting Author: Rajesh Kumar Radhakrishnan

Co-authors: Abhinav Vankayalapati, Olamipejo Durojaye, Padmaja Paidipally, Bismark Owusu-Afriyie, Tanmoy Mukherjee, Ramakrishna Vankayalapati, Rajesh Kumar Radhakrishnan

Background & Rationale: *Mycobacterium tuberculosis* (*Mtb*) infects one-third of the world's population and causes almost 1.3 million deaths per year. Diabetes enhances the risk of developing primary tuberculosis infection. Previously, we developed an experimentally induced type 2 diabetes (T2DM) model in wild-type C57BL/6 mice and found that *Mtb* infection in T2DM mice drives pathological immune responses and mortality. In the current study, we determined the defective mechanisms that make T2DM mice alveolar macrophages more susceptible to *Mtb* infection.

Methods: In this study, we induced type 2 diabetes mellitus (T2DM) in C57BL/6 mice using streptozotocin and nicotinamide. Alveolar macrophages (AM's) from control and T2DM mice and infected with *Mtb* H37Rv. After 3 days of infection, the cells were collected for mRNA, protein expression and for confocal microscopy. For metabolite studies, we collected AM's cell lysates from *Mtb* infected control and T2DM mice in methanol and analyzed through LC/MS. For in vivo studies control and T2DM mice were treated with either 2-Ketohexanoic acid or pyridoxine and determined the lung bacterial burden and inflammation.

Results: In the current study, using a T2DM *Mtb* infection model, we determined the mechanisms that make T2DM mice AMs more inflammatory upon *Mtb* infection. Among various cell death pathways, necroptosis is a major pathway involved in inflammatory cytokine production by T2DM mice AMs. Anti-TNFR1 antibody treatment of *Mtb*-infected AMs from T2DM mice significantly reduced necroptosis and inflammatory cytokine (TNF-α and IL-6) production. Metabolic profile comparison of *Mtb*-infected AMs from T2DM mice and *Mtb*-infected AMs of nondiabetic control mice indicated that 2-ketohexanoic acid and deoxyadenosine monophosphate were significantly abundant, and acetylcholine and pyridoxine were significantly less abundant in T2DM mice AMs infected with *Mtb* (**Fig. 1A**). 2-Ketohexanoic acid enhanced TNFR1 expression, necroptosis and inflammatory cytokine production in the lungs of *Mtb*-infected nondiabetic mice and *Mtb*-infected AMs. In contrast, pyridoxine inhibited TNFR1 expression, necroptosis and inflammatory cytokine production in the lungs of *Mtb*-infected T2DM mice and *Mtb*-infected AMs (**Fig. 1B-C**).

Conclusions: Our findings demonstrate that hyperglycemia-induced metabolic changes in Mtb-infected T2DM mice enhance TNFR1-mediated necroptosis of AMs, which leads to excess inflammation and lung pathology.

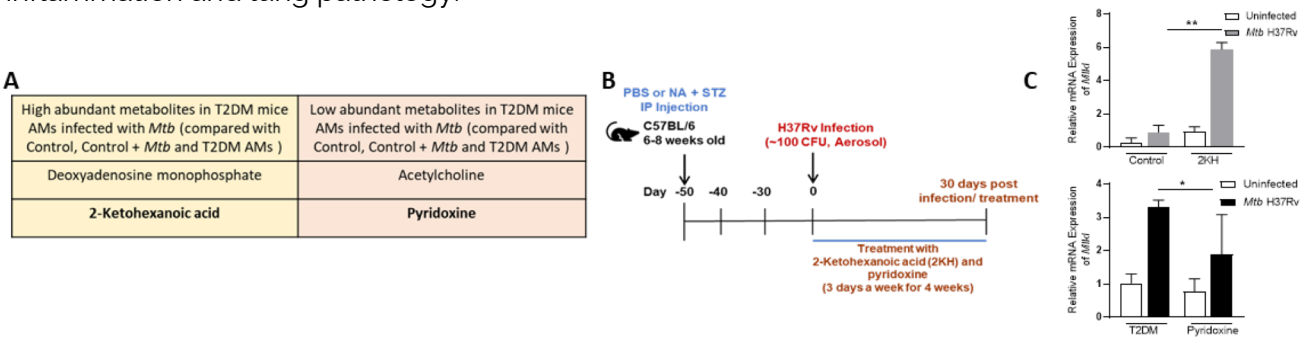


Fig 1. Metabolites treatment alters necroptosis in the lungs of Mtb-infected mice. **(A)** LC/MS analysis shows high and low abundant metabolites in *Mtb*-infected T2DM mouse alveolar macrophages **(B)** A schematic representation of T2DM induction and intranasal metabolite treatment in C57BL/6 mice is shown. **(C)** Expression of Mlkl was determined in the lungs by qRT-PCR. Five mice per group were used for each independent experiment (n=2). The data are shown as the mean ± SD. The statistical analysis was performed by one-way ANOVA followed by Tukey's multiple comparison test. *, $p<0.05$ and **, $p<0.01$.

Differential cytokine profiles in tuberculous meningitis: Unveiling distinctive markers for definite diagnosis

Submitting Author: Arul Nancy P

Co-authors: Nathella Pavan Kumar, Deepa Shankar, Rajasekar Sekar, T Balamugesh, D. J. Christopher, Subash Babu

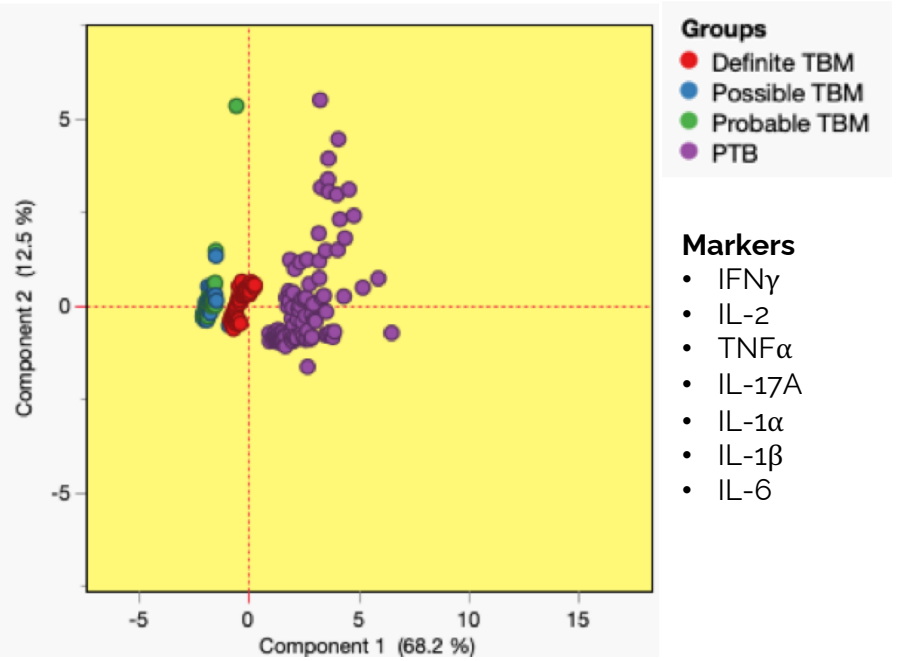
Background & Rationale: Tuberculous meningitis (TBM) represents a rare but highly fatal manifestation of extra-pulmonary tuberculosis. Clinical classification into definite, possible, and probable TBM is complicated by nonspecific symptoms, the necessity for lumbar puncture in cerebrospinal fluid (CSF) diagnosis, the limited sensitivity of existing imaging techniques, and the atypical nature of the disease. The potential of cytokines as biomarkers for TBM diagnosis remains uncertain.

Methodology: This study enrolled participants from a cohort consisting of four distinct groups: definite TBM (n=57), possible TBM (n=81), probable TBM (n=68), and an active pulmonary TB group (PTB) serving as a positive control (n=106). Conducted at CMC, Vellore, and ICER India, Chennai, the study aimed to delineate cytokine levels using a comprehensive 45-plex cytokine panel in plasma.

Results: Seven plasma cytokines (IFNγ, IL-2, TNFα, IL-17A, IL-1α, IL-1β, and IL-6) demonstrated significant elevation in definite TBM compared to possible and probable TBM groups. Principal Component Analysis (PCA) highlighted distinct discrimination between definite TBM and the other TBM groups, as well as the PTB group (illustrated in Fig. 1). ROC analysis indicated that IFNγ, TNFα, and IL-17A could serve as biomarkers distinguishing definite TBM from possible TBM (IFNγ: sensitivity-100%; specificity-83%; AUC-0.976; TNFα: sensitivity-97%; specificity-100%; AUC-0.990; and IL-17A: sensitivity-100%; specificity-98%; AUC-0.999) and probable TBM (IFNγ: sensitivity-98%; specificity-78%; AUC-0.956; TNFα: sensitivity-95%; specificity-100%; AUC-0.972; and IL-17A: sensitivity-97%; specificity-100%; AUC-0.999).

Conclusion: This study's data reveal a unique cytokine profile in definite TBM, distinguishing it from possible and probable TBM, as well as the PTB group. The findings suggest the potential utility of IFNγ, TNFα, and IL-17A as distinctive biomarkers in TBM diagnosis and differentiation.

Fig 1: Principal Components Analysis



Do High Treg cells and low CD14+ monocytes render children susceptible to TB?

Submitting Author: Kamakshi Prudhula Devalraju

Co-authors: Venkata Sanjeev Kumar Neela, Rajesh Radhakrishnan, Anvesh Kumar Bogam, Varalakshmi Mallidi, Mohammad Soheb Ansari, Sindhu Joshi, Ramakrishna Vankayalapati, Vijaya Lakshmi Valluri

Background & Rationale: In households with active TB index cases, following exposure to *M.tb*, children are at high risk of progressing first to tuberculosis infection, then tuberculosis disease and possibly disseminated forms, with accompanying high morbidity and mortality. While it is known that children are at increased risk of progression from TB infection to TB disease, understanding of risk factors for this transition is limited. Following exposure to *M.tb*, almost 90% of immunocompetent adults establish an asymptomatic, latent TB infection (LTBI), which carries a 5–10% lifetime risk of reactivation disease. In addition to an increased susceptibility to TB, prompt diagnosis in children is complicated by the fact that children with progressive primary infections seldom present with a positive sputum acid-fast bacillus smear, which is commonly seen in adult pulmonary reactivation disease. Early detection is essential since the disease progresses during the period of diagnostic delay. Understanding the basis for the increased susceptibility of children to developing TB is likely to lead to improved vaccines and immunodiagnostics.

Methods: HIV- children between the ages (6 and 18 years) were recruited and followed for 2 years for conversion to LTBI+/ development of Active TB. After 2 years, depending on the outcome, children were categorised into converters (n=16), non-converters (n=57), and non-progressors (n=69). Children with ATB (n=36) were also recruited to compare the immune markers. Blood was collected, peripheral blood mononuclear cells (PBMCs) were isolated and flow cytometry was used to identify various immune cell populations viz, (NK, macrophage and T-cell subpopulations including T-regulatory cells (Tregs)). Remaining PBMC were cultured with ESAT-6 and CFP-10. The culture supernatants were collected to measure cytokine and chemokine levels by ELISA. Serum hormones T3, T4, TSH concentrations were measured by ELISA following the manufacturer's instructions.

Results: In this study we determined immune mechanisms in children who develop LTBI and/or active TB to understand whether specific changes in the immune profile precede susceptibility to *M.tb* infection. Children who developed LTBI on follow-up had significantly high $CD16^+$, $CD56^+$, $CD4^+$ and $CD4^+CD25^+FoxP3^+$ cells and low $CD14^+$ cells at baseline compared to LTBI resistors. Children with ATB had significantly high $CD3^+$, $CD3^-CD27^+CD56^+CCR7^+$, $CD4^+CD25^+FoxP3^+$ cells and low $CD14^+$, $CD56^+$, $CD56^+CD16^+$ cells compared to $LTBI^+$ children who never develop ATB. In cells stimulated with *M.tb* antigens, we observed that LTBI converters produced significantly low IL-6, IFN-γ, and IL-10 but high IL-1β compared to those who never developed LTBI. Children with ATB produced significantly high TNFα and IL-6 at baseline compared to $LTBI^+$ children who never developed ATB. LTBI converters had high serum TSH compared to TB resistors. Children with ATB had low T3 hormone in their serum compared to $LTBI^+$, who never developed ATB.

Conclusions & Recommendations: We observed distinct immune patterns in children who develop LTBI and those with ATB. However, low $CD14^+$ and Treg cells can be used as markers to identify the risk of development of LTBI or ATB in children. Combining these cell phenotypes with cytokines and hormone profiles can improve the screening of children at high risk for developing active TB disease.

Funding: This study was supported by DBT, GoI - CRDF, USA and NIH as a part of RePORT India consortium.

Prevalence of helminth infection and its modulation of cytokine and chemokine immune response in latent TB infected household contact of pulmonary TB patients

Submitting Author: Abilasha Narayanan

Co-authors: Abilasha Sathishkumar, Komal Jain, Chelsie Clinton, Madolyn Dauphinais, Senbagavalli Prakash Babu, Sonali Sarkar, Natasha Hochberg, Padmini Salgame, Pranay Sinha, Subitha Laksminarayanan, Prakash Babu Narasimhan

Background & Rationale: The study investigates the co-occurrence of *Mycobacterium tuberculosis* (*Mtb*) and helminth infections in low- and middle-income countries, posing a significant health challenge due to immunological antagonism between the pathogens. Helper type 2 responses induced by helminths downregulate Th1 responses crucial for *Mtb* protection, potentially predisposing individuals to active TB.

Methods: Data from 833 household contacts of active pulmonary TB patients were analyzed, focusing on helminth prevalence in IGRA+ve individuals and its immune modulatory effects on latent TB infection. Nutritional status and helminth infection were categorized into four groups, with latent TB diagnosed using the IGRA Quantiferon-TB gold (QFT) test. Stool and blood samples were collected for PCR testing of soil-transmitted helminths and cytokine/chemokine measurements, emphasizing the interplay between nutrition, helminth infection, and latent TB immunity.

Results: The study assessed latent TB infection prevalence in household contacts (HHC) and helminth infection in IGRA+ve individuals. Among 833 HHC, 326 (39%) tested positive for latent TB, while 501 (60%) tested negative. Among IGRA+ve participants (n=266), 55 (28%) well-nourished individuals and 31 (42%) undernourished individuals exhibited helminth positivity, significantly higher than the general community ($P \leq 0.05$). Necator americanus predominated (82%) in helminth-infected undernourished individuals. Cytokine analysis showed decreased IFNg levels in TB2-nil tubes and elevated levels of TNF-a, IL-1b, IL-4, IL-5, IL-10, IL-12p, IL-17, and MIP-1b in helminth-infected undernourished individuals. After TB antigen stimulation, IFNg, IL-10, IL-12p, IL-17, and MIP-1 levels significantly increased in helminth-infected undernourished individuals compared to those without helminth infection.

Conclusion: The study reveals a higher helminth infection prevalence in undernourished individuals compared to well-nourished counterparts. Moreover, the diminished response to TB antigen in helminth-infected undernourished individuals may heighten TB risk in this subgroup of household contacts. Further research is needed to understand the complex interaction among helminth infections, nutritional status, and immune responses in latent TB infection.

