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NIRT
NATIONAL INSTITUTE FOR RESEARCH IN TUBERCULOSIS

आई सी एम आर - राष्ट्रीय यक्ष्मा अनुसंधान संस्थान
स्वास्थ्य अनुसंधान विभाग, स्वास्थ्य और परिवार कल्याण मंत्रालय, भारत सरकार
ICMR - National Institute for Research in Tuberculosis, Department of Health Research, Ministry of Health and Family Welfare, Government of India.

Azadi Ka Amrit Mahotsav

WHO Collaborating Centre for Tuberculosis Research & Training
International Centre of Excellence in Research

ANNUAL REPORT
2022 - 2023

G20 भारत 2023 INDIA

ICMR-National Institute for Research in Tuberculosis, Chennai
Department of Health Research,
Ministry of Health & Family Welfare, Government of India

CONTENTS

PREFACE

I am happy to place before you yet another edition of the Annual Report of the institute highlighting our continued efforts to conduct high quality research and generate evidence to support tuberculosis (TB) control not only in India but in other parts of the world as well.

During the year under review, our efforts to evolve patient friendly and cost-effective shorter regimens for the treatment of TB continued. This included studies to shorten the duration of treatment for both drug-sensitive and drug-resistant TB using newer drugs and regimens. We also worked closely with the TB control programme in identifying and answering key operational research questions to strengthen its efforts to implement TB control in the country.

Major laboratory activities included studies on molecular biology and immuno-genetics of TB. Molecular validation studies of various in-country and external kits are being performed. In addition, whole genome sequencing and targeted next generation sequencing and lineage based studies have been initiated this year. We also expanded our work to include non-sputum based diagnostics for TB, Zoonotic and reverse zoonotic transmission of TB, estimation of serum levels of newer drugs like bedaquiline. Our work in HIV, COVID and Health Technology assessement continue to progress. The Centre also provides valuable statistical support to investigators not only within the institute but all over the country and plays a lead role in modeling and projection exercises.

This year, the institute has initiatied many new activites including a pan India “Socio-Behavioural Research Network” for TB with participation from multiple organisations with an aim to address social aspects of TB; nation-wide Drug-resistant surveillance by Next generation sequencing technology to help predict drug resistance and transmission dynamic, construction of an independent Viral Research and Diagnostic Lab (VRDL) at Tiruvallur campus of NIRT. As part of Supranational National Reference Laboratory (SNRL) activity, we extended support to SEARO member countries namely Myanmar and Timor Leste. We have also provided support to conduct drug resistance surveillance to Timor Leste.

As we continue to work towards End TB targets with continued enthusiasm, vigour and commitment, I place before you this Annual Report that presents the combined efforts of all the staff members of NIRT and invite your valuable suggestions to help us improve our research efforts.

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ABBREVIATIONS

ACE2	Angiotensin Converting Enzyme 2
ACF	Active Case Finding
ADAR	Adenosine Deaminase Acting on RNA
ADR	Adverse Drug Reactions
AI	Artificial Intelligence
ARDS	Acute Respiratory Distress Syndrome
ARREST-TB	Accurate, Rapid, Robust & Economical Diagnostic Technologies For Tuberculosis
ART	Anti –Retroviral Treatment
ATT	Anti-TB Treatment
BCG	Bacille Calmette-Guérin
BDQ	Bedaquiline
BEAT	Building evidence against TB
BMI	Body Mass Index
BPaL	Bedaquiline, Pretomanid, Linezolid
BSEM	Bayesian Structural Equation Model
Btb	Bovine Tuberculosis
CAD	Computer-Aided Detection
CAPRISA 002	Acute HIV Infection Cohort Study
CAS	Current Awareness Service
CBC	Complete Blood Count
CBL	Clinical Biochemistry Laboratory
CFP	Culture Filtrate Protein
CFU	Colony Forming Unit
COVID-19	Coronavirus Disease – 19
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CTAB	Hexadecyltrimethiammonium Bromide
CVD	Cardiovascular Disease
CXCL	Chemokines
CXR	Chest X-Ray
DC	Dendritic Cells
DHR	Department of Health Research
DLAS	District Level Annual Survey
DLM	Delamanid
DM	Diabetes Mellitus
DNA	Deoxyribo Nucleic Acid
DRMs	Drug Resistance Mutations
DRS	Drug Resistance Survey
DR-TB	Drug Resistant-TB
DST	Drug Susceptibility Test
DTG	Dolutegravir
Dx	Diagnostic

EGFP	Enhanced Green Fluorescent Protein
EID	Early Infant Diagnosis
ELISA	Enzyme Linked Immunosorbent Assay
EMB	Ethambutol
EPTB	Extra Pulmonary TB
EQA	External Quality Assurance
ETH	Ethionamide
FDC	Fixed Dose Combination
FDGs	Focus Group Discussions
FQ	Fluoroquinolone
GIS	Geographical Information System
HATS	Histone Acetyl Transferases
HDACs	Histone deacetylases
HEPS	HIV-1 Multiply-Exposed Seronegative Cohort Study
HHC	Healthy Household Contacts
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPLC	High Performance Liquid Chromatography
HRQoL	Health Related Quality of Life
HTA-In	Health Technology Assessment In India
ICT	Immuno Chromatography
IEF	Iso Electric Focusing
IGRA	Interferon Gamma Release Assay
IMCs	Infectious Molecular Clones
INF	Interferon
INH	Isoniazid
INSTI	Integrase Strand-Transfer Inhibitor
IPT	Isoniazid Preventive Therapy
ISG	Interferone Stimulated Genes
KII	Key Informant Interviews
LATE-PCR	Linear After the Exponential PCR
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LIMS	Laboratory Information Management System
LOD	Limit of Detection
LPA	Line Probe Assay
LTBI	Latent Tb Infection
LZD	Linezolid
MAM	Moderate Acute Malnutrition
MBPaL	Modified Bpal
MDMs	Monocyte Derived Macrophages
MDDC	Monocyte Derived Dendritic Cells
MDR	Multidrug Resistant
MDR-TB	Multi-Drug Resistant TB

MDRTI/NR	Multi-Drug Resistant Treatment Intolerant/Non Responsive
MGIT	Mycobacterium Growth Indicator Tube
MIC	Minimum Inhibitory Concentration
MIS-C	Multisystem Inflammatory Syndrome in Children
MMP	Matrix Metalloproteinases
MO	Medical Officer
MoHFW	Ministry of Health and Family Welfare
MOX	Moxifloxacin
MOIs	Multiplicities of Infections
MSM	Men Having Sex with Men
MTA	Material Transfer Agreement
MTB	Mycobacterium Tuberculosis
MTBC	Mycobacterium Tuberculosis Complex
NABL	National Accreditation Board for Testing And Calibration Laboratories
Nabs	Neutralizing Antibodies
NACO	National Aids Control Organization
NDRS	National anti-TB Drug Resistance Survey
NE	North East
NETS	Neutrophil Extracellular Traps
NK	Natural Killer
NRL	National Reference Laboratory
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NSP	National Strategic Plan
NTEP	National TB Elimination Programme
NTM	Non-Tuberculous Mycobacteria
OSE	Onsite Evaluation
Pa	Pretomanid
PBMC	Peripheral Blood Mononuclear Cells
PCR-RFLP	Polymerase Chain Reaction - Restriction Fragment Length Polymorphism
PD	Positive Deviance
pDCs	Plasmocytoid dendritic cells
PFT	Pulmonary Function Test
PK	Pharmacokinetic
PMDT	Programmatic Management of Drug-Resistant Tb
PPD	Purified Protein Derivative
PR	Pulmonary Rehabilitation
Pre XDR	Pre-Extensive Drug Resistant Pulmonary Tuberculosis
PRE-EMPT	Predictors Resistance Emergency evalution multidrug resistant tuberculosis patient and treatment.
PTB	Pulmonary Tuberculosis
PZA	Pyrazinamide
QFT	Quantiferon TB Gold Plus
raBCG	Recombinant Bacille Calmette Guerin
raMTB	Recombinant Mycobacterium Tuberculosis

RePORT	Regional Prospective Observational Research In TB
RFT	Renal Function Tests
RMP/RIF	Rifampicin
RNA	Ribo Nucleic Acid
RRL	Regional Research Laboratory
RTPCR	Reverse Transcriptase Polymerase Chain Reaction
RUSF	Ready to eat Supplementary Food
SARS-CoV2	Severe Acute Respiratory Syndrome – Coronavirus – 2
SDI	Selective Dissemination of Information
SDS PAGE	Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis
SEARO	South East Asia Regional Office WHO
SGRQ	St Georges Respiratory Questionnaire
SLI	Second Line Injectable
SNPs	Single Nucleotide Polymorphism
SNRL	Supranational Reference Laboratory
SPAD	Single Photon Avalanche Diode
SSI	Semi Structured Interviews
STREAM	Shortening of Treatment Regimen For MDR-TB Patients
TAT	Turnaround Time
TB	Tuberculosis
TDM	Therapeutic Drug Monitoring
TF	Transmitted Founder
TIMP	Tissue Inhibitors of Matrix Metalloproteinases
TNF	Tumour Necrosis Factor
TNGS	Targeted Next Generation Sequencing
TST	Tuberculin Skin Test
TTP	Time to culture Positivity
TU	TB Units
VAP	Vaccine Action Programme
VPM1002	Recombinant BCG Vaccine
VRDL	Viral Diagnostic and Research Laboratory
WGS	Whole Genome Sequencing
WHO	World Health Organization
XDR	Extensively Drug Resistant

CLINICAL STUDIES

DEPARTMENT OF CLINICAL RESEARCH

DEPARTMENT OVERVIEW AND MANDATES

The department of clinical research probably the oldest division within ICMR-NIRT has conducted world renowned studies starting from the Home Sanatorium study. Doctors, Nursing and support staff play a major role in the research studies undertaken by the Department. They are well trained and experienced in the recruitment and retention of participants in Clinical trials in TB. The Department of Clinical Research conducts multicentric collaborative studies with Govt. and private Institutions across India. The department offers support to laboratory studies by facilitating sample collection.

The focus of research studies of the Department of Clinical research is towards elimination of TB. In this context, the mandates of the Department include undertaking Clinical trials and observational studies which focus on addressing determinants of TB, shortening TB treatment in drug sensitive and drug resistant TB, effectiveness of adjunctive therapy in TB, evaluation of TB preventive therapy and vaccines in the prevention of TB. Strategic interventions for TB free Districts are planned to be undertaken. The Department supports diagnostic studies which evaluates newer TB diagnostic tools and pharmacokinetic studies in establishment of drug estimation methods and determination of drug levels. The Department conducts training as part of capacity building initiative in TB and research.

Studies in progress

1. **Evaluate the effectiveness, safety and tolerability of various doses of Linezolid in combination with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-Resistant (Pre-XDR), Or Treatment Intolerant/Non-responsive Multidrug-Resistant (MDRTI/NR) Pulmonary Tuberculosis in India.**

Principal Investigator	:	Dr. C. Padmapriyadarsini, Director
Participating Institutes	:	Sarvodaya Charitable Trust Hospital, Mumbai Shatabdi Centenary Hospital, Mumbai King's George Medical University (KGMU), Lucknow SN Medical College, Agra Govt. Medical College, Bhavnagar Govt. Medical College, Surat NITRD, New Delhi RBIPMT, Delhi Govt. Rajaji Hospital, Madurai
Source of funding	:	UNION
Study period	:	2021 - 2024
Category	:	TB
Pillar	:	Treat

Background

Early diagnosis, prompt treatment initiation, and completion of treatment play a vital role in Drug Resistant -TB management. Currently, longer regimens with injectables and toxic drugs often lead to poor drug adherence and poor treatment outcomes. Modified BPaL (mBPaL) study is proposed with varying doses of Lzd along with Bdq and Pa as planned reduction of Lzd for the treatment of Pre-XDR and MDRTI/NR pulmonary TB patients for 26-39 weeks. Given the poor tolerability and increased frequency of dose interruption in regimens containing Lzd, this trial will help us in deciding the effective dosing of Lzd to be given with Bdq and Pa for a fully oral short-course regimen to treat highly drug-resistant TB in the field setting.