REPORT INDIA

Related Grants & Substudies

BJGMC

JIPMER

CMC

RePORT International & CFAR Supplemental Funded Projects

TITLE	PARTNERS	CRDF #	START DATE	INVESTIGATORS
Local Capacity Building to Develop Novel Drug-Resistant TB Testing and High-Throughput Multiplex Protein Measurement Programs in Pune, India	BJGMC	RiCC	2023	
RePORT India Consortium Strengthening Equipment Funding	BJGMC, Hinduja	RiCC	2023	Tornheim J, Udwadia Z, Ashavaid T, Rodrigues C, and the BJMC team
TB-RiCC Laboratory Enhancement and Capacity Building	JIPMER	RiCC	2023	
IFNg-independent T cell-mediated protection in Mycobacterium tuberculosis infection	Rutgers, JIPMER, BJGMC, JHU	RiCC	2023	
Innovative Modelling for Predicting TB Treatment Outcomes in Global Cohorts	JHU, FIOTEC, Vanderbilt U, RePORT India, RePORT Brazil	RiCC	2022	Krishnan S, Robinson M, Andrade B, Sterling T, Gustavo, Gupta A, Gupte N, RePORT India, RePORT Brazil
Impact of Latent TB Infection and Trained Immunity on Susceptibility to SARS-CoV-2 Infection in India and the Philippines	Rutgers, JIPMER, University of Philippines Manila	RiCC	2021	Salgame P, Sarkar S, Marissa AM (RePORT Philippines)
Associative BRICS Research in COVID-19 and Tuberculosis (ABRICOT)	FIOTEC, Wits Health Consortium, NIRT-ICER	RiCC	2021	
Signature of Profiling and Staging the Progression of TB from Infection to Disease	JIPMER, BU	RiCC	2020	
T Cell Biomarkers and T-Regulatory Responses to Pediatric TB	Emory, JHU, BJGMC, NIRT	65373	2020	Rengarajan J, Kagal A, Kinikar A, Mave V, Padmapriyadarsini C, Hanna L, Paradkar M
Pregnancy Associated Immune Responses to TB and HIV in India and South Africa (PARTHISA study)	JHU, BJGMC, Wits Health Consortium, Cornell	65344	2020	Gupta A, Martinson N, Mathad J, Bhosale R, Kagal A, Alexander M, Kulkarni V
Pharmacokinetic Assessment of MDR-TB Drugs in the Treatment of TB Meningitis	JHU, PD Hinduja, Beijing Chest Hospital, BJG MC, Wits Health	65351	2020	Tornheim JA, Ashavaid T, Rodrigues C, Udwadia Z, Duan H, Sangle S, Varaiava E, Dooley K, Ignatius E, Mave V, Gupta A, Shivakumar SVBY, Chawla P, Patil S, Kulkarni V

RePORT International & CFAR Supplemental Funded Projects (Continued)

TITLE	PARTNERS	CRDF #	START DATE	INVESTIGATORS
Inflammasome Genetics and TB Treatment Outcomes	UPenn, JHU, UMass, BU, NIRT, MVDRC, BGJMC	65375	2020	Bisson G, Gupte A, Viswanathan V, Gupta A, Kornfeld H, Hanna L, BabuS, Andrade B, Dhanasekaran M
Host RNA Expression for Diagnosis and Monitoring of Pediatric TB in Africa and India	NIRT, BGJMC, JHU, Univ. Cape Town, Imperial College, London	64080	2019	Kinikar A, Paradkar M, Hissar S, Workman L, Dawre R, Gupte N, Tornheim JA, Kulkarni V
Determination of Efficacy of Xpert PCR Ultra And Transcriptional Signatures In The Diagnosis of Pleural Tuberculosis	CMC, Vellore & University of Cape Town, SA	64074	2018	Christopher DJ, Keertan D
Validation of Transcriptional Signature to Predict Active TB Disease among Advanced HIV Patients	RePORT Brazil, BMC, BJGMC, JHU, Rutgers	63158	2017	Mave V, Rolla V, Salgame P, Kadam D, Andrade B, Gupta A, Meshram S, Kulkarni V, Ellner J
Molecular Signatures of Tuberculosis-Diabetes Interaction (MSTDI) Study	JHU, UMass, BJGMC, NIRT, BU, MVDRC	63459	2017	Kornfeld H, P Chandrasekaran, Gupte A, Mave V, Bharadwaj R, Golub J, Andrade B, Paradkar M, Luke H, Kulkarni V, Gupte N, Shivakumar SVBY, Gupta A
Biomarkers for TB Diagnosis and Treatment Response	BJGMC, NIRT, Emory, JHU	63069	2016	Rengarajan J, Hanna LE, Mave V, Padmapriyadarsini C, Thiruvengadam K, Toidi A, Gupte N, Kulkarni V, Gupta A and CTRIUMPH team
Impact of HIV and Diabetes Mellitus on TB Drug Resistance and Recurrence	BJGMC, NIRT, JHU, MVDRC, UMass, Rutgers	63221	2016	Mave V, Devi U, Padmapriyadarsini C, Mathema B, Vishwanathan V, Kornfeld H, Kreiswirth B, Golub J, Gupte N, Shivakumar SVBY, Gupta A
MDR-TB and HIV at RePORT Sites India	BJGMC, NIRT, JIPMER, JHU, BMC	63076	2016	Horsburgh R, Padmapriyadarsini C, Mave V, Gupta A, Sarkar S
Validation and Fine Tuning of the Computer Aided Diagnosis of Pulmonary TB Model for the Indian Subcontinent	CMC	62922	2016	Christopher DJ, Thangakunam B, Lal B, Agrawal A

RePORT International & CFAR Supplemental Funded Projects (Continued)

TITLE	PARTNERS	CRDF #	START DATE	INVESTIGATORS
Extracranial Involvement as Detected by Positron Emission Tomography Scan in Patients with Tubercular Meningitis	CMC	62906	2016	Thangakunam B, Christopher DJ
Inflammatory Biomarkers as a Triage Test for Screening Symptomatic TB	JIPMER, Rutgers, BMC	63466	2016	Ellner J, Salgame P, Sarkar S, Pleskunas J
Characterization of Monocyte Responses in Pulmonary TB Patients with or without Type 2 Diabetes	NIRT-NIH – ICER, MVDRC	62911	2016	Kumar P
Effect of Malnutrition on Latent TB	Approved: JIPMER, Rutgers, BMC	23719	2016	Hochberg NS, Negi VS, Mahalakshmy T, Johnson WE, Salgame P, Pleskunas J
Determining Barriers to TB Care	JIPMER, BMC/BU	64020	2016	Sabin L, Sarkar S, Hochberg NS, Fernandes P, Pleskunas J, Amsaveni
TH17 Cell Subsets as Potential Risk Markers of Latency and Active TB Infection in Household Contacts	BMMRC, SLU	62916	2016	Devalraju KP, Neela VSK, Valluri VL, Vankayalapati K
Comparison of Available Purified-Protein Derivative (PPD) Tuberculin Skin Test (TST) Antigen Solutions in Detecting Latent Tuberculosis Infection in India	CMC, BJGMC, JIPMER, BMMRC, NIRT, JHU, BMC	61783	2015	Christopher DJ, Shankar D, Roy G, Sarkar S, Prakash Babu S, Gupta A, Deluca A, Cox SR, Hochberg NS, Horsburgh R

Grants Awarded

TITLE	PARTNERS	GRANT SOURCE	START DATE
Interleukin-6 signaling, lung injury and post-TB lung disease in TB/HIV	CMC, BJGMC, BU, JHU	NIH R01	*Pending*
Baseline pRescription According to Direct from Sputum Sequencing and TArgeted drug Concentration Strategy	Hinduja, JHU, UCT, UCSD, Vanderbilt	NIH R01	2023
Multiplexed Detection of Cell-free M. Tuberculosis DNA and Its Drug-resistant Variants in Blood	Hinduja, JHU, Tulane	NIH R01	2023
InTGS: Whole Genome Sequencing of MTB Clinical Strains for Determining Drug Resistance and Strain lineage in India: A Structured Nationwide approach	JIPMER, NII, ICGEB, CCMB, NIBMG, BMMRC, BJGMC, PGI, Hinduja, NIRT	DBT, India	2023
Learning Effect of Parasites and Reinforcing Diets on TB (TB-LEOPARD)	JIPMER, BU	Burroughs-Wellcome Fund	2022
Childhood 'Omics' and Mycobacterium tuberculosis-derived BIOsignatures (COMBO) for TB Diagnosis	UCSF, BJGMC	NIH R01	2021
A Nanopore Biosensor for Leveling MTB Antigens in Blood	Tulane, JHU, BJGMC	NIH R01	2021
Rapid Research for Diagnostics Development in TB Network	CMC Vellore, UCSF	NIH/NIAID R01	2021
Innate Immune Response of LTBI+HIV+ Children	BMMRC, SLU	NIH/NIAID R01	2021
Learning about Experience with Nutritional Supplementation in Tuberculosis (LENS): An Exploratory Study	JIPMER, BU	Boston University of India (Seed Grant)	2021
Understanding Mycobacterium tuberculosis Mediated Host Metabolomics in Pulmonary Tuberculosis: Correlation with Disease Severity and Treatment Course	JIPMER IISER, Pune	PEER Women in Science SEED Grants 2021: National Academies	2021
Hybrid Trial for Alcohol Reduction among People with TB and HIV in India (HATHI)	BJGMC, JHU, London School of Hygiene and Medicine, DY Patil	NIH NIAAA R01	2020
VITAL TB (Vitamins And Latency in Tuberculosis)	JIPMER, BU	U.S. Department of State's Partnership 2020 educational initiative	2020

Grants Awarded (Continued)

TITLE	PARTNERS	GRANT SOURCE	START DATE
Thyroxine (T4) Hormone Inhibits Expansion of Immunosuppressive CD4CD25+Foxp3+ (Tregs) Cells (Administrative Supplement for current R01 "IFN- independent inhibition of MTB growth in human macrophages")	BMMRC, SLU	R01	2020
Host and Microbiome Transcriptional Profiling in the Upper Airways for TB Susceptibility	JIPMER	CTSI Pilot Grant, BU, US	2020
Immune Responses and Effect of Disulfiram on MTB Infected PBMCs as a Potential Host Directed Therapy	BJGMC, NIRT, JHU, THSTI	Funding from Translational Health Sciences and Technology (THSTI)	2019
Dried Plasma Spots as a Simple Sampling Strategy to Measure Rifampicin Concentration to Facilitate this Service In Resource Limited Settings	CMC	Internal fluid research grant	2019
Evaluation of Diagnostic Potential of Aptamer-based Assays for Pulmonary Tuberculosis: A Pilot Study	CMC	THSTI	2019
Tuberculosis: Learning the Impact of Nutrition (TB LION)	JIPMER, BMC, Rutgers, Tufts, NIRT	Warren Alpert Foundation	2018
Whole Genome Sequencing of Drug Resistant Tuberculosis in India: Genotype-Phenotype Correlation, Clinical Impact of Resistance, and Sequencing Directly from Sputum	Hinduja, JHU	NIH/NIAID K23	2018
Validating a Th17 Switch as a Novel Correlate of Protective Immunity to TB	NIRT, BJMC, IISc, Bangalore, JHU	DBT/ IISc	2018
Characterization of Genomics and Metabolomics among Individuals (TB-GWAS)	Emory, JHU, BJGMC, JIPMER, BMMRC, NIRT, PHRU, McGill	NIH/NIAID R01	2018
Prevalence of Latent Tuberculosis in Rheumatoid Arthritis and Ankylosing Spondylitis	CMC	Internal fluid research grant	2018
The Effect of Appropriate Anti Tuberculous Treatment on Recovery of Pulmonary and Pleural Tuberculosis and the Impact of Tuberculosis on Lung Function and Quality of Life in Newly Diagnosed Patients	CMC	Internal fluid research grant	2018
Validation of Indigenously Developed Technology (TruNat MTB) for Diagnosis of Extra-pulmonary Tuberculosis: Multi-centric Validation	CMC, Hinduja, NIRT, AIIMS	ICMR	2018
Multicenter Phase II/III Double-Blind, Randomized, Placebo Controlled Study to Evaluate the Efficacy and Safety of VPM1002 in the Prevention of TB Recurrence in Pulmonary TB Patients after Successful TB Treatment.	RePORT India Sites	Serum Institute of India	2017-2022

Grants Awarded (Continued)

TITLE	PARTNERS	GRANT SOURCE	START DATE
Predictors of Resistance Emergence Evaluation in MDR-TB Patients on Treatment - (PREEMPT)	JIPMER, NIRT, BJGMC, Brazil, Vanderbilt, Rutgers, CDC, JHU, BMC, Hinduja	NIH/NIAID: R01	2017
Transcriptomic and Metabolomic Analysis of Microbiologically Confirmed Pediatric Tuberculosis Patients and Uninfected Household Contacts	BJGMC, JHU	Ujala Foundation Wyncote Foundation BWI-CTU C-TRIUMPH	2017-2022
Therapeutic Outcomes with Second-Line Drug Exposures in a Cohort of South African and Indian Patients with Drug Resistant TB: A Pharmacokinetic-Pharmacodynamic Assessment	Hinduja, PHRU, JHU	DBT/South Africa MRC	2017
Association of Lipid Mediators of Inflammation with TB Treatment Outcomes	JHU, NIRT, BJGMC	CTRIUMPH and Gilead Foundation	2017
The Role of Innate Immunity in the Acquisition of Sterile Protection Against TB Infection	U Colorado, JHU, BJMC	NIH R21	2017
IFN-γ Independent Inhibition of MTB Growth in Human Macrophages	BMMRC, SLU	NIH/NIAID R01	2017
MDR-TB Free: Monitoring Adverse Effects, Utilizing Resources Optimally, Knowing Resistance Patterns, and Treatment Strategy (MDR TB – MUKT)	Hinduja, JHU	Hinduja	2017
The Role of Monocyte Subpopulation in HIV+LTB+ Individuals and Development of Active TB	BMMRC, SLU	NIH R21 Indo-US Vaccine Program, RePORT India Cohort	2016-2018
Measuring TB Drugs in Hair as a Tool to Monitor Adherence, Exposure and Response	BJGMC, NIRT, JHU	NIH/NIAID: R21	2016-2018
Role of Iron Deficiency in Resistance of Women of Child-Bearing Age to Tuberculosis	JIPMER, BMC	NIH	2016-2017
Studying T cell Memory Responses for Understanding Protective Immune Response in Tuberculosis (TB)	CMC, NIRT, Saint Louis U	American Society of Tropical Medicine and Hygiene/ Burroughs Wellcome Fund)	2016
Impact of Immune Changes of HIV and Stages of Pregnancy on TB (PRACHITI)	BJGMC, NIRT, JHU	NIH/NICHD R01	2015-2020
Impact of Pregnancy on Tuberculosis	JIPMER, BMC	NIH/NIAID R01	2015-2018

Grants Awarded (Continued)

TITLE	PARTNERS	GRANT SOURCE	START DATE
Residual Respiratory Impairment Following Pulmonary Tuberculosis: The Lung Health Sub-Study	BJGMC, NIRT, JHU	UJALA/ Gilead Foundation/ RePORT India	2015-2017
D4GDI-mediated Immune Responses in LTBI+HIV+ Individuals	BMMRC, SLU	NIH R21 Indo-US Vaccine Program, RePORT India	2015-2017
Understanding of Tuberculosis Infection and Preventive Therapy Among Skin-Test Positive Household Contacts of Tuberculosis Cases	BJGMC, NIRT, JHU	NIH CFAR Fogarty D43	2015
T-regs Mediated Immune Responses in LTBI+HIV+ Individuals	BMMRC, SLU	SLU	2015
Compare Drug Levels in Newly Diagnosed or Relapsed PTB/ EPTB Following Daily ATT vs DOTS Regimen	CMC	Internal fluid research grant	2015
Impact of Personal Exposure to Black Carbon on Pulmonary Tuberculosis Severity	JIPMER BMC	Potts Memorial Foundation	2014-2018
Yield of TB using GeneXpert (Xpert MTB-Rif) by Induced Sputum Compared to Standard Sputum Samples	CMC	Internal fluid research grant	2014

Substudies

Childhood 'Omics' and Mycobacterium tuberculosis-derived BIOsignatures (COMBO) for TB Diagnosis

Principal Investigators	Population	Funding
Adithya Cattamanchi (UCSF) Joel Ernst (UCSF) Devan Jagannath (UCSF) Aarti Kinikar (BJGMC) Vidya Mave (BJGMC-JHU CRS) Mandar Paradkar (BJGMC-JHU CRS)	BJGMC Pune site will contribute stored samples (plasma, urine) of eligible pediatric participants enrolled in the CTRIUMPH, RICC Pediatric, and TB Elispot studies.	NIAID

Design: We will utilize banked blood and urine specimens among children being evaluated for TB in India, Uganda, South Africa, The Gambia, and Peru. We will measure Mtb-specific proteins and host proteins, and metabolites in the discovery and initial validation set of banked samples from 150 children with Confirmed TB, 150 children with Unconfirmed TB, and 300 children with Unlikely TB per NIH consensus definitions with and without HIV infection.