Objectives

To determine the effectiveness of various doses and duration of Linezolid in combination with Bedaquiline and Pretomanid after 26 weeks of treatment in adults with either Pre-Extensively Drug-Resistant (Pre-XDR) OR Treatment Intolerant / Non-responsive multidrug-resistant ($MDR_{TI/NR}$) Pulmonary Tuberculosis.

Methods

This is a multicentric, randomized pragmatic clinical trial to establish the study objective. The treatment arms will receive Bdq and Pa along with different dosing of Lzd – Arm 1 will receive Lzd 600mg for 9 weeks followed by 300mg for 17 weeks while Arm 2 will receive Lzd 600mg for 13 weeks followed by 300mg for 13 weeks. The control group will receive Bdq, Pa, and Lzd 600mg daily for 26 weeks. The primary endpoint is the proportion of patients with favorable outcomes in terms of cure and treatment completed while the secondary endpoints include unfavorable outcomes comprising of deaths, treatment failure, and loss to follow-up. Safety and tolerability of the various combinations along with TB recurrence will be recorded till 48-weeks post-treatment.

Study progress

403 pulmonary Pre-Extensively Drug-Resistant (Pre-XDR) OR Treatment Intolerant/ Non-responsive multidrug-resistant ($MDR_{TI/NR}$) Pulmonary Tuberculosis patients were enrolled in New Delhi, Gujarat, Mumbai, Lucknow, Agra and Madurai sites. The study is ongoing and all recruited patients are currently under follow-up.

2. Multi-centric prospective cohort study of TB recurrence-free cure among microbiologically confirmed new pulmonary tuberculosis patients treated under NTEP with the 4-month moxifloxacin-containing daily regimen.

Principal Investigator	: Dr. V.V. Banu Rekha, Scientist E
Participating Institutes	: ICMR, Govt. and Private Institutes across India
Source of funding	: ICMR - India TB Research Consortium (ITRC)
Study period	: 2022-2024
Category	: TB
Pillar	: Treat

Background

Shortening the duration of tuberculosis (TB) treatment from the currently recommended 6 months in drug-sensitive pulmonary TB (PTB) is a research priority. An earlier randomised clinical trial conducted by ICMR-NIRT showed promising results with the 4-month moxifloxacin-containing daily regimen (2HRZEM $_7$ / 2HRM$_7$) with a TB recurrence rate of 4.1%. The effectiveness of the 4-month shorter regimen needs to be studied in field settings.

Objective

To determine the TB recurrence-free cure rate among microbiologically confirmed new PTB patients treated under the TB Program with the 4-month moxifloxacin-containing daily regimen (2 HRZEM $_7$ / 2HREM$_7$).

Methods

In this multicentric, single-arm study, eligible adult microbiologically confirmed PTB patients sensitive to isoniazid, rifampicin and quinolone will receive 2 months of HRZEM followed by 2 months of HREM daily (2 HRZEM $_7$ / 2HREM$_7$). Tab. Moxifloxacin 400mg will be given along with the weight-based Fixed dose Combination (FDC) of HRZE. The enrolled patients will be followed up for 2 years post-treatment. Sputum examination will be done for response to treatment and for TB recurrence. In addition, drug adverse events will be documented.

Study progress

The recruitment to the study was completed with 557 patients. Follow-up of study participants is ongoing.

3. Role of Vitamin C supplement as an adjunct to tuberculosis treatment in new smear sputum positive pulmonary tuberculosis – An exploratory trial

Principal Investigator	: Dr. D. Bella Devaleenal, Scientist E
Participating Institutes	:ICMR-National Institute for Research in Tuberculosis(NIRT)
Source of funding	: ICMR Intramural
Study period	: 2023 -2024
Category	: TB
Pillar	: Treat

Background

Vitamin C in combination with pyrazinamide was shown to promote bacterial clearance by current first line TB drugs. This effect was demonstrated not only in in-vitro cultures but also in a cell infection model. Cells exposed to vitamin C maintain homeostasis and boost host immune defence functions. Therefore, vitamin C can be seen to modulate two key determinants of TB drug efficacy, namely host factors and antibiotic efficacy in bacteria, offering an unique opportunity to assess its utility in adjunctive therapy for shortening the duration of treatment.

Objectives

Primary objective

To determine the time to sputum culture conversion when Vitamin C 500mg is given

once daily/ twice daily along with the standard first line anti-TB treatment (HRZE) for 8 weeks duration in drug sensitive new sputum positive pulmonary TB patients.

Secondary objectives

- To estimate the proportion who are culture negative at each week up to 8 weeks of treatment
- To estimate the time to culture positivity (TTP) in liquid culture
- To estimate the safety and tolerability to Vitamin C
- To understand the Pharmacokinetic profile of Vitamin C and ATT (HRZE) when co administered among new smear positive patients
- To compare the radiological improvement among patients who are on standard HRZE and along with Vit. C
- To study the immune responses among new smear positive TB patients when treated with HRZE with or without Vitamin C

Methods

This is a phase 2b randomized (open-label) parallel arm controlled clinical trial done among new smear positive pulmonary TB patients with drug sensitive TB diagnosed in NTEP centers in Chennai Corporation. The participants were randomized to any one of the following arms

Arm 1: HRZE + Vitamin C 500mg OD for 8 weeks/4 HRE

Arm 2: HRZE + Vitamin C 500mg BD for 8 weeks/4HRE

Arm 3: HRZE (Control arm) for 8 weeks/4HRE

Plasma vitamin C will be analyzed by reverse phase HPLC method and the levels will be measured at baseline (before inducting into the study arm), week 1, at the end of intensive phase (i.e. 8^{th} week) and at the end of treatment. The primary endpoint will be the time from treatment initiation to the first of the two consecutive negative sputum cultures without an intervening positive culture in MGIT culture within the first 8 weeks

Study progress

The study was initiated in June 2022 and currently ongoing. A total of 82 new smear positive drug sensitive TB patients were screened for the study and 38 were enrolled.