Aims:

1. Quantify levels of known Mtb proteins using an Electrochemiluminescence (ECL)-based assay ultra-sensitive
2. Perform an untargeted, shotgun proteomic and metabolomic approach to identify host proteins and metabolites that can serve as biomarkers for detection of childhood TB
3. Derive and validate the diagnostic accuracy of Mtb and/or host biosignatures for childhood TB.

Status: Plasma and urine sample testing ongoing at UCSF and Emory

Validating a th17 Switch as a Novel Functional Correlate of Immune Protection of Tuberculosis

Principal Investigators	Sites	Population	Funding
Annapurna Vyakarna (Indian Institute of Science, Bangalore & USA St. Johns National Academy of Health Sciences) Amita Gupta (JHU) Vidya Mave (BJGMC-JHU CRS) Padmapriyadarsini Chandrasekaran (NIRT) Rajesh Karyakarte (BJGMC)	NIRT BJGMC St. Johns National Academy of Health Sciences	Cohort I: TB Progressors among adults (>1 15 years household contacts: Longitudinal PBMC samples archived from a minimum of N=12 (maximum of 20) adults disease free for TB before and after they progress to TB. Cohort 2: TB Non-Progressors among adults (>1 15 years household contacts: Longitudinal PBMC samples, age and sex-matched archived from a minimum of N=12 (maximum of 20) adults disease free for TB over the same time frame as cohort I.	RePORT India DBT

Design: Longitudinal assessment of PBMC samples of progressors and non-progressors among adult household contacts of active TB patients

Aims:

1. Validate using advanced 16-color flow cytometry in CTRIUMPH longitudinal samples, if TB-free adults who progress to TB (cohort 1), is associated with loss of DosR antigen-specific Th17 regulatory CD4 T cell responses with a concomitant increase in DosR antigen-specific Th17 proinflammatory CD4 T cells.
2. Further validate using advanced 16-color flow cytometry in cTRIUMPH longitudinal samples of adults who do not progress to TB in the same time frame as cohort I (cohort 2), are associated with preservation of DosR antigen-specific, Th17 regulatory CD4 T cell responses.
3. Undertake a comparative analysis of the DosR antigen-specific Th17 regulatory and proinflammatory response in cohorts I and 2 with responses to the Mycobacterium tuberculosis (Mtb) immunodominant secretory antigen ESAT6/CFP10 as well as recall response to stimulation with BCG vaccine, which can stimulate responses to multiple T cell epitopes of Mtb antigens.

Substudies (Continued)

Markers of Lung Impairment in HIV-TB Coinfected Indian Adults

Principal Investigators	Sites	Population	Funding
Akshay Gupte (BU) Amita Gupta (JHU) Sanjay Gaikwad (BJGMC) Rajesh Karyakarte (BJGMC)	BJGMC	1. Adults (>18 years) with drug-susceptible pulmonary TB and HIV co-infection (HIV-TB group). 2. Adults with drug-susceptible pulmonary TB without HIV co-infection (TB group).	TREAT Asia NIAID/amfAR DBT

Design: A retrospective cohort study of already collected clinical samples and data from the CTRIUMPH study at BJGMC. BJGMC, Pune, India

Aims:

1. We will compare the degree of lung impairment between HIV-TB and TB participants at the completion of TB therapy. Lung impairment will be measured by pre-and post-bronchodilator spirometry. The primary outcome will be z-score standardized FEVI using the Global Lung Initiative (GLI) reference equations. Secondary outcomes will include z-score standardized FVC and FEV1/FVC ratio. We will use linear regression to compare the degree of lung impairment in TB cases with and without HIV, adjusting for potential confounders. With 15 HIV-TB and 30 TB participants, we will have 80% power at 5a % significance level to detect a 4.5 or higher percentile difference in lung function parameters between the two groups.
2. We will compare concentrations of inflammatory and metabolomic markers between HIV-TB and TB participants during TB therapy. Marker concentrations will be measured at individual time-points

Status: Sample testing completed; analysis ongoing

Inflammasome Genetics and Tuberculosis Treatment Outcomes

Principal Investigators	Sites	Population	Funding
Gregory Bisson (UPenn) Amita Gupta (JHU) Akshay Gupte (BU) Luke Hanna (NIRT) Subash Babu (NIH-NIRT-ICER) Vijay Vishwanathan (MVDRC) Sanjay Gaikwad (BJGMC) Rajesh Karyakarte (BJGMC)	BJGMC NIRT MVDRC	Adults (>18 years) with drug-susceptible pulmonary TB enrolled in the CTRIUMPH or EDOTS studies.	RICC

Design: Retrospective case-cohort analysis of already collected clinical samples and data from the CTRIUMPH and EDOTS studies.

Aims:

1. To determine the association between single nucleotide polymorphisms (SNPs) in candidate genes related to inflammasomes and microbiologic treatment outcomes in adults being treated for drug-susceptible pulmonary TB.
2. To determine the association between SNPs in candidate genes related to inflammasomes and pulmonary involvement in adults who successfully complete treatment for a new diagnosis of drug-susceptible pulmonary TB.

Status: Sample testing & analysis completed; manuscript in draft

Substudies (Continued)

Molecular Signatures of Tuberculosis-Diabetes Interaction (MSTDI) Study—Metabolomics

Principal Investigators	Sites	Population	Funding
Amita Gupta (JHU) Akshay Gupte (BU) Hardy Kornfeld (UMass) Rajesh Karyakarte (BJGMC) Padma Chandrasekaran (NIRT) Vidya Mave (BJGMC-JHU CRS) Bruno Andrade (RePORT Brazil)	NIRT BJGMC MVDRC RePORT Brazil	1. TB with DM (TBDM) 2. TB without DM (TB) 3. DM without TB (DM) 4. Healthy controls (HC)	RICC

Design: We will conduct a retrospective cohort study using collected demographic and clinic data and archived whole blood samples in the CTRIUMPH study as well as a small cross-sectional study of MTB uninfected adults with DM.

Aims:

1. Compare baseline metabolomic signatures between newly diagnosed drug-sensitive PTB patients with and without DM.
2. Characterize and compare longitudinal change in metabolomic signatures in response to A TT between newly diagnosed drug-sensitive PTB patients with and without DM.

Status: Testing & analysis completed; manuscript in draft

Molecular Signatures of Tuberculosis-Diabetes Interaction (MSTDI) Study—Transcriptomics

Principal Investigators	Sites	Population	Funding
Amita Gupta (JHU) Akshay Gupte (BU) Hardy Kornfeld (UMass) Rajesh Karyakarte (BJGMC) Padmapriyadarsini Chandrasekaran (NIRT) Vidya Mave (BJGMC-JHU CRS) Bruno Andrade (RePORT Brazil)	NIRT BJGMC MVDRC RePORT Brazil	1. TB with DM (TBDM) 2. TB without DM (TB) 3. DM without TB (DM) 4. Healthy controls (HC)	RICC

Design: We will conduct a retrospective cohort study using collected demographic and clinic data and archived whole blood samples in the RePORT India and RePORT Brazil study.

Aims:

1. Compare baseline whole blood RNA-seq transcriptional signatures between newly diagnosed drug-sensitive PTB patients with and without DM in Pune and Chennai, India and Salvador, Brazil.
2. Characterize and compare longitudinal change in transcriptional signatures in response to A TT between newly diagnosed drug-sensitive PTB patients with and without DM in Chennai, India.

Status: Testing & analysis completed; manuscript in draft

Immune Responses & Effect of Disulfiram on MTB Infected PBMCs: Disulfiram as a Potential Host Directed Therapy

Principal Investigators	Sites	Population	Funding
Amit Singhal (Singapore Immunology Network, Agency for Science, Technology and Research [A*STAR]) Ramandeep Singh (NCR Biotech Science Cluster) Rajesh Karyakarte (BJGMC) Amita Gupta (JHU) Padmapriyadarsini Chandrasekaran (NIRT) Vidya Mave (BJGMC-JHU CRS)	NIRT BJGMC	1. Adult PTB patients on TB treatment with an AUDIT score ≥ 8 (n = Up to 20) 2. Adult PTB patients on TB treatment with an AUDIT score < 8 (n = Up to 40) 3. Adult healthy contacts (n=Up to 20)	DBT NIH

Design: We will conduct a cross-sectional study using already collected CTRIUMPh and RePORT India common protocol data (baseline demographic, clinical) and archived whole blood PBMC samples from the baseline visit to assess those with and without harmful use of alcohol as assessed by AUDIT scores 2::8. immunophenotyping will be performed by flow cytometry. Additional plasma cytokine and chemokine will also be considered.

Aims:

1. To assess immune responses among adult PTB patients with harmful alcohol use defined by an AUDIT score >=8 compared to those with AUDIT scores < 8 at the time of treatment initiation.
2. Aim 2: To assess the effects of disulfiram on Mtb growth in PBMCs of alcoholic and nonalcoholic individuals

Status: Study discontinued

Substudies (Continued)

Evaluation of a Urinary Biomarker Assay for Diagnosis and Test of Cure for Tuberculosis

Principal Investigators	Population	Funding
Jeffrey Tornheim (JHU) Sanjay Gaikwad (BJGMC) Rajesh Karyakarte (BJGMC) Aarti Kinikar (BJGMC) Vidya Mave (BJGMC-JHU CRS)	Stored samples	NIH CFAR

Design: We will conduct a case-control diagnostic study nested within the CTRIUMPh cohort study using stored urine samples to identify positive results by the urine FujiLAM, conventional LAM, and the LAM and ESAT-6 nanocage assays. Samples have been collected from patients at multiple time points during treatment, and we will evaluate samples at enrollment (start of treatment), 2 months into treatment, and at the end of treatment (6 months).

Aims::

1. To assess the ability of the FujiLAM kit and a urine lipoarabinomannan glycan (LAM) nanocage assay and a urine ESAT-6 nanocage assay to diagnose tuberculosis (TB) among Indian adults and children with HIV and CD4 counts >100 as well as among age-matched Indian TB patients without HIV,
2. To compare the TB treatment response as measured by urine LAM and ESAT-6 nanocage assays to TB treatment response as measured by sputum conversion, radiographic improvement, and clinical improvement among Indian TB patients with HIV and CD4 counts> 100 as well as among age-matched Indian TB patients without HIV.
3. (Exploratory): To assess the ability of FujiLAM kits and urine LAM and ESAT-6 nanocage assays to diagnose pediatric TB in Indian children with confirmed and unconfirmed TB.

Status: Complete

A Nanopore Biosensor for Leveling MTB Antigens in Blood

Principal Investigators	Sites	Population	Funding
Tony Ye Hu (Tulane U) Robert C Bollinger (JHU) Amita Gupta (JHU) Rajesh Karyakarte (BJGMC)	BJGMC Tulane U JHU	The purpose of the CTRIUMPH study was to evaluate the risk factors for TB among adults and children < 15 in India. Three cohorts were established: 1. Active TB cohort included adults with newly diagnosed active pulmonary TB (PTB) and children with TB 2. Household contacts cohort enrolling household members of active TB cases Stored plasma samples from participants enrolled in these three cohorts at the Pune site will be utilized for the proposed study for assessment and the performance of the portable prototype system of the protein-based nanopore technology to quantify Mtb target peptides. These CTRIUMPH samples, as well as their linked clinical and microbiological data, will be analyzed to evaluate the performance of the peptide detection assay.	NIH R01

Design: This ROI will employ components of our current platform in a study to develop and optimize a robust and portable protein nanopore-based platform (QuantiPep) that meets WHO guidelines for new TB diagnostics and which can sensitively detect Mtb antigens in adult and pediatric blood samples. Shifting the assay from a mass spectrometry- to a nanopore-based system will allow rapid, sensitive and cost-effective TB detection and management in leaner clinical environments worldwide. Single channel recording technology is sensitive, specific, fast and affordable alternative to mass spectrometry. Nanopore ion currents are very sensitive to target molecule interactions as they occupy and translocate through the pore, and such interactions can generate signatures (current-time relationships) that are characteristic for a given target.

Aims:

1. Develop a sensitive and specific QuantiPep TB assay suitable for resource-limited settings:
2. Validate Mtb antigen-derived peptides for TB diagnosis in a well-characterized cohort of adults and children with serially collected clinical, radiological and bacteriological data.
3. Evaluate how serum levels of Mtb antigens change in adult PTB cases in during anti-TB therapy.

Status: Samples sent; analysis ongoing

Substudies (Continued)

Identification of Biomarkers that Can Predict Progression from Latent TB Infection to Active TB Disease

Principal Investigators	Sites	Population	Funding
Subash Babu (NIH-NIRT-ICER) Rajesh Karyakarte (BJGMC) Vidya Mave (BJGMC-JHU CRS) Luke Hanna (NIRT) Padmapriyadarsini Chandrasekaran (NIRT) Amita Gupta (JHU)	NIRT BJGMC NIH-NIRT-ICER	Adult and child household contacts of adult PTB cases from India enrolled in CTRIUMPh study: 1. HHCs of adult PTB cases, who progressed to active TB disease 2. HHCs of adult PTB cases, who did not progress to active TB disease	ICMR DBT NIH

Design: Case-control analysis of stored specimens and associated data between progressors and non-progressors

Aims:
1. To measure the plasma biomarker profiles at baseline in HHC who progress versus those who do not.
2. To profile microRNAs at baseline in HHC who progress versus those who do not.
3. To measure the unstimulated, TB-antigen, and mitogen-stimulated cytokine and chemokine responses at baseline in HHC who progress versus those who do not.
4. To measure the unstimulated, TB-antigen, and mitogen-stimulated growth factors and other immune factors at baseline in HHC who progress versus those who do not.

Status: Study closed; first paper published; second manuscript with miRNA in draft

Biomarkers for Tuberculosis Diagnosis and Treatment Response

Principal Investigator	Sites	Population	Funding
Jyothi Rengarajan (Emory)	NIRT BJGMC JHU Emory	Stored samples of participants enrolled in the Active TB cohort and Household contact cohort in the CTRIUMPh study	RePORT India

Design: Cross-sectional longitudinal study

Aims:
1. To evaluate biomarker performance on PBMCs from confirmed pulmonary TB and difficult-to-diagnose cases such as sputum smear-negative and HIV-infected individuals, extrapulmonary and pediatric TB patients.
2. To assess the ability of our biomarkers to monitor treatment response by selecting PBMCs from a subset of adult ATB patients, obtained at Time O (pre-treatment) and 1, 2, 6, and 12 after treatment initiation.
3. To use comprehensive immune profiling by mass cytometry (CyTOF) and multiparameter flow cytometry on a subset of ATB and control samples, to generate antigen-specific signatures of Adult TB, with the goal of discovering new markers that could further increase the sensitivity of our candidate biomarkers, particularly for difficult-to diagnose TB cases.