4. Effect of Pulmonary rehabilitation on the exercise tolerance in sputum positive pulmonary TB patients

Principal Investigator	: Dr.N.Poorana Ganga Devi, Scientist D
Participating Institutes	: ICMR-National Institute for Research in Tuberculosis(NIRT)
Source of funding	: ICMR Intramural
Study period	: 2022 -2025
Category	: TB
Pillar	: Treat

Background

Treated TB patients may remain lifelong sufferers of disabling sequelae of the disease which subsequently impair their quality of life. Studies with longer follow-up have revealed that a large percentage of patients with treated pulmonary tuberculosis (PTB) show signs of permanent airflow obstruction or restrictive impairment. Post TB pulmonary impairment, therefore has emerged as a distinct clinical entity. Pulmonary Rehabilitation (PR) is a low cost, high impact intervention that reverses the disability and has been shown to improve symptoms, exercise tolerance and health-related quality of life (HRQL) in these patients.

Objectives

Primary Objective

To evaluate the effect of a 16-week pulmonary rehabilitation program on the exercise capacity using 6 minutes walk test.

Secondary Objective

To assess the clinical, radiological, functional status and health related quality of life (HRQoL) of these patients one year after ATT completion.

Methods

The study is a cluster randomized controlled trial with two parallel groups with simple random sampling, comparing PR versus standard care for patients with PTB. All patients those who had been started on ATT at selected NTEP centres and with smear negative status at the end of Intensive phase will be screened for the study. Those patients with MRC dyspnoea grade of ≥2 will be recruited for the study. Investigations at baseline include two sputum examination by smear for tubercle bacilli, chest x-ray, baseline Dyspnoea Index, Pulmonary function test (PFT) by Spirometry and a 6-minute walk test. The quality of life will be assessed using the St. Georges respiratory questionnaire (SGRQ). Sunsequently, the patient will be assigned to one of the two arms. Both the arms will continue with daily ATT in the continuation phase at NTEP centres. Pulmonary Rehabilitation (PR) (Study intervention arm) consist of a 16-week programme offered to participants, with sessions occurring twice weekly for 45 mins to 60 mins- 6 weeks initially on an outpatient basis, and 6 weeks later at home followed by two weeks each on outpatient basis and at home. At home PR adherence will be ensured over telephonic communication. Sputum, CXR, 6MWT, SGRQ Questionnaire and PFT will be done at the end of 16 weeks in both arms and also at 6 months interval thereafter for a 2-year period.

Study progress

The study was started in November 2022 and 47 TB patients have been enrolled. The study is ongoing.

5. A Phase III, Randomized, Double-blind, Three arm Placebo controlled study to Evaluate the Efficacy and Safety of two vaccines VPM1002 and Immuvac (M*w*) in Preventing Tuberculosis (TB) in Healthy Household Contacts of Newly Diagnosed Sputum Positive Pulmonary TB patients.

Principal Investigator	: Dr. V.V. Banu Rekha, Scientist E
Participating Institutes	: ICMR, Govt. and Private Institutes across India
Source of funding	: ICMR - India TB Research Consortium (ITRC)
Study period	: 2018-2024
Category	: TB
Pillar	: Prevent

Background

Research for newer vaccines for tuberculosis (TB) is essential to achieve the End TB targets. Household contacts of sputum smear-positive pulmonary TB (PTB) patients are at high risk for contracting TB. Prevention of TB among household contacts of PTB patients is crucial. VPM 1002 is a recombinant BCG vaccine from Serum Institute and Immuvac is a heat killed suspension of Mycobacterium W from Cadila Pharma.

Objective

To evaluate the efficacy and safety of VPM1002 and Immuvac in comparison to placebo among healthy household contacts of newly diagnosed sputum positive PTB patients.

Methods

The Phase III, double-blind, multicentric, randomized clinical trial is being conducted across India and in ICMR-NIRT sites in Chennai, Thiruvallur, Tambaram, Madurai and Vellore. HIV sero-negative household contacts aged ≥ 6 years, with no evidence of TB disease are randomized to receive intra-dermal VPM1002, Immuvac or placebo. The first dose (0.1ml) is administered in both upper arms at baseline and the second single dose is given in the right or left arm at one month. Participants are followed up once fortnightly during initial 2 months and thereafter once in 4 months for development of TB disease over a follow-up period of 3 years. Solicited and unsolicited adverse events are documented. The immune responses are studied at baseline, 2 months, 6 months and at TB disease breakdown in a sub-set of participants.

Study progress

The enrolment to the trial was completed in December 2020. A total of 2214 household contacts were enrolled and vaccinated. The follow-up of enrolled household contacts is ongoing.

6. Predictors of unfavourable treatment outcomes and emerging drug resistance among patients started on drug regimen for isoniazid (INH) mono-resistant pulmonary TB under NTEP

Principal Investigator	:	Dr Leeberk Raja. I , Scientist E
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis(NIRT) & State TB cell
Source of funding	:	ICMR Intramural
Study period	:	2023 - 2025
Category	:	TB
Pillar	:	Treat

Background

Isoniazid mono-resistance is the most common type of drug-resistance in TB. It reduces the treatment success and increases the risk of acquiring additional drug resistance such as rifampicin and fluroquinolones. Isoniazid resistance is 11.06% and 25.09% among new and previously treated TB patients respectively in India. Studies across the globe have reported unfavourable outcome rates of 7-44% among these patients treated with first line drugs. There is a paucity of literature on the exact estimation on the incidence of multi drug or emerging resistance among patients detected to have INH resistance. Similarly, genetic variations when there is a bacteriological reversion after the conversion has not been studied yet. This study aims to address this gap by following up patients with INH resistance over a period of 24 months after treatment initiation in the state of Tamil Nadu and Kerala, India.

Objectives

1. To identify predictors for unfavourable treatment outcomes in patients among patients with pulmonary TB who initiated on treatment regimen for INH mono resistance under NTEP in the state of Tamil Nadu and Kerala.
2. To explore emerging drug resistance among patients treated for INH mono-resistant pulmonary TB.
3. To describe genetic traits and compare the lineage of *M.Tuberculosis* isolate before and after bacteriological reversion using whole genome sequencing (WGS).

Methods
In this prospective cohort study, all newly diagnosed pulmonary TB patients initiated on treatment regimen for INH mono resistance under NTEP will be approached. Patients with additional resistance for rifampicin or fluroquinolones will be excluded. Demographic details and sputum sample will be collected at the baseline. Subsequently, sputum samples are collected during month 2, 3 and 6 during the treatment and month 3, 6, 9, 12 post- treatment. During the follow up, details regarding change of regimen, adverse events and TB recurrence are collected. The samples will be sent for smear, first and second line LPA, culture and DST. In case of TB recurrence, whole genome sequencing will be performed and compared with the baseline sample.

Study progress
The study has been initiated in 11 districts of Tamil Nadu. We have enrolled 301 patients out of 843 sample size as on June 2023.

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

Principal Investigator	:	Dr. C. Padmapriyadarsini, Director
Participating Institutes	:	NIRT, Chennai; YR Gaitonde Centre for AIDS Research and Education (YRG Care), Chennai; Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry; BJMC, Pune; Hinduja Hospital, Mumbai.
Source of funding	:	National Institutes of Health (NIH), Bethesda, USA
Study period	:	2018-2022
Category	:	TB
Pillar	:	Detect

Background
The emergence of multi-drug resistant (MDR) and extensively drug resistant (XDR) TB has exacerbated the threat to public health and created a renewed sense of urgency to control the disease. Currently available MDR-TB treatment regimens failed to cure 30-50% of patients leading to continued spread of drug resistant organisms in the community. Moreover, resistance to the two new anti-tuberculosis drugs for MDR and XDR TB, Bedaquiline and Delamanid, is already emerging. This problem will continue to worsen unless the mechanism by which resistance develops is understood and steps are taken to prevent it.

Objectives
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

Methods
A total of 400 adult (age > 18 years) patients with pulmonary TB who are about to initiate MDR-TB treatment and fulfilling the eligibility criteria will be followed up for the duration of the MDR-TB treatment and for up to 12 months post completion of treatment. Sputum samples and PK samples will be collected as per study schedule.

Study progress
101 MDR patient with and without HIV have been enrolled from Chennai. All Patients are under follow up and the study is ongoing

8. The Regional Prospective Observational Research for Tuberculosis (Report) India Phase II Common Protocol.

Principal Investigator	:	Dr Bhavani, P.K, Scientist E
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT), Institute of Thoracic Medicine, District Tuberculosis Centre, Poonamallee District, Institute of Social Pediatrics, and Stanley Medical College. Chandigarh, Hyderabad, Mumbai, Puducherry, Pune, Shillong, and Christian Medical College (CMC), Vellore
Source of funding	:	Indian Department of Biotechnology (DBT), Ministry of Science and Technology CRDF Global (Lab Support)
Study period	:	2020 -2025
Category	:	TB
Pillar	:	Detect

Background

Towards the ambitious goal of eliminating TB by 2030, DBT-GOI and NIH-US, jointly funded the Regional Prospective Observational Research in Tuberculosis (RePORT) Phase I for 5 years (2013 - 2018) under the Indo-US VAP. Phase II proposed to collect and utilize data & specimens for TB research, leveraging the existing infrastructure, processes, and scientific partnerships established under RePORT India consortium. Establishment of three prospective, observational cohorts for collection of specimens and associated data and analysis of stored specimens and associated data will be done.

Objectives

1. To evaluate novel diagnostics and biomarkers of diverse states of *M tb* infection
2. To identify markers of treatment response
3. To identify markers of lung injury and impairment associated with unfavourable TB treatment outcomes.
4. Resistance to infection: Mechanisms of protection against TB in exposed persons
5. Progression to Disease: Identify immunologic markers of persons at highest risk of progress of Latent TB Infection to TB

Methods

In this prospective observational cohort study, adult and child participants will be enrolled into

- Diagnostic (Dx) Cohort: presumptive TB patients of all age groups
- Cohort A: active TB patients (> 18years) New enrolments include:
- Diagnostic Cohort - 325 (Aim 1) - Adult TB -150, Paediatric TB -100, EPTB-75
- Cohort A – 90 New adult (>18years) PTB participants

Additional follow-up for previously-consented Cohort B participants (n=223) to identify persons with sustained IGRA conversion, reversion and sustained infection-free status after TB exposure

Study progress

Study started recruiting patients from March 2022 and is on going

9. Systems biology and immunology of the effect of tuberculosis chemoprophylaxis in HIV infection.

Principal Investigator	:	Dr. S. Syed Hissar, Scientist E
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis(NIRT); Madras Medical College (MMC) & Rajiv Gandhi Government General Hospital (RGGGH), Chennai; Government Hospital of Thoracic Medicine (GHTM), Tambaram; and Kilpauk Medical College (KMC), Chennai.
Source of funding	:	ICMR AD-HOC
Study period	:	2021-2023
Category	:	TB/HIV
Pillar	:	Detect

Background

TB is the leading cause of mortality in people infected with HIV. HIV infection increases the risk of TB by a factor of up to 26 times and alters its clinical presentation, complicates diagnosis and treatment, and worsens outcome. HIV infection is the strongest risk factor for TB, both TB and HIV have profound effects on the immune system, as they are capable of disarming the host's immune responses through mechanisms that are not fully understood.