Status: Study on hold

T-Cell Biomarkers and T-Regulatory Responses to Pediatric TB

Principal Investigators	Sites	Population	Funding
Jyothi Rengarajan (Emory) Vidya Mave (BJGMC-JHU CRS) Anju Kagal (BJGMC) Aarti Kinikar (BJGMC)	BJGMC	Stored samples of participants enrolled in the CTRIUMPh Pediatric Active TB cohort and RICC Pediatric study.	RICC

Design: We will use cryopreserved PBMC samples from CTRIUMPH cohorts: pediatric unconfirmed TB, confirmed TB, latent TB and no TB controls. We will also be leveraging the data and specimens from the RePORT International Coordinating Centre (RICC) Pediatric Diagnostic Cohort study at BJGMC, Pune and analyze PBMCs isolated from pediatric TB suspects.

Aims
1. Validate host T cell biomarkers for diagnosis of pediatric TB
2. Investigate the phenotype and functions of T-regulatory cells in pediatric TB

Status: Testing underway

Substudies (Continued)

Host RNA Expression for Diagnosis & Monitoring of Pediatric TB in Africa & India RICC Pediatric Transcriptomic Study

Principal Investigators	Sites	Population	Funding
Lesley Workman (U of Cape Town) Aarti Kinikar (BJGMC) Mandar Paradkar (BJGMC-JHU CRS) Syed Hissar (NIRT)	Cape Town BJGMC NIRT	Baseline samples from 365 South African children will be tested as part of the existing Levin biomarker validation study and are not budgeted here. Follow up samples from a subset of 200 South African children will be included as part of the proposed study.	RICC

Design: This study involves the collaboration of two RePORT consortia, South Africa and India, both high burden TB and TB-HIV settings with well-established pediatric cohorts of children with TB disease, together with the Imperial College group leading the current NIH-supported pediatric TB biomarker validation study.

Aims:

1. Primary Objectives: To derive and validate a global RNA expression signature for the diagnosis of pulmonary TB, and extra-pulmonary TB in children; and to identify longitudinal changes in RNA expression with TB treatment in children who have microbiologically confirmed or clinically diagnosed TB, using bio-banked samples from the South Africa and Indian cohorts and clinical information from the TB RePORT Common Protocol (CP) and India parent protocol databases.
2. Secondary Objectives: To establish a biorepository of samples that can be used for future pediatric TB diagnostic and pathogenesis studies.

Status: Testing complete; analysis ongoing

Residual Respiratory Impairment Following Pulmonary Tuberculosis: The Lung Health Sub-Study

Principal Investigators	Sites	Population	Funding
Rahul Lokhande (BJGMC) Shashikala Sangle (BJGMC) Sriram Selvaraju (NIRT) Akshay Gupte (BU) Amita Gupta (JHU)	BJGMC NIRT	1. Active TB cohort comprising 400 new adult pulmonary TB (PTB) cases. 2. Reference cohort comprising 400 adults without TB. 3. Cohort of 200 adults with chronic obstructive pulmonary disease (COPD) Each study site will enroll approximately 50% of the total sample size. COPD controls will be enrolled at BJGMC only.	NHLBI K99

Design: Prospective cohort study nested within the CTRIUMPH study.

Aims:

1. To characterize trends in respiratory impairment among new adult PTB cases undergoing anti-tuberculous treatment (ATT) in India.
2. To identify host factors measured during the first 2 months of ATT initiation that are associated with respiratory impairment at ATT completion among new adult PTB cases in India.
3. To explore the impact of TB disease; alone and in combination with smoking exposure, indoor air pollution (IAP) exposure, HIV infection and diabetes mellitus (DM); on respiratory impairment up to 42 months following ATT completion among successfully treated adult PTB cases in India.
4. Characterize the chronicity and progression of lung impairment, and its responsiveness to bronchodilator therapy, in successfully treated PTB cases

Status: Study ongoing; 2 papers published

Substudies (Continued)

Characterization of Genomics and Metabolomics among Individuals Highly Exposed, but Resistant to Mtb Infection (TB-GWAS)

Principal Investigators	Sites	Population	Funding
Neel Gandhi (Emory) Yan Sun (Emory) Sanjay Gaikwad (BJGMC) Rajesh Karyakarte (BJGMC) Amita Gupta (JHU) Vidya Mave (BJGMC-JHU CRS) Padmapriyadarsini Chandrasekharan (NIRT) Neil Martinson (Perinatal HIV Research Unit, SA)	BJGMC JIPMER BMMRC	Household contacts of adult pulmonary TB cases from parent protocols study, RePORT India Common Protocol phase I at all sites; and Prospective TB GWAS study enrollments at BJGMC, Pune site.	NIH R01

Aims:

1. To characterize a phenotype for resistance to Mtb infection using TST and IGRA results among household contacts recently exposed to TB.
2. To determine genetic predictors for resistance to Mtb infection.
3. To identify metabolomic markers associated with resistance to Mtb infection.

Status: Epi analysis final; GWAS analysis ongoing; Metabolomic samples shipped from BJGMC to Medgenome in April for further transfer along with other site/CP CBR samples, to Emory

Identifying TB Treatment Response Biomarkers Using qRT-PCR Signature for TB Treatment Response and TB NanoString for Tx

Principal Investigators	Funding
Hardy Kornfeld (UMass) Padmini Salgame (Rutgers)	RICC

Design: To validate five signatures (RESPONSE5, ACS6, RISK4, Khatri 3-gene, and Maertzdorf4-gene) as blood biomarkers in predicting TB treatment response to favorable and unfavorable treatment outcomes in the RePORT cohorts

Aims: To develop a promising blood biomarker for identifying response to TB treatment among active TB cases

Status: Analysis ongoing

Proteomic Discovery of Protein-based TB Recurrence and Death Signatures (IIT-M Proteomics Study)

Principal Investigators	Funding
Sanjeeva Srivastava (IIT-Bombay) Sonia Krishnan (JHU) Amita Gupta (JHU) Mandar Paradkar (BJGMC-JHU CRS) Sanjay Gaikwad (BJGMC) Rajesh Kayakarte (BJGMC) Vandana Kulkarni (BJGMC-JHU CRS)	DBT NIH Phase 2

Aims: To identify markers of TB recurrence/death by mass spectrometry

Status: Specimen processing complete; mass spectrometry to be performed at ITT Mumbai

Substudies (Continued)

The Role of Innate Immunity in the Acquisition of Sterile Protection Against TB Infection

Principal Investigators
Adriana Weinberg (University of Colorado)
Vandana Kulkarni (BJGMC-JHU CRS)
Rajesh Kayakarte (BJGMC)

Funding
NIH R21

Design: To identify potential targets for new TB vaccines by characterizing the immune responses that distinguish individuals with sterilizing protection against TB (TB-resisters), defined by presence of TB-specific immune responses and absence of latent infection, from individuals with latent TB infection (LTBI-participants)

Status: Study closed; paper published

Epidemiologic Factors Associated with TB Treatment Outcomes across RePORT International Consortia

Principal Investigators
Bruno Andrade (RePORT Brazil)
Timothy Sterling (RePORT Brazil)
Mark Hatherill (RePORT South Africa)
Thomas Scriba (RePORT South Africa)
Amita Gupta (RePORT India)
Sonali Sarkar (RePORT India)
Retna Mustika Indah (RePORT Indonesia)
Muhammad Karyana (RePORT Indonesia)
Yuhong Liu (RePORT China)
Jingtao Gao (RePORT China)
Marrissa Alejandria (RePORT Philippines)
Ray (Sang Nae) Cho (RePORT Philippines)

Funding
RICC

Design: Analysis of data collected from a prospective multi-site cohort study to determine the Impact of key non-communicable and communicable diseases on tuberculosis treatment outcomes and recurrence using data from multiple RePORT International consortia

Aims:
1. To create a harmonized analytical dataset from multiple RePORT International consortium sites
2. To determine the Impact of non-communicable diseases, including prediabetes and diabetes mellitus, and communicable diseases, including HIV, on tuberculosis treatment outcomes and recurrence, both globally and regionally

Status: Analysis ongoing

Therapeutic Outcomes with Second Line Drug Exposures in a Cohort of Patients with Drug Resistant TB: A Pharmacokinetic-Pharmacodynamic Assessment

Principal Investigators
Tester F. Ashavaid (Hinduja)
Camilla S. Rodrigues (Hinduja)
Neil Martinson (PHRU, SA)
Ebhrahim Variava (PHRU, SA)

Sites
Hinduja (India)
PHRU (South Africa)

Population
Cohort A: Adults and adolescents ≥15 years of age with MDR-TB (n=200)

Funding
SA MRC
DBT

Design: The study is designed to study the pharmacokinetic (PK) and pharmacodynamics (PD) profiles of second line TB drugs and develop PK-PD models to help understand efficacy of these drugs.

Aims:
1. To determine the pharmacokinetic parameters of second-line agents in South African and Indian patients receiving DR-TB treatment regimens with particular attention to moxifloxacin, linezolid, clofazimine, bedaquiline and SLI (Kanamycin, Amikacin)
2. To assess the MIC of these drugs using Thermoscientific Fisher Sensititre panels.
3. To characterize the population pharmacokinetics of these drugs in the study population and determine factors associated with low drug exposures
4. To study the association between drug exposures of second-line TB drugs and therapeutic outcomes in a pharmacokinetic-pharmacodynamic analysis among patients with DR-TB

Status: Data analysis ongoing

Substudies (Continued)

MDR-TB Free: Monitoring Adverse Effects, Utilizing Resources Optimally, Knowing Resistance Patterns, and Treatment Strategy (MDR TB MUKT)

Principal Investigators	Sites	Population	Funding
Zarir F. Udwadia (Hinduja) Camilla S. Rodrigues (Hinduja) Tester F. Ashavaid (Hinduja) Amita Gupta (JHU) Jeffrey A Tornheim (JHU)	Hinduja	1. Cohort A: Adults and adolescents ≥15 years of age with MDR-TB (n=200). 2. Cohort B: Adult and child household contacts of MDR-TB Cohort A participants with pulmonary TB (n=60).	Hinduja Foundation RePORT India NIH: K23

Design: This study is comprised of two prospective observational cohorts. Cohort A will enroll adults and adolescents ≥15 years with active multidrug resistant tuberculosis (MDR-TB). Cohort B will enroll adult and child household contacts of participants in Cohort A pulmonary MDR-TB cases.

Aims: To establish well-characterized prospective cohorts of active MDR-TB cases and their household contacts with associated biorepositories.

Cohort A Primary Objectives: To document participant outcomes including early treatment response, MDR-TB treatment-associated adverse events, mortality, and loss to follow-up.

Cohort B Primary Objectives: To assess rates of prevalent and incident TB infection and disease in household contacts of MDR-TB cases.

Cohort A Secondary Objectives

1. To evaluate the impact of comorbid diseases including diabetes mellitus, prediabetes, HIV, COPD, smoking status, alcoholism, depression, quality of life, and malnutrition on treatment outcomes and TB treatment-associated adverse events.
2. To assess the genotype-phenotype correlation among resistant TB isolates through MIC-based phenotypic drug susceptibility testing and next generation sequencing of TB isolates, including assessment of strain evolution, drug susceptibility pattern changes during treatment, and impact of strain on treatment outcomes.
3. To derive pharmacokinetic parameters of second-line agents in participants receiving multidrug treatment regimens with particular attention to linezolid, clofazimine, high-dose moxifloxacin, aminoglycosides, and any new drugs that become available including bedaquiline and delamanid.
4. To assess host biomarkers of treatment response and correlates of progression from exposure to TB disease using multiomics approaches (e.g. transcriptomics, metabolomics, cellular markers, and immunity- and inflammation-associated soluble biomarkers).
5. To assess microbial markers of treatment response including smear and culture conversion, quantitative burden, and the time to conversion.
6. To assess standard and novel imaging approaches to monitor treatment responses.
7. To assess the impact of TB on the quality of life and mental health of subjects with MDR-TB, and in turn their impact on treatment adherence and outcomes.
8. To assess host immune responses to and inflammation following TB exposure and TB treatment and correlate these responses with clinical outcomes.
9. To ascertain true outcomes and self-reported barriers to treatment retention of MDR-TB participants lost to follow-up (>=2 consecutive months of missed visits) during treatment through prospective phone follow-up and/or home visits.

Cohort B Secondary Objectives

1. To determine the feasibility of enrolling household contacts of index adult MDR TB cases.
2. To explore the proportion of contacts with prevalent TB disease and infection, what proportion develop new TB disease and infection during follow-up, and what are prevalent comorbidities (diabetes mellitus, prediabetes, HIV, COPD, smoking status, alcoholism, depression, quality of life, and malnutrition) among the household contacts.
3. To contribute samples to a global repository for the study of biomarkers of incident TB and progression from exposure to TB disease using multiomics approaches (e.g. transcriptomics, metabolomics, cellular markers, and immunity- and inflammation-associated soluble biomarkers).

Status: Multiple papers published & multiple in draft; supported success of BRASS-TACS study

Substudies (Continued)

Impact of Latent TB Infection and Trained Immunity on Susceptibility to SARS-CoV- 2 Infection in India and the Philippines

Principal Investigators	Sites	Population	Funding
Padmini Salgame Sonali Sarkar Alejandria Marcelo Marissa	JIPMER University of the Philippines	HHCs of pulmonary TB patients from RePORT India Phase I studies; Index COVID cases and their HHCs (Philippines)	RICC

Design: About 300 household contacts of pulmonary TB patients enrolled through RePORT Phase 1 studies will be reconsented and stratified into 4 groups based on the presence of LTBI +/- and SARSCoV +/-. About 300 SARS-CoV-2 positive patients identified from the hospital database (index cases) and an additional 250 of their household contacts will be enrolled in Philippines. For each of the 4 groups, 20 subjects will be selected and the trained immunity of their monocytes and NK cells will be examined.

Aims:

1. Examine whether there is a correlation between LTBI and SARS-CoV-2 IgG seroconversion and/or COVID-19 disease severity
    1. In India, determine the seroprevalence of COVID-19 in healthy household contacts of prior active PTB cases stratified according to the presence of LTBI
    2. In the Philippines, determine the prevalence of LTBI in patients with confirmed COVID-19 infection and in their household contacts; and the association of LTBI with disease severity
2. Examine in a subset if enhanced trained immunity in LTBI positively correlates with protection from SARS-CoV-2 infection

Abdominal and Thoracic Ultrasound for the Diagnosis of Pulmonary and Extra-pulmonary Tuberculosis. Assessing the Accuracy of Point-of-care Ultrasound for the Diagnosis and Therapy Monitoring in Patients with Presumed Tuberculosis in India and Germany

Principal Investigators	Sites	Population
D.J. Christopher (India) Claudia M. Denkinger (Germany)	CMC Vellore, India Heidelberg University, University Clinics Cologne University Clinics Frankfurt, Germany	Patients aged 18 years or older presenting with: clinical constellation compatible with Pulmonary (PTB) and extra-pulmonary TB (EPTB)

Design: A prospective, multicentre study (Germany, India), we will enroll patients with presumed active TB of any anatomic site and in both in- and outpatient settings.