Objectives

1. Characterize systems biology of the effect of TB chemoprophylaxis in HIV
2. Characterize immunology response of the effect of TB chemoprophylaxis in HIV

Methods

HIV seropositive individuals attending the study sites will be screened for latent TB by Quantiferon TB gold plus (QFT) and recruited prior to the administration of INH preventive therapy (IPT). At enrolment and after six months of IPT, peripheral blood mononuclear cells (PBMC) will be collected and preserved from the participants. NK cell responses, Monocyte responses and DC responses will be studied using flow cytometric analysis of activation markers and cytokine expression.

Study progress

A total of 103 participants have been enrolled and 84 have completed IPT. The study is ongoing.

10. The impact of malnutrition on immune responses to tuberculosis in Indian children

Principal Investigator	:	Dr Aishwarya Venkataraman, Scientist-E
Participating Institutes	:	Institute of Child Health and Hospital for Children (ICH), Stanley, Kanchi Kamakoti CHILDS Trust Hospital (KKCTH)
Source of funding	:	Department of Biotechnology
Study period	:	2019-2024
Category	:	TB
Pillar	:	Detect

Background

Malnourished children have an elevated risk of mortality from infections like TB, possibly due to immunodeficiency caused by undernutrition; however, immune function in malnourished children has not been well characterised to date. Similarly, data regarding the impact of malnutrition on TB immunity is very limited. Therefore, we aim to characterise the immune responses to Mycobacterium tuberculosis (Mtb) in children less than 5 years of age with moderate acute malnutrition (MAM) compared to well-nourished children and to

evaluate the impact of a nutritional intervention on these immune responses.

Objectives

1. Characterise innate and T-cell immune responses to *Mycobacterium tuberculosis* (Mtb) in moderately malnourished and well-nourished children with tuberculosis (TB) disease.
2. Characterise innate and T-cell immune responses to *Mycobacterium tuberculosis* (Mtb) in moderately malnourished and well-nourished children with latent TB infection (LTBI).
3. Assess the impact of a nutrition intervention on immune responses to *Mycobacterium tuberculosis* (Mtb) in children with malnutrition.

Methods

We are prospectively enrolling BCG vaccinated and HIV negative children (total 220) of either sex, aged 1 to 5 years who were household contacts of pulmonary TB patients. Children are categorised into four groups depending on their TB diagnostic test results and nutritional status: 1) MAM with TB disease; 2) Well-nourished with TB disease; 3) MAM with LTBI; 4) Well-nourished with LTBI. Children with Multi drug resistant (MDR) TB disease and contacts of MDR TB patients were excluded. In all groups, 5 ml blood is taken at baseline (prior to anti-tuberculous chemoprophylaxis or therapy) to compare immune responses between the groups, focusing on innate and adaptive immune responses to *Mtb*, monocyte: lymphocyte ratios and mycobacterial growth inhibition. Children of group 1 receive 12 weeks of ready to eat supplementary food (RUSF) along with ATT or isoniazid prophylaxis. All children are followed up at weeks 12 and 24 for immunological and clinical assessment.

Study progress

Recruitment and follow up of 119 children in the LTBI group is completed. Follow-up of 49 children recruited in the TB group is ongoing.

11. A longitudinal observational study on the impact of SARS-CoV-2 infection on Immune responses to Tuberculosis in children and adolescents

Principal Investigator	:	Dr Aishwarya Venkataraman, Scientist E
Participating Institutes	:	Institute of Child Health and Hospital for Children (ICH), Madurai
Source of funding	:	ICMR Intramural, International Centre for Excellence in Research (ICER).
Study period	:	2021-2023
Category	:	TB and COVID
Pillar	:	Detect

Background

Data regarding the impact of COVID-19 on paediatric TB is very limited. Therefore, in this study we aim to characterise the immune responses to Mycobacterium tuberculosis (Mtb) in children with previous COVID-19 infection and TB.

Objectives

1. To characterise the TB specific immune responses in TB children and adolescents with or without evidence of previous SARS-CoV-2 infection (SARS-CoV-2 IgG positive).
2. To study the effect of previous SARS-CoV-2 infection on the disease spectrum in children and adolescents with TB.

Methods

We are prospectively enrolling children aged 0 to 18 years with TB disease. They are then categorised into SARS-COV-2 seropositive or seronegative based on their SARS-CoV-2 IgG results. In both groups, 5 ml blood is drawn at baseline (prior to anti-tuberculous chemoprophylaxis or therapy) to compare immune responses between groups, focusing on innate and adaptive immune responses to *Mtb*, monocyte: lymphocyte ratios and mycobacterial growth inhibition. All children are followed up at weeks 12 and 24 for immunological and clinical assessment.

Study progress

70 children and adolescents have been recruited. The follow-up is ongoing.

12. Acceptability and feasibility of Mobile app in Adverse Drug Reactions (ADRs) reporting in National TB Elimination Programme Centres (NTEP) centres.

Principal Investigator	: Dr.S.Ramesh Kumar, Scientist E
Participating Institutes	: Indian Pharmacopiea Commission National TB Elimination Programme (NTEP) centres
Source of funding	: ICMR Intramural
Study period	: 2019 – 2023
Category	: TB
Pillar	: Build

Background

Adverse drug reactions (ADR) can lead to a patient interrupting TB treatment contributing to avoidable morbidity, treatment failure, reduced quality of life, or death. The overall burden of ADRs directly attributable to anti-TB medicines is poorly quantified and it is not usually well profiled under TB programme. NTEP is committed to improve pharmacovigilance. Mobile app has been proved to be better than the classical ADR reporting. Govt of India has released a mobile app for ADR reporting namely PVPI mobile app. We propose to assess the acceptability and feasibility of implementing the Mobile app launched by the Govt of India that is 'PvPI ADR reporting App' in the NTEP centres for reporting ADRs

Objective

To assess the acceptability, feasibility of implementing Adverse Drug Reactions(ADRs) reporting using 'PvPI ADR reporting App' of Govt of India in the NTEP Centres

Methodology

Fifteen NTEP centres in Madurai, were randomly selected from both rural and urban areas and the Medical Officers (MO) in the centres were sensitized and trained in using the 'PvPI ADR reporting App' for reporting the ADRS during the TB treatment. ADR reporting by the MOs were assessed periodically for one year. A baseline assessment of the ADRs reported by the Medical Officers of study centres was done by capturing the information in the required study form. After a year, ADRs reported by the Medical Officers of study centres following the sensitization and training are being captured in the required study form. A Qualitative analysis of the data captured from the Medical Officers to assess the feasibility and acceptability, will be done.

Study progress

29 MOs were trained and ADR reporting is being captured periodically. The study is ongoing

13. Evaluation and Certification of Sub-national progress towards 'TB Free' status in India, using district level annual survey-DLAS (2021-24).

Principal Investigator	:	Dr. S. Syed Hissar, Scientist E
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis(NIRT); ICMR- National Institute of Epidemiology (NIE); Central TB Division(CTD); World Health Organisation(WHO) - India; and Indian Association of Preventive and Social Medicine (IAPSM)
Source of funding	:	Central TB Division and Global Fund to fight AIDS, Tuberculosis and Malaria.
Study period	:	2021-2024
Category	:	TB
Pillar	:	Build

Background

To achieve the targets of elimination of communicable diseases including TB at a large scale, it is essential to take disease control initiatives to the grass root level. Incentivizing and rewarding well performing states/districts for achieving target that are within their control and capacity, will not only motivate states/districts to prioritize and undertake implementation of the National Tuberculosis Elimination Programme (NTEP) in elimination mode, but will also generate a sense of healthy competition among States/Districts. Accordingly, it is considered to have sub-national level progress towards ending TB documented at defined milestones and "Awards" be presented to respective State/Districts upon achievement of these milestones.

Objectives

1. To evaluate the progress of all the districts in India towards TB Free status based on reported trends in TB incidence and prevalence, number needed to test and TB score in all the districts.
2. To verify the eligibility of the districts/states that have submitted TB free claims based on reported trends in TB incidence and prevalence, number needed to test and TB score.

Methods

Mixed method study with a triangulation design. The quantitative component will include cross-sectional primary data collection through a survey and secondary data review (review of records from NIKSHAY notification systems and NTEP reports, utilisation of drugs in public and private sector). The qualitative component will involve nominal focus group discussions (FGD) and key informant interviews (KII) done by the data collectors among chemists and private providers on anti-TB drug sale in the private sector. The incidence of TB and decline in incidence (from 2015) of TB will be obtained and the progress of all the districts towards TB Free status will be evaluated. This will also help in understanding the bacteriological burden of TB at district level.

Study progress

For the year 2022, 10 states/UTs and 302 district claims from NTEP were submitted for verification. These states and districts were verified in different categories of progress towards TB free status based on the decline in incidence of TB in 2022 compared to 2015.

14. Prevalence of cardiopulmonary perfusion defects and vascular damage among Post-COVID-19 patients using Q-SPECT/CT hybrid imaging and correlation with biomarkers for prognostication – a longitudinal study (POCOS)

Principal Investigator	:	Dr G. Narendran, Scientist F
Participating Institutions	:	ICMR-National Institute for Research In Tuberculosis(NIRT) Tamil Nadu Government Multi Super Specality Hospital (TNGMSSH), Chennai Sree Guru Heart Clinic, Chennai Institute of Thoracic Medicine, Chennai Madras Medical College, Chennai Mehtas Hospital
Source of funding	:	ICMR – Call for COVID-19 proposals
Study period	:	2022-2024
Category	:	COVID-19

Background

Cardiopulmonary sequelae continue to affect the survivors of the acute phase of COVID-19 illness even after recuperation. A visual understanding of the extent and consequence of the disturbed vascular topography of the cardiopulmonary tree could provide vital information that ultimately decides the need for post-COVID-19 surveillance

Objective

Primary Objective

To estimate the proportion of vascular defects in the cardiopulmonary tree and structural changes in the lung parenchyma by Q-SPECT during the post/ long COVID period among patients with minimal (Mild) and advanced covid disease (Moderate +severe) at the time of initial COVID disease,

Secondary objectives

- To determine if these vascular defects form a prelude to defining clinically overt events of cardio-pulmonary vascular insufficiency in future demanding medical intervention, by following them for one year from COVID-19 onset.
- To ascertain if biomarkers could function as a surrogate, providing early clues towards plausible deterioration subsequently.
- To correlate if the severity of initial presentation (acute phase of COVID-19) has a bearing on the presentation and severity of post-COVID-19 sequelae after adjusting for comorbidities.

Methods

Post-COVID-19 patients from the first and second wave of COVID would be categorized into minimal (mild), and advanced (moderate + severe) disease based on initial COVID-19 presentation as per guidelines. Using a longitudinal observational cohort of post-COVID-19 patients segregated into minimal and advanced disease, clinical evaluation, cardio-pulmonary vascular defect evaluation using QSPECT/CT hybrid for occult vascular insufficiency in the cardio-pulmonary bed will be done. In addition, ECHO, cardiac markers and immunological markers will be done to validate if these could act as surrogate markers for the QSPECT.

Study progress

137 patients have been recruited so far, 81 (total sample size- 90) in the advanced group and 56 (total sample size-60) in the Minimal group and 124 have completed the first round of all baseline basic investigations and immunological work up. Q SPECT cardiac and the overall 1st visit is completed in 105 patients. 48 patients had completed the 2nd follow up visit and 15 patients had completed 3rd visit.