Objectives:

- To assess the accuracy of the FASH-protocol for diagnosing TB in extra-pulmonary sites (i.e. abdominal lymph nodes, splenic micro-abscesses, pleural or pericardial effusions, liver micro-abscesses) using a microbiological reference standard (MRS), an extended microbiological (eMRS) and composite reference standard (CRS) in presumptive adult TB-patients in Germany and separately in India
- To assess the accuracy of lung ultrasound for the diagnosis of pulmonary tuberculosis (unilateral large pleural effusion, especially with stranding, subpleural nodules (SUN) pattern, consolidation with an additional sign of TB (SUN, abdominal nodes, splenic lesions, pericardial effusions)) using a microbiological (MRS), extended microbiological (eMRS) and composite reference standard (CRS) in presumptive adult TB-patients in Germany and separately in India

Dynamics and Immune Mechanisms of QFT Response in Close Contacts of TB Cases

Principal Investigators	Site	Population	Funding
Padmini Salgame (Rutgers) Sonali Sarkar (JIPMER) Vidya Mave (BJGMC)	JIPMER BJGMC	HHCs of TB patients	NIH

Design: Establish a prospective observational cohort of 1000 household contacts (HHC) of TB patients at JIPMER and BJMC. The proposed cohort will be classified after 12 months of follow-up into four groups: sustained QFT negatives, sustained QFT positives, QFN converters and QFN reverters.

Objectives:

1. Determine the clinical implications of dynamic changes in the QFT response in 12 months following close contact with a TB patient.
2. Examine if dynamic changes in the QFT response are associated with activation of phenotypically and functionally distinct subsets of T cells.
3. Examine if the dynamic changes in the QFT response are associated with altered macrophage anti-mycobacterial effector responses.

Status: In progress

Substudies (Continued)

Analysis of Host Biomarkers Associated with Adverse TB Treatment Outcomes Across RePORT International Sites

Principal Investigators			Funding
Sheetal Verma (Rutgers) Senbagavalli Prakash Babu (JIPMER) Artur Queiroz (Oswaldo Cruz Foundation, Brazil) Mariana Araújo-Pereira (Oswaldo Cruz Foundation, Brazil)	Beatriz Barreto-Duarte (Oswaldo Cruz Foundation, Brazil) Simon Mendelsohn (South African Tuberculosis Vaccine Initiative) John Carlo Malabad (University of Philippines-Manila)	Erlina Burhan (INA RESPOND, Persahabatan Hospital) Sri Ram Pentakota (Rutgers) Dr. Arthur Vanvalkenburg (Rutgers)	RiCC

Design: Host biomarkers will be assessed in nested case-control cohorts using archived Paxgene RNA and plasma samples from Common protocols that were collected at baseline and treatment month 2 and 6; Participants with microbiological treatment failure or recurrence will be matched 1:2 with controls with lasting cure. Samples from EOT will assess the risk of recurrence after cure. Testing at baseline addresses response prediction prior to ATT initiation. Month-2 evaluates response kinetics, that may provide insights into mechanisms of treatment failure when analyzed in the context of host and microbial parameters. Testing at month-6 is an approach to confirm cure and predict recurrence at ATT completion.

Aims:

1. To validate a small panel of host blood RNA signatures that predict the outcome of tuberculosis treatment using the Fluidigm (Standard Biotools™) platform.
2. To develop a parsimonious and generalizable signature of failure from a large panel of existing signatures using the digital NanoString platform.
3. To validate host blood protein signatures that predict the outcome of tuberculosis treatment using Luminex platform and derive a reduced proteome signature.
4. To develop a novel "cure" signature using RNA-seq as a discovery-based approach.

Status: In preparation

Rapid Research in Diagnostics Development for TB Network (R2D2 TB Network) Study

Principal Investigators	Sites	Population	Funding
D.J. Christopher (India) Adithya Cattamanchi (USA) Payam Nahid (USA) Claudia Denkinger (Germany)	CMC Vellore, India Hanoi Lung Hospital, Vietnam De La Salle Medical and Health Sciences Institute, Philippines Stellenbosch University, SA Makerere University College of Health Sciences, Uganda	Adult outpatients (age ≥18 years) with cough ≥2 weeks' duration, a commonly accepted criterion for identifying patients with presumed pulmonary TB	NIH

Design: For the novel TB triage and diagnostic tests, we will conduct large-scale evaluation of design-locked tests in a cohort of adults with presumed TB, with nested feasibility/pilot studies of early and late prototype tests. The large-scale evaluation is a prospective cross-sectional study of 3,000 participants (600/clinical study site).

Objectives:

1. To conduct pilot studies of the diagnostic accuracy and usability of early and late prototypes of novel TB tests in settings of intended use to inform their further development.
2. To conduct large-scale validation studies of the diagnostic accuracy and usability of design-locked novel TB tests to inform policy development.

Our study hypotheses are:

1. Early and late prototypes of novel TB tests will meet pre-specified decision thresholds for advancement to the next phase of assessment.
2. Design-locked novel TB tests will meet updated WHO target product profile (TPP) requirements for minimum diagnostic accuracy.

Status: Study ongoing; paper published

Substudies (Continued)

Predictors of Resistance Emergence Evaluation in Multidrug Resistant-Tuberculosis Patients on Treatment (PREEMPT)

Principal Investigators	Sites	Population	Funding
Zarir F. Udwadia (Hinduja) Camilla S. Rodrigues (Hinduja) Tester F. Ashavaid (Hinduja) C. Robert Horsburgh (BU)	NIRT (India) BJGMC (India JIPMER (India) Hinduja (India) NEGRIMS (India) YRJCARE (India) INI – FIOCRUZ (Brazil) UFRJ (Brazil)	Adult PTB MDR patients on TB treatment (N=400 for India and 200 for Brazil)	NIH: R01

Design: In this observational cohort study, we propose to study the contribution of potential causes to resistance and develop the knowledge base required to stop resistance from developing by analyzing AUC and sputum samples.

Aims:

1. Determine whether low serum antimycobacterial drug concentrations are associated with the clinical emergence of drug resistance in MDR-TB patients.
2. Determine whether HIV seropositivity is a risk factor for low serum drug concentrations.
3. Determine the contribution of increased DNA mutation to clinical emergence of drug resistance in patient isolates.
4. Determine the earliest time at which mutations responsible for drug resistance can be detected during treatment

Status: Enrollment of 400 complete; follow up ongoing

Whole Genome Sequencing of Drug Resistant Tuberculosis in India: Genotype-Phenotype Correlation, Clinical Impact of Resistance, and Sequencing Directly from Sputum (K23)

Principal Investigators	Sites	Population	Funding
Camilla S. Rodrigues (Hinduja) Jeffery A. Tornheim (JHU)	Hinduja	Cohort A (MDR-TB MUKT): Adults and adolescents ≥15 years of age with MDR-TB (n=200)	NIH: K23

Design: The K23 analysis will correlate mutations identified by whole genome sequencing with both MGIT and MIC drug susceptibility test results, correlate those results with plasma drug levels and participant outcomes, and compare the results obtained by sequencing the isolates without culture to those obtained by sequencing MGIT cultures and solid cultures.

Aims

1. To characterize MIC distribution for mutations identified on WGS in Indian MDR-TB strains and compare the frequency and predictive value of WGS-derived mutations in Mtb isolates from Indian MDRTB patients with those from South African MDR-TB patients in the ReSeqTB Data Platform.
2. To assess the impact of partial resistance (identified by WGS and MIC-testing) and drug exposures (using PK-PD analysis) on patient outcomes in a cohort of MDR-TB patients.
3. To assess a new direct-from-sputum method for WGS compared to culture-based WGS for DST.

Status: Sample processing complete; Data analysis ongoing

Validation of Transcriptional Signature to Predict Active TB Disease among Advanced HIV Patients

Principal Investigators	Funding
Vandana Kulkarni (BJGMC-JHU CRS)	RICC

Design: The 1:1 case-control study to assess the performance of the 15 gene signature to detect TB among patients with advanced HIV. The cases would be advanced HIV patients (CD4 <100 cells/ul) with confirmed active TB and controls would be advanced HIV patients without any clinical and microbiologic evidence for active TB. The study was performed at BJGMC, Pune, India, Rio de Janeiro and Manaus at Brazil.

Study Exploratory Objectives: To assess and compare changes in the T cell activation of HLA-DR+ and CD38+ T cell subsets, cytokine profiles of inflammatory markers and co-relate blood transcriptional and cytokine signatures of TB among advanced HIV patients with or without TB.

1. To conduct testing and validation of the 15-gene signature to predict active TB disease among advanced HIV patients with CD4 <100 cells/ul.
2. To assess and compare the cytokine/chemokine signature that may be predictive for active TB among advanced TB-HIV and HIV patients in India and Brazil.

Status: Study complete; paper published

Substudies (Continued)

Pharmacokinetic Assessment of MDR-TB Drugs in the Treatment of TB Meningitis (MDR-TBM PK)

Principal Investigators	Sites	Population	Funding
Jeffrey A Tornheim (JHU) Tester F. Ashavaid (Hinduja) Hongfei Duan (Beijing Chest Hospital) Ebrahim Variava (Perinatal HIV Research Unit) Rohidas Tanku Borse (BJGMC)	BJGMC Hinduja International Sites Johns Hopkins Beijing Chest Hospital PHRU Wits Health	Adult MDR TBM patients on TB treatment (N=70 all sites) - (Hinduja site n=20)	CRDF Global

Design: Patient suspected of TBM will be screened for the eligibility of enrolment in the study. Eligible participants will be consented, enrolled and followed up for a 6-month period after enrollment with a total of 8 clinical encounters each. On enrolment, a baseline lumbar puncture (LP) will be performed to confirm the diagnosis of TBM. If suspected patients have already undergone an LP, the sample will be retrieved from the labs and stored for biorepository. This LP will be a part of standard of care (SOC). For the PK studies, participants will be followed up for Week 1 & Week 4 with repeat LP. These LP may be as a part of SOC or for research use only for PK studies.

Aims:

1. Penetration coefficient of each drug into the CSF
2. Relationship between PK parameters, survival, and functional status.

Status: Sample processing ongoing

Baseline pRescription According to Direct from Sputum Sequencing and TArgeted drug Concentration Strategy (BRASS TACS)

Principal Investigators	Site	Population	Funding
Tester F. Ashavaid (Hinduja) Camilla S. Rodrigues (Hinduja) Zarir F. Udwadia (Hinduja) Jeffrey A. Tornheim (JHU)	Hinduja	Adult with Pulmonary RR/MDR-TB (n=210)	NIH: R01

Design: This study is an observational study of a combined treatment strategy informed by NGS, TDM, and MIC testing. The study will enroll adults starting treatment at Hinduja Hospital for RR/MDR-TB of the lungs. All data will be provided to clinicians to help personalize therapy. Outcome and side effect data will be compared to data from historical controls with MDR-TB enrolled in previous RePORT-India associated cohort studies at Hinduja Hospital using propensity score matching by disease severity and resistance to assess the impact of the BRASS TACS treatment strategy to outcomes among similar patients treated without this strategy.

Aims:

1. To determine the proportion of patients with MDR-TB in Mumbai, India with resistance-associated mutations that would prevent treatment with moxifloxacin, linezolid, bedaquiline, clofazimine, or cycloserine using culture-free NGS.
2. To identify the proportion of cohort participants with MDR-TB that achieve model-derived steady-state plasma levels meeting efficacy and toxicity targets.
3. To assess the time to final regimen, frequency of treatment-associated side effects, time to culture conversion, and final outcome of cohort participants who complete culture-free NGS and TDM.

Status: Beginning soon

Substudies (Continued)

Identification of M. tuberculosis and Prediction of Drug-resistance among Adults with Pulmonary Tuberculosis Using a Novel Urine Collection and Target Concentration Device, Followed by Cartridge-based Nucleic Acid Amplification Testing (Urigami and CBNAAT Study)

Principal Investigators	Site	Population	Funding
Tester F. Ashavaid (Hinduja) Camilla S. Rodrigues (Hinduja) Jeffrey A. Tornheim (JHU)	Hinduja	1. Adult PTB MDR patients on TB treatment (N=400 for India and 200 for Brazil) 2. Adult healthy contacts (n=Up to 20)	CFAR NIH: R21

Design: We will transfer the novel urine capture and affinity bait method developed at the Liotta Lab in the USA to the PD Hinduja National Hospital and Medical Research Centre in Mumbai, India where it will be used to assess the baseline and 6-month urine samples collected from newly diagnosed adults with drug susceptible pulmonary tuberculosis, as well as the de-identified baseline and 6-month urine samples collected from participants in the MDR-TB MUKT cohort with pulmonary MDR-TB and fluoroquinolone resistance stored in the MDR-TB MUKT biorepository. Specificity will be assessed by repeating the assay among de-identified samples collected from household contacts of pulmonary TB patients stored in the MDR-TB MUKT biorepository.

Aims:

1. To assess the diagnostic accuracy of the combination of a collapsible urine collection device with hydrogel nanocage affinity baits for Mtb cfDNA and the Xpert MTB/RIF and Xpert Ultra for the detection of pulmonary Mtb and rifampin resistance from freshly collected urine.
2. To assess the accuracy of this combination method to identify resistance to isoniazid, fluoroquinolones, and second-line injectable drugs using the Xpert XDR cartridge on de-identified samples in a well-characterized biorepository.
3. To implement this novel concentration technology in a high burden setting by transferring technology developed in a US laboratory to the Indian context. To achieve an analytical sensitivity for genomic DNA of 10 pg/mL in urine matrix.

Status: Study did not initiate due to delay in administrative approvals and lack of funding

InTGS: Whole Genome Sequencing of MTB Clinical Strains for Determining Drug Resistance and Strain lineage in India: A Structured Nationwide approach

Principal Investigators	Site	Population	Funding
Dr. Sonali Sarkar (JIPMER) Dr. Vinay Kumar Nandicoori (CCMB) Dr. Dhiraj Kumar (ICGEB) Dr. G. Aneeshkumar Arimbasseri (NII) Dr. Arindam Maitra (NIBMG) Dr. Camilla Rodrigues (P.D.Hinduja) Dr. S. Siva Kumar (NIRT)	JIPMER, NII, ICGEB, CCMB, NIBMG, BMMRC, BJGMC, PGI, Hinduja, NIRT	Cohort A participants of parent protocol from JIPMER, CMC, NIRT and BJGMC Microbiologically confirmed TB patients from participating sites	DBT

Design: We propose to use both retrospective and prospective approaches for sample collection. Retrospective approach will use samples collected under the Regional Prospective Observational Research in Tuberculosis (RePORT) India studies or samples (sputum/extra pulmonary specimens) from studies involving TB positive patients (smear/CBNAAT/TrueNat) from participating institutions. Prospective samples (MTB positive sputum/extra-pulmonary specimens), will be obtained from selected Intermediate Reference Laboratories (IRL) culture drug susceptibility testing (C-DST) centers and in-patient and out-patient departments of participating hospitals/institutions

Aims:

1. To perform WGS of 32,200 clinical strains from active TB patients and to develop a centralized biorepository of clinical MTB strains in India.
2. To map genetic diversity of pulmonary and extrapulmonary isolates of MTB from newly reported active TB cases in India and the associated treatment outcomes.
3. Association of mutations of MTBC to phenotypic drug resistance patterns.
4. To combine epidemiological data with WGS results to extract actionable public health data-driven information

Status: Ongoing study.

Substudies (Continued)

CRISPR - Multiplexed detection of cell-free M. tuberculosis DNA and its drug-resistant variants in blood

Principal Investigators	Site	Population	Funding
Prerna Arora (Hinduja) Jeffrey A Tornheim (JHU) Tony Hu (Tulane)	Hinduja Tulane JHU	Adults with drug resistant and drug susceptible disease and their household contacts	NIH R01

Design: A diagnostic accuracy and treatment response study nested within MDR-TB MUKT and BRASS TaCS to evaluate a novel assay to detect cell-free Mtb DNA fragments in the blood of people with active tuberculosis, to evaluate the ability of the same assay to detect markers of drug-resistance, and to assess the response to successful treatment using biorepository specimens.

Aims:

1. To optimize our CRISPR-TBD POC assay to analyze Mtb-cfDNA in blood samples.
2. To evaluate the performance of the CRISPR-TBD assay for TB diagnosis and treatment evaluation.
3. To conduct an in-field validation of the multiplex CRISPR-TBD POC assay in an Indian clinical laboratory whose population faces a high burden of drug resistant TB

Status: Laboratory work has begun, analysis anticipated in 2025

Understanding Mycobacterium tuberculosis Mediated Host Metabolomics in Pulmonary Tuberculosis: Correlation with Disease Severity and Treatment Course

Principal Investigators	Sites	Population
Senbagavalli Prakash Babu Sonali Sarkar	JIPMER IISER	Adult participants enrolled in the Active TB cohort (Cohort A) and Household contact (Cohort B) of common protocol phase I

Design: We will use plasma samples collected from common protocol cohorts to measure the metabolomic markers; active pulmonary TB (n=20) grouped as per disease severity (mild and severe) and their household contacts (n=10). For cohort A participants, samples will be analyzed at baseline, Month 1 and End of treatment; for cohort B at baseline

Aims

1. To study the differences in MTB influenced host metabolomics in mild and severe disease groups.
2. To study the dynamic changes of host metabolites at baseline, during and at the end of the standard anti-TB treatment regimen.
3. To examine whether there is a correlation between host metabolomics with disease severity and course of standard anti-TB treatment.

Innate immune response of LTBI+HIV+ children

Principal Investigators	Funding
Ramakrishna Vankayalapati	NIH R01

Description: Mycobacterium tuberculosis (Mtb) infects one-third of the world's population and causes almost 1.3 million deaths per year, including 100, 000 children. Approximately 90% of infected persons have latent tuberculosis infection (LTBI), have protective immunity and remain well, but 10% develop primary tuberculosis (TB) soon after infection or reactivation TB many years later. TB is the leading cause of death in HIV-infected persons and more than half a million coinfected people die annually. Children are more susceptible to TB infection, due to an immature immune system. HIV infection in children markedly increases susceptibility to TB. To develop adequate prophylaxis or therapy, it is important to understand immune responses to Mtb. Identification of HIV+ children with LTBI who are at greatly increased risk for development of TB would allow treating only high-risk children, facilitating completion of therapy for LTBI and preventing future development of TB. To identify these children, it is important to pinpoint the nature of the defective immune responses that permit development of active TB in HIV+LTBI+ pediatric patients. This proposal will identify a novel memory-like NK cell subpopulation mediated mechanisms that regulate immune responses and pinpoint the nature of the defective responses that permit development of active TB in HIV-LTBI+ and HIV+LTBI+ children. These studies will lay the groundwork for strategies to develop novel anti-tuberculosis vaccines that stimulate strong NK cell mediated immunity in HIV+ and HIV- children with LTBI, and reduce development of TB

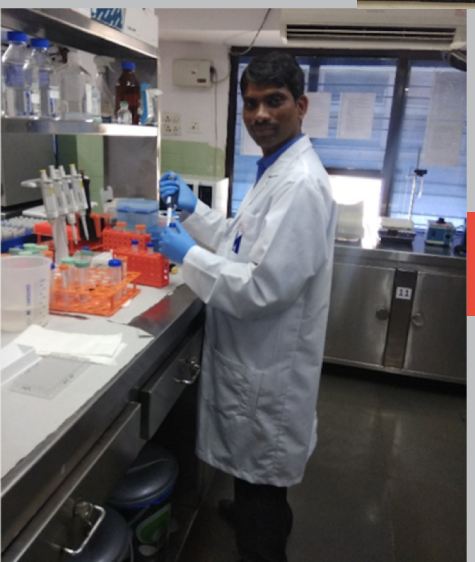
Publications

CMC Vellore

ICER Lab

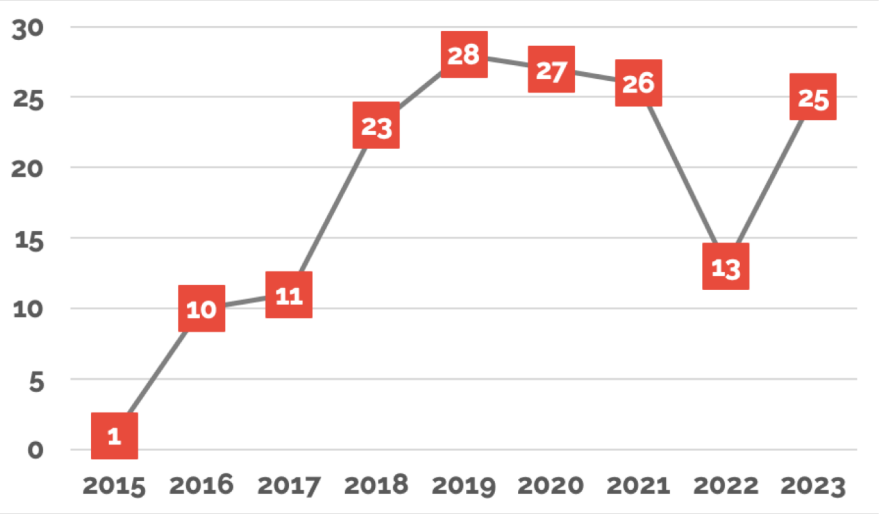
NIRT

JIPMER



BMMRC

Publications 2015-2023



2023 Publications

Publications for all years are accessible on RePORT India's website

Cross Country Collaborations

1. **A multi-center, prospective cohort study of whole blood gene expression in the tuberculosis-diabetes interaction**
   Queiroz ATL, Vinhaes CL, Fukutani ER, Gupte AN, Kumar NP, Fukutani KF, Arriaga MB, Sterling TR, Babu S, Gaikwad S, Karyakarte R, Mave V, Paradkar M, Viswanathan V, Gupta A, Andrade BB, Kornfeld H; RePORT Brazil; RePORT India Consortia. Sci Rep. 2023 May 12;13(1):7769. doi: 10.1038/s41598-023-34847-9. PMID: 37173394; PMCID: PMC10180618.
2. **The sound of silent RNA in tuberculosis and the lncRNA role on infection**
   Rocha EF, Vinhaes CL, Araújo-Pereira M, Mota TF, Gupte AN, Kumar NP, Arriaga MB, Sterling TR, Babu S, Gaikwad S, Karyakarte R, Mave V, Kulkarni V, Paradkar M, Viswanathan V, Kornfeld H, Gupta A, Andrade BB, Queiroz ATL; RePORT Brazil; RePORT India Consortia. iScience. 2023 Dec 8;27(1):108662. doi: 10.1016/j.isci.2023.108662. PMID: 38205253; PMCID: PMC10777062.

RePORT India Multi-site Collaborations

1. **Impact of undernutrition on tuberculosis treatment outcomes in India: A multicenter, prospective, cohort analysis**
   Sinha P, Ponnuraja C, Gupte N, Prakash Babu S, Cox SR, Sarkar S, Mave V, Paradkar M, Cintron C, Govindarajan S, Kinikar A, Priya N, Gaikwad S, Thangakunam B, Devarajan A, Dhanasekaran M, Tornheim JA, Gupta A, Salgame P, Christopher DJ, Kornfeld H, Viswanathan V, Ellner JJ, Horsburgh CR, Gupte AN, Padmapriyadarsini C, Hochberg NS. Clin Infect Dis. 2023 Apr 17;76(8):1483-1491. doi: 10.1093/cid/ciac915. PMID: 36424864; PMCID: PMC10319769.
2. **Impact of baseline nutritional status on tuberculosis severity in India: A multicenter prospective cohort analysis**
   Du X, Ponnuraja C, Gupte N, Sarkar S, Gupta A, Christopher DJ, Kornfeld H, Viswanathan V, Ellner J, Horsburgh CR Jr, Padmapriyadarsini C, Sinha P. 1953. Open Forum Infect Dis. 2023 Nov 27;10(Suppl 2):ofad500.107. doi: 10.1093/ofid/ofad500.107. PMCID: PMC10677348.

RePORT India Multi-site Collaborations

3. **Tuberculin test using Indian indigenous purified-protein derivative (PPD) shows only moderate agreement with international standard PPD**
   Christopher DJ, Priya N, Shankar D, Isaac B, DeLuca A, Sarkar S, Prakash Babu S, Samuel P, Cattamanchi A, Gupta A, Ellner J, Srinivasan S, Cox S, Thangakunam B. J Clin Tuberc Other Mycobact Dis. 2023 Dec 1;34:100404. doi: 10.1016/j.jctube.2023.100404. PMID: 38174327; PMCID: PMC10761766.

Byramjee Jeejeebhoy Government Medical College
National Institute for Research in Tuberculosis
Johns Hopkins University (CRUs 106 & 105)

1. **Characterising cause of death among people treated for drug-susceptible TB in India**
   Cox SR, Padmapriyadarsini C, Mave V, Seth B, Thiruvengadam K, Gaikwad S, Sahasrabudhe TR, Sane M, Tornheim JA, Shrinivasa BM, Lokhande R, Barthwal MS, Shivakumar SVBY, Krishnan S, Santhappan R, Kinikar A, Kakrani AL, Paradkar M, Bollinger RC, Sekar K, Gupte AN, Hanna LE, Gupta A, Golub JE. Int J Tuberc Lung Dis. 2023 Jan 1;27(1):78-80. doi: 10.5588/ijtld.22.0454. PMID: 36853129.

2. **Predictive performance of interferon-gamma release assays and the tuberculin skin test for incident tuberculosis: an individual participant data meta-analysis**
   Hamada Y, Gupta RK, Quartagno M, Izzard A, Acuna-Villaorduna C, Altet N, Diel R, Dominguez J, Floyd S, Gupta A, Huerga H, Jones-López EC, Kinikar A, Lange C, van Leth F, Liu Q, Lu W, Lu P, Rueda IL, Martinez L, Mbandi SK, Muñoz L, Padilla ES, Paradkar M, Scriba T, Sester M, Shanaube K, Sharma SK, Sloot R, Sotgiu G, Thiruvengadam K, Vashishtha R, Abubakar I, Rangaka MX. EClinicalMedicine. 2023 Jan 5;56:101815. doi: 10.1016/j.eclinm.2022.101815. PMID: 36636295; PMCID: PMC9829704.

3. **Sex differences in TB clinical presentation, drug exposure, and treatment outcomes in India**
   Deshmukh S, Sane M, Gaikwad S, Sahasrabudhe T, Barthwal M, Lokhande R, Raskar S, Kagal A, Dharmshale S, Pradhan N, Gupte A, Alfarisi O, Gupta A, Dooley KE, Gupte N, Golub JE, Mave V. Chest. 2023 Apr;163(4):778-789. doi: 10.1016/j.chest.2022.09.024. Epub 2022 Sep 26. PMID: 36174745; PMCID: PMC10258435.

4. **QuantiFERON supernatant-based host biomarkers predicting progression to active tuberculosis disease among household contacts of tuberculosis patients**
   Daniel EA, Thiruvengadam K, Rajamanickam A, Chandrasekaran P, Pattabiraman S, Bhanu B, Sivaprakasam A, Paradkar M, Kulkarni V, Karyakarte R, Shivakumar SVBY, Mave V, Gupta A, Babu S, Hanna LE. Clin Infect Dis. 2023 May 24;76(10):1802-1813. doi: 10.1093/cid/ciac979. PMID: 36582115.

5. **Comparative immune responses to Mycobacterium tuberculosis in people with latent infection or sterilizing protection**
   Jalbert E, Liu C, Mave V, Lang N, Kagal A, Valvi C, Paradkar M, Gupte N, Lokhande R, Bharadwaj R, Kulkarni V, Gupta A, Weinberg A. iScience. 2023 Jul 20;26(8):107425. doi: 10.1016/j.isci.2023.107425. PMID: 37564701; PMCID: PMC10410524.

6. **Early microbiologic markers of pulmonary tuberculosis treatment outcomes**
   Paradkar MS, Pradhan NN, Balaji S, Gaikwad SN, Chavan A, Dharmashale SN, Sahasrabudhe T, Lokhande R, Deshmukh SA, Barthwal M, Atre S, Raskar SS, Sawant TU, Gupte AN, Kakrani A, Golub J, Padmapriyadarsini C, Gupta A, Gupte NA, Mave V. Ann Am Thorac Soc. 2023 Dec;20(12):1760-1768. doi: 10.1513/AnnalsATS.202302-144OC. PMID: 38038600; PMCID: PMC10704230.

Christian Medical College, Vellore
University of Cambridge–University of Washington (CRU 101)

1. **Pharmacokinetics of rifampicin, isoniazid & pyrazinamide during daily & intermittent dosing: A preliminary study**
   Ramachandran G, Hemanth Kumar AK, Kannan T, Thangakunam B, Shankar D, Christopher DJ. Indian J Med Res. 2023 Feb-Mar;157(2&3):211-215. doi: 10.4103/ijmr.IJMR_1835_19. PMID: 36861539; PMCID: PMC10319390.
2. **Continuous cough monitoring: a novel digital biomarker for TB diagnosis and treatment response monitoring**
   Huddart S, Asege L, Jaganath D, Golla M, Dang H, Lovelina L, Derendinger B, Andama A, Christopher DJ, Nhung NV, Theron G, Denkinger CM, Nahid P, Cattamanchi A, Yu C. Int J Tuberc Lung Dis. 2023 Mar 1;27(3):221-222. doi: 10.5588/ijtld.22.0511. PMID: 36855045; PMCID: PMC9983626.
3. **Placing the values and preferences of people most affected by TB at the center of screening and testing: an approach for reaching the unreached**
   Kerkhoff AD, West NS, del Mar Castro M, Branigan D, Christopher DJ, Denkinger CM, Nhung NV, Theron G, Worodria W, Yu C, Muyoyeta M, Cattamanchi A. BMC Global Public Health. 2023 Nov 21;1(27). https://doi.org/10.1186/s44263-023-00027-0

Jawaharlal Institute of Postgraduate Medical Education & Research
Boston Medical Center/Boston University
Rutgers (CRU 102)

1. **M. tuberculosis infection before, during and after pregnancy**
   Knudsen S, Babu SP, Ramakrishnan J, Jenkins HE, Joseph N, Cintron C, Narasimhan PB, Salgame P, Hochberg NS, Hom DL, Ellner J, Horsburgh CR, Sarkar S. Int J Tuberc Lung Dis. 2023 Jan 1;27(1):72-74. doi: 10.5588/ijtld.22.0390. PMID: 36853122.
2. **Not business as usual: Engaging the corporate sector in India's TB elimination efforts**
   Carwile M, Cintron C, Jain K, Buonomo G, Oliver M, Dauphinais M, Narasimhan PB, Prakash Babu S, Sarkar S, Locks L, Kulatilaka N, Hochberg N, Lakshminarayanan S, Sinha P. Glob Public Health. 2023 Jan;18(1):2120405. doi: 10.1080/17441692.2023.2216321. PMID: 37252903.
3. **Effect of treatment adherence on the association between sex and unfavourable treatment outcomes among tuberculosis patients in Puducherry, India: a mediation analysis**
   Barathi A, Krishnamoorthy Y, Sinha P, Horsburgh C, Hochberg N, Johnson E, Salgame P, Govindarajan S, Senbagavalli PB, Lakshinarayanan S, Roy G, Ellner J, Sarkar S. J Public Health (Oxf). 2023 Jun 14;45(2):304-311. doi: 10.1093/pubmed/fdac062. PMID: 35692180; PMCID: PMC10273348.
4. **Development of prognostic scoring system for predicting 1-year mortality among pulmonary tuberculosis patients in South India**
   Krishnamoorthy Y, Ezhumalai K, Murali S, Rajaa S, Majella MG, Sarkar S, Lakshminarayanan S, Joseph NM, Soundappan G, Prakash Babu S, Horsburgh C, Hochberg N, Johnson WE, Knudsen S, Pentakota SR, Salgame P, Roy G, Ellner J. J Public Health (Oxf). 2023 Jun 14;45(2):e184-e195. doi: 10.1093/pubmed/fdac087. PMID: 36038507; PMCID: PMC10273380.
5. **Predictors of weight loss during the intensive phase of tuberculosis treatment in patients with drug-susceptible pulmonary tuberculosis in South India**
   Kalva J, Babu SP, Narasimhan PB, Raghupathy K, Ezhumalai K, Knudsen S, Horsburgh CR, Hochberg N, Salgame P, Roy G, Ellner J, Sarkar S. J Public Health (Oxf). 2023 Aug 28;45(3):545-552. doi: 10.1093/pubmed/fdac141. PMID: 36451280; PMCID: PMC10470329.

MVDRC, NIRT-ICER, UMass

1. **Chitinase and indoleamine 2, 3-dioxygenase are prognostic biomarkers for unfavorable treatment outcomes in pulmonary tuberculosis**
   Kumar NP, Nancy A, Viswanathan V, Sivakumar S, Thiruvengadam K, Ahamed SF, Hissar S, Kornfeld H, Babu S. Front Immunol. 2023 Feb 6;14:1093640. doi: 10.3389/fimmu.2023.1093640. PMID: 36814914; PMCID: PMC9939892.

2. **Longitudinal trends in glycated hemoglobin during and after tuberculosis treatment**
   Kornfeld H, Procter-Gray E, Kumpatla S, Kane K, Li W, Magee MJ, Babu S, Viswanathan V. Diabetes Res Clin Pract. 2023 Feb;196:110242. doi: 10.1016/j.diabres.2023.110242. Epub 2023 Jan 7. PMID: 36627027.

3. **Effect of prediabetes on tuberculosis treatment outcomes: A study from South India**
   Viswanathan V, Devarajan A, Kumpatla S, Dhanasekaran M, Babu S, Kornfeld H. Diabetes Metab Syndr. 2023 Jul;17(7):102801. doi: 10.1016/j.dsx.2023.102801. Epub 2023 Jun 8. PMID: 37354752; PMCID: PMC10528008.

P.D. Hinduja National Hospital & Medical Research Center Johns Hopkins University (CRU 108)

1. **Pharmacokinetic analysis of linezolid for multidrug resistant tuberculosis at a tertiary care centre in Mumbai, India**
   Resendiz-Galvan JE, Arora PR, Abdelwahab MT, Udwadia ZF, Rodrigues C, Gupta A, Denti P, Ashavaid TF, Tornheim JA. Front Pharmacol. 2023 Jan 4;13:1081123. doi: 10.3389/fphar.2022.1081123. PMID: 36686664; PMCID: PMC9846493.

2. **Swimming against the STREAM: Why STREAM 2 data cannot be easily applied to MDR-TB patients across India**
   Udwadia ZF, Patel JM, Batyala M, Tornheim JA, Rodrigues C. Lung India. 2023 May-Jun;40(3):290-291. doi: 10.4103/lungindia.lungindia_74_23. PMID: 37148033; PMCID: PMC10298808.

RePORT INDIA

Data

CMC

BJGMC

BMMRC

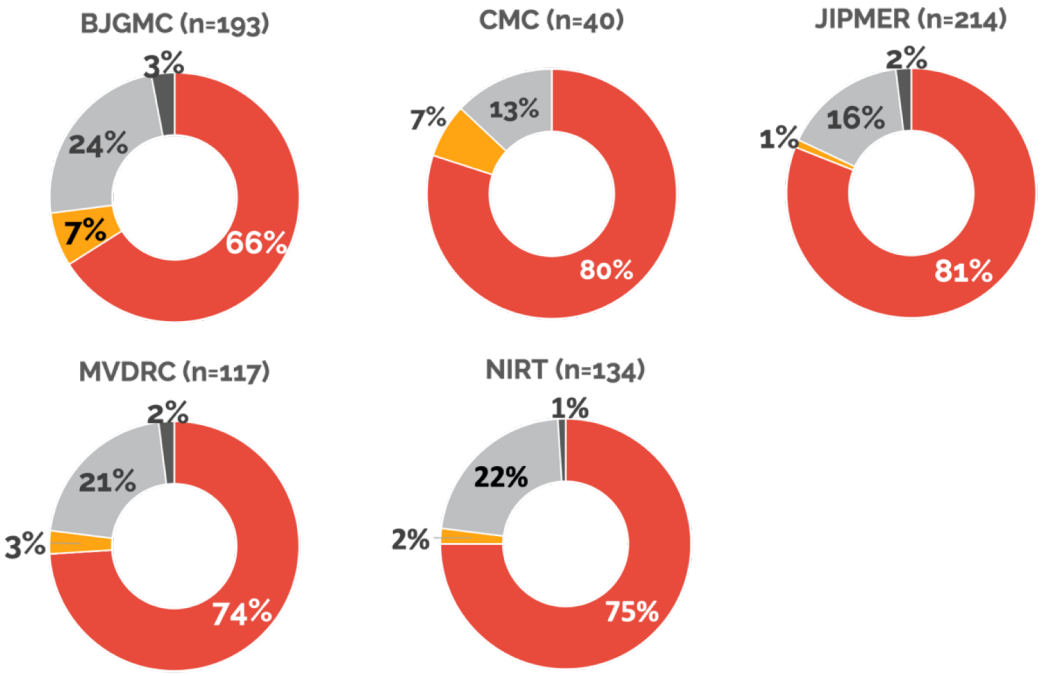
JIPMER

Prof. M. Viswanathan Diabetes Research Centre

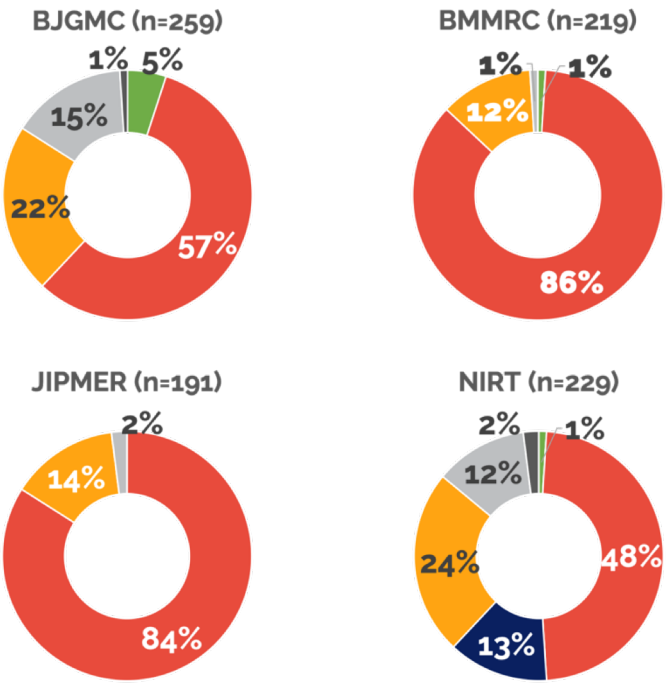
Hinduja

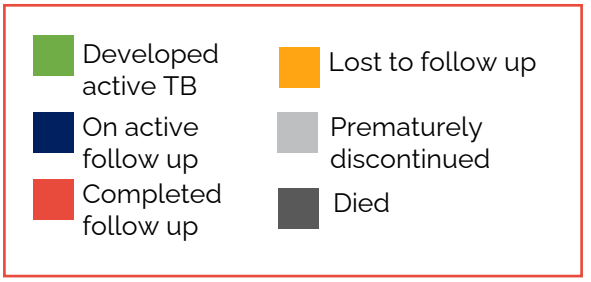
NIRT

Phase 1: Common Protocol Cohort A: Accrual

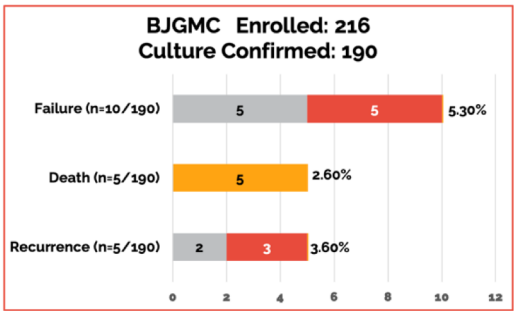


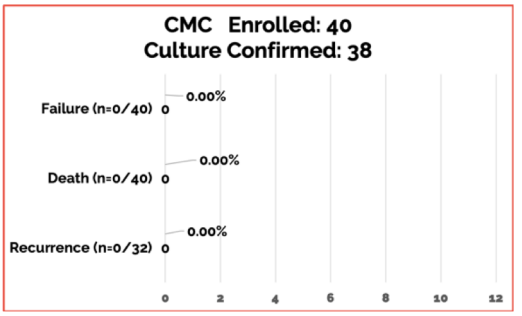
Phase 1: Common Protocol Cohort B: Accrual

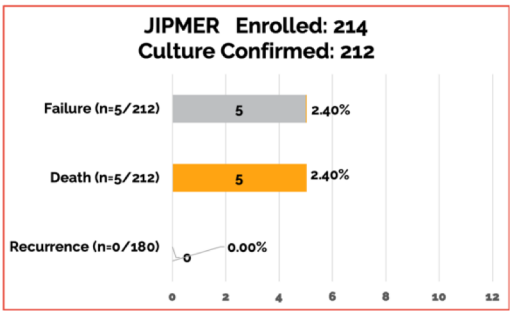


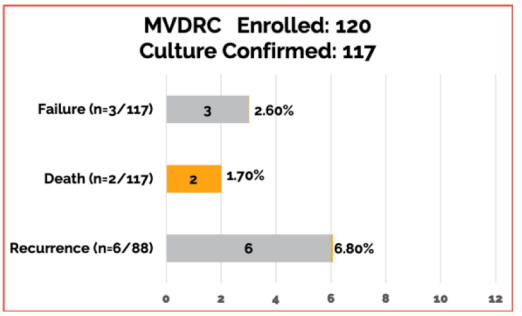


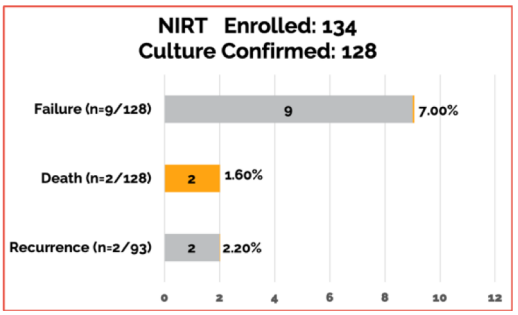
Phase 1: Cohort A Treatment Outcomes

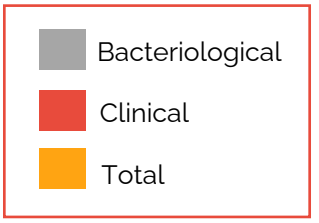






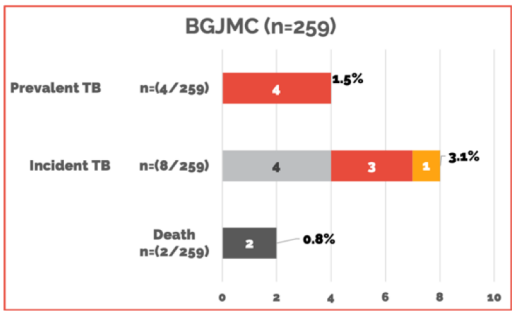


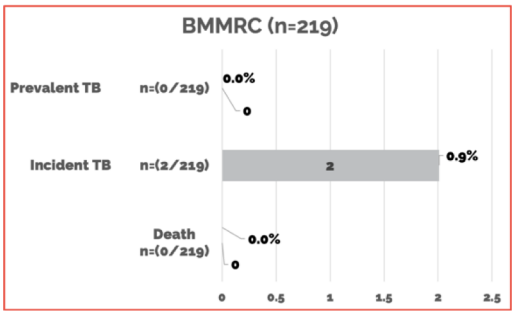


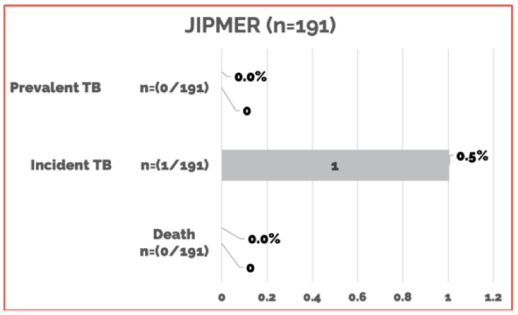


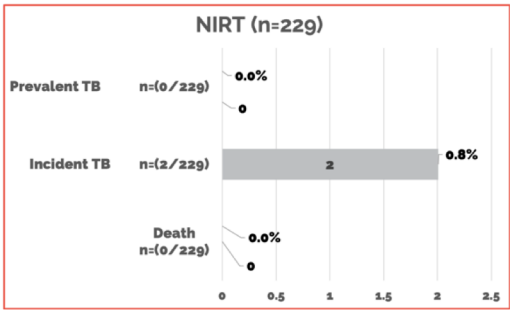
Outcomes

Phase 1: Cohort B Study Outcomes





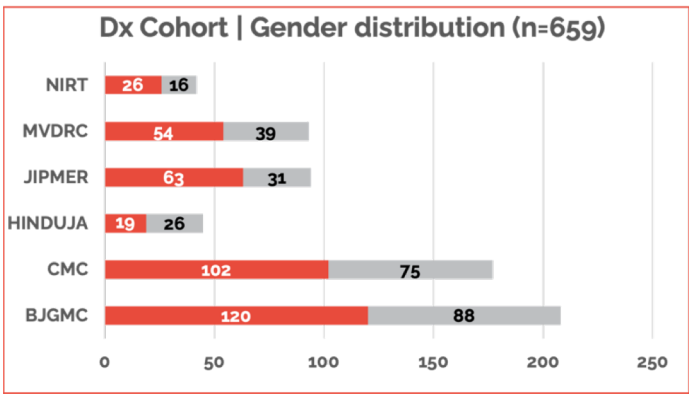


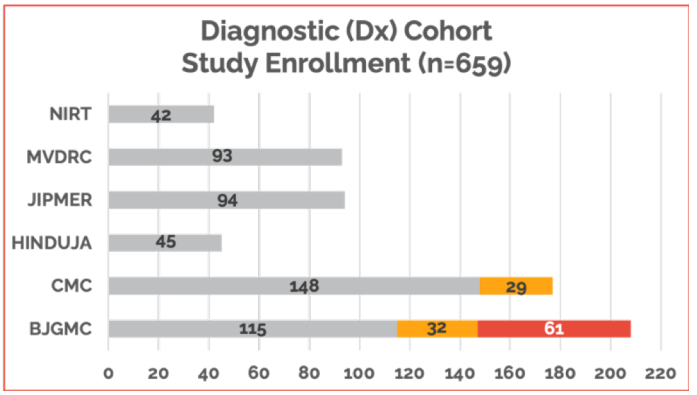


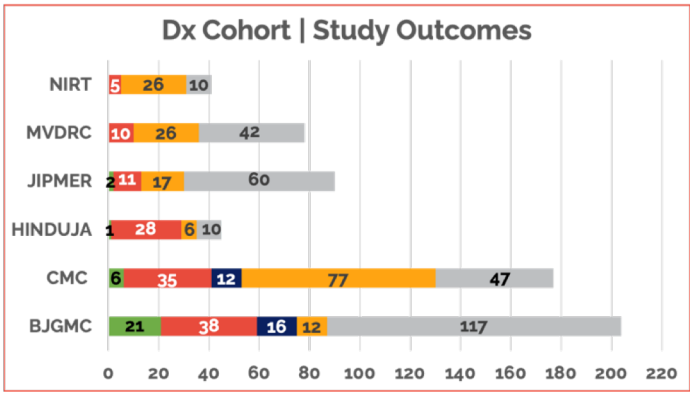
Participants

Phase 2 Common Protocol

Diagnostic Cohort Enrollment & Outcomes

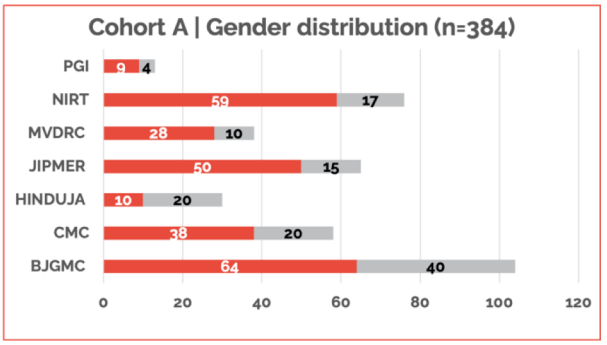


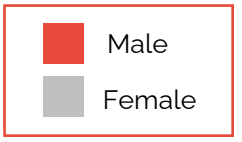


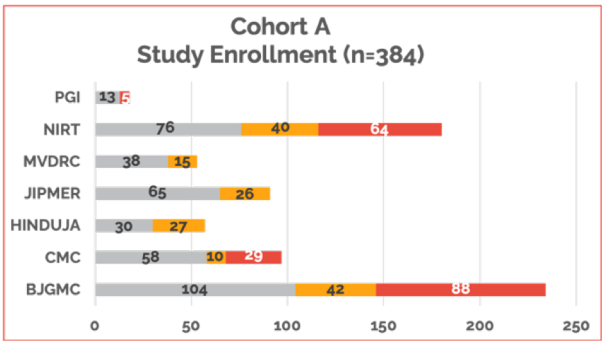


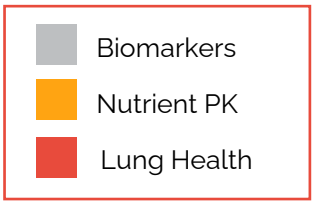
Phase 2 Common Protocol

Cohort A Enrollment

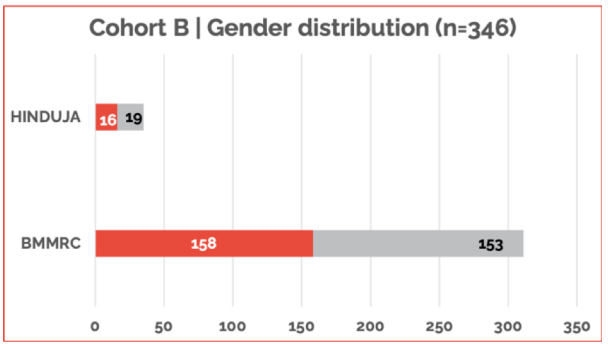


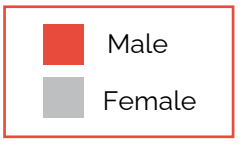


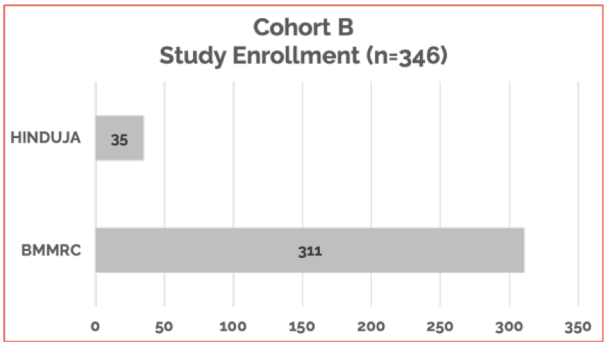




Cohort B Enrollment







Phase 2 Common Protocol: Accrual Status Cohort A

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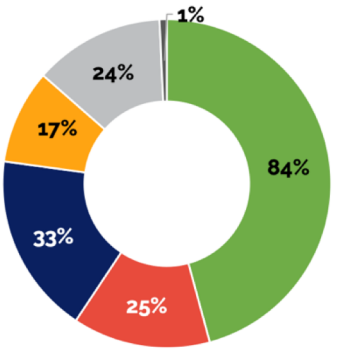

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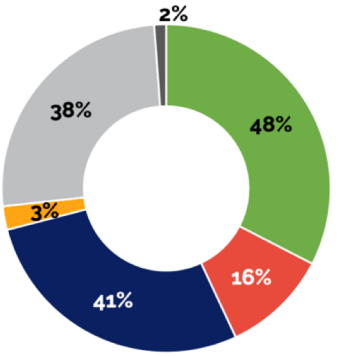
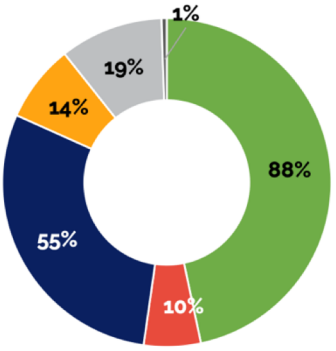
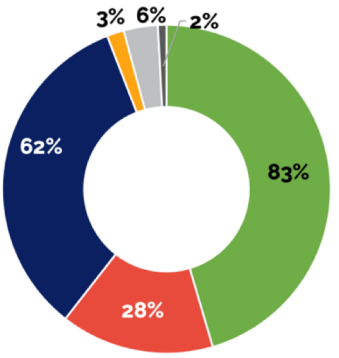


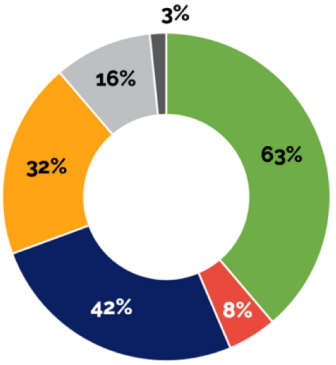
HINDUJA (n=30)



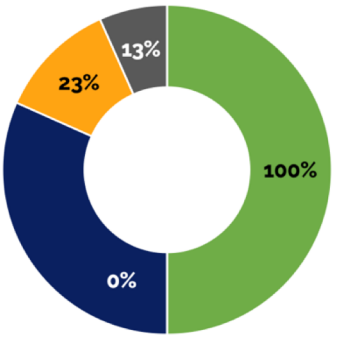
JIPMER (n=65)



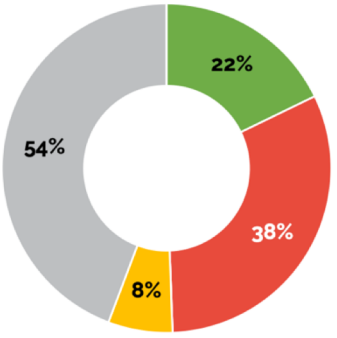
MVDRC (n=38)



NIRT (n=76)

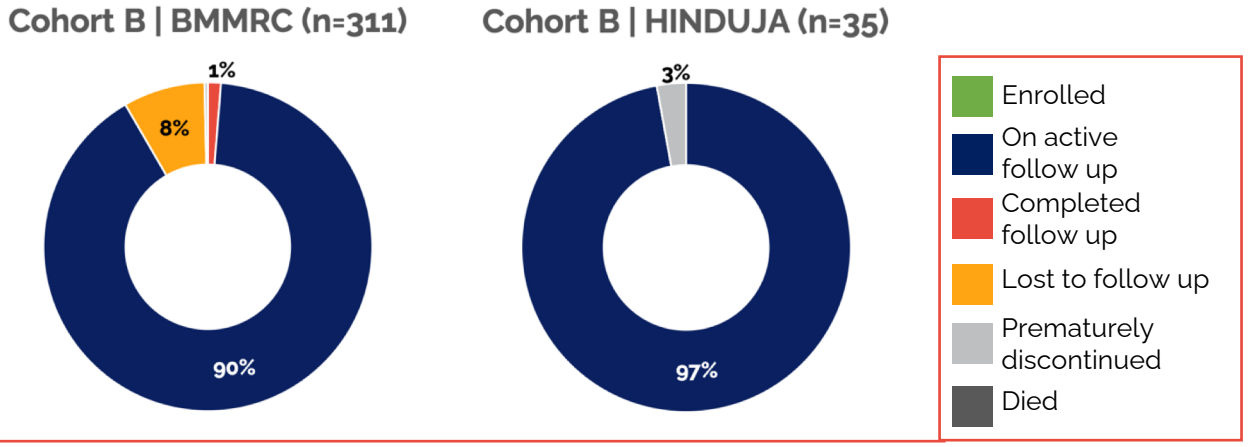


PGI (n=13)



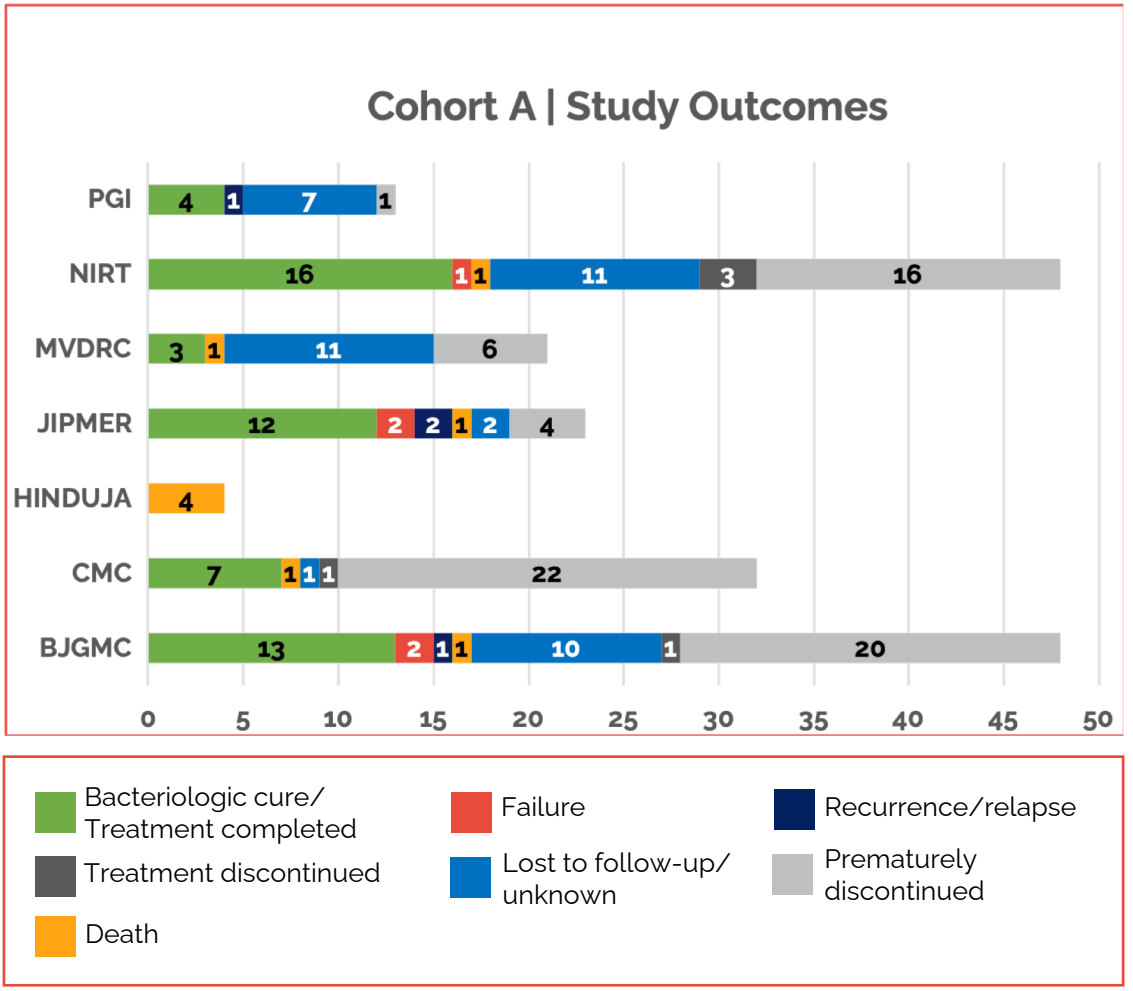
Phase 2 Common Protocol: Accrual Status

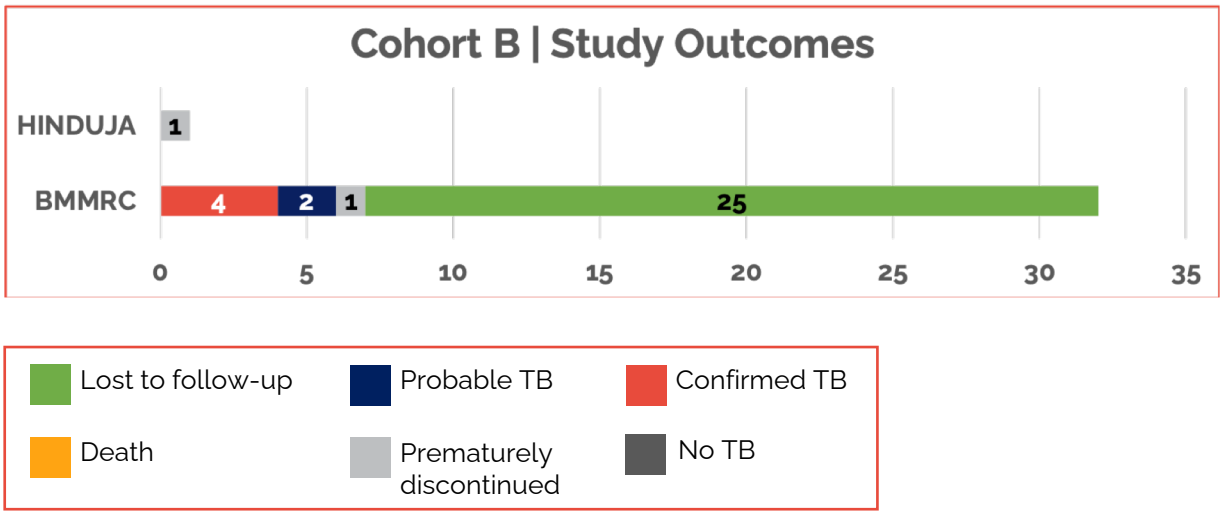
Cohort B



Diagnostic Cohort

Phase 2 Common Protocol: Outcomes





BMMRC

Hinduja

BJGMC

JIPMER

Looking forward to meeting again!

Wishing You Happiness & Good Health

RePORT INDIA

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