Figure 1. Appearance of the Normal Q-SPECT in an Asymptomatic COVID 19 participant

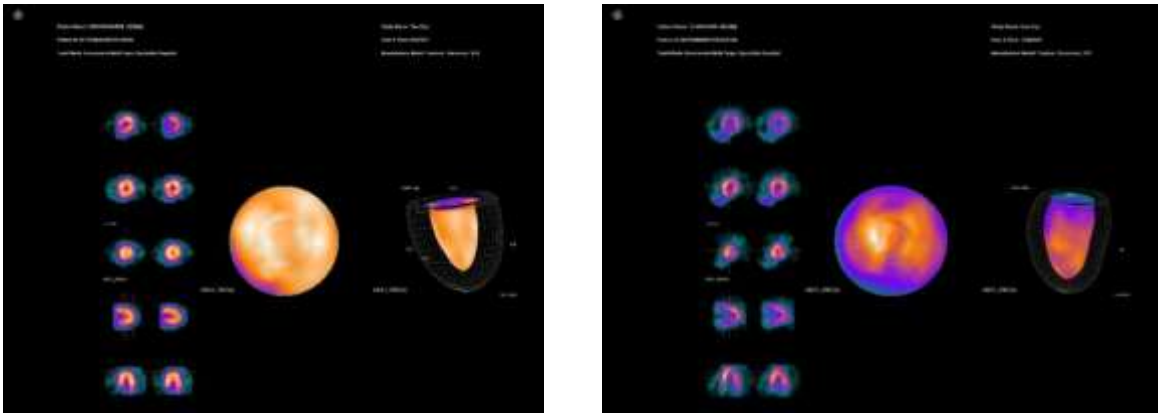
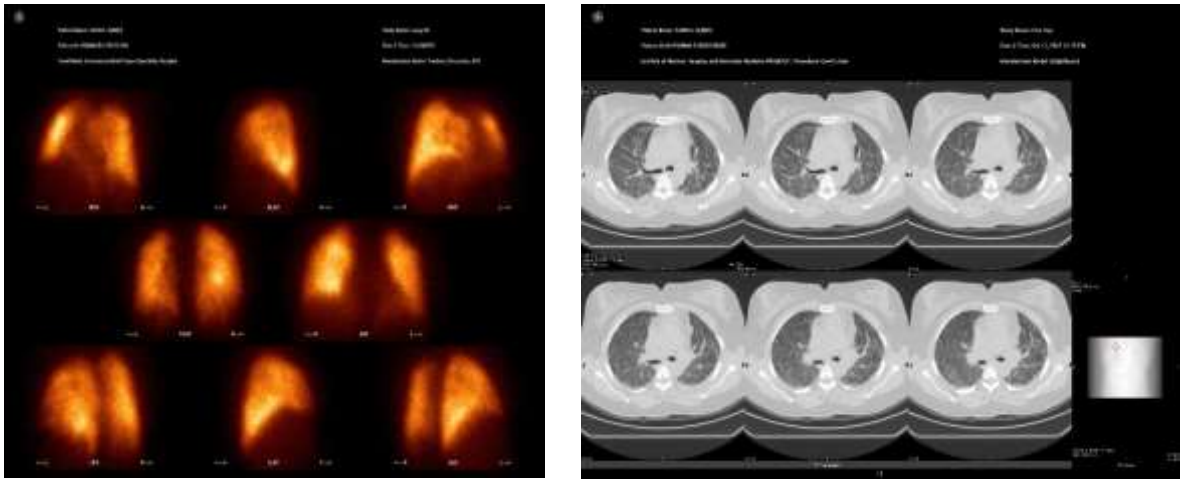


Figure 2: Extensive fibrosis in the CT with normal perfusion pattern in the Tech MAA scan, obviating the need for prolonged anticoagulation



Completed studies

S.no	Title of the project	Name of PI Designation	Source of funding	Category / Pillar
1	Randomised clinical trial to study the efficacy and tolerability of a 4-month regimen containing ofloxacin compared to the standard 6-month regimen in the treatment of patients with superficial lymph node tuberculosis.	Dr. D. Baskaran, Scientist F	ICMR Intramural	TB/Treat
2	Evaluation of the Efficacy and Safety of a Combination regimen of Bedaquiline, Delamanid, Linezolid and Clofazimine in Adults with Pre-extensive (Pre-XDR) and Extensively Drug-resistant Pulmonary Tuberculosis (XDR-TB): Prospective Cohort Study (BEAT Study).	Dr.C. Padmapriyadarsini, Director	USAID	TB/Treat
3	The evaluation of a Standard Treatment Regimen of Anti-tuberculosis drugs for patients with MDR-TB (STREAM – Stage 2).	Dr G. Narendran, Scientist F	USAID and Janssen Research & Development, LLC., MRC, UK (DFID) , EDCTP2 programme supported by the European Union	
4	Host RNA Expression for Diagnosis and Monitoring of Pediatric TB in Africa and India: RICC Pediatric Transcriptomic Study.	Dr Syed Hissar, Scientist E	CRDF Global – RePORT International Supplemental Funding, NIH, USA	TB/Detect
6	Serial inflammatory responses in children receiving different treatment regimen for Multisystem Inflammatory Syndrome (MIS-C) - Longitudinal observational study from Southern India	Dr Aishwarya Venkataraman Scientist E	ICMR Intramural	COVID-19

SOCIO - BEHAVIOURAL STUDIES

DEPARTMENT OF SOCIAL AND BEHAVIOURAL RESEARCH

DEPARTMENT OVERVIEW AND MANDATES

Department of Social and Behavioural Research (DSBR) remains integral to the vision and mission of ICMR- NIRT.DSBR plays a key supportive role in the clinical trials which are undertaken at ICMR-NIRT and other research studies which require effective patient support activities. The department had undertaken multiple social behavioural studies in TB and HIV at the state and national level which have policy implications. Qualitative and quantitative research studies in assessing the psycho-social factors which drive TB patient health seeking-behaviour, treatment adherence and completions are undertaken by the department. DSBR has conducted Randomised control trials to test the effectiveness of psychosocial interventions on various target groups. The department had also implemented operational and implementation research projects for TB at the national and sub national level and had been contributing to the NTEP program in various aspects. DSBR had developed a range of research tools, interventions materials and research findings which are actively disseminated to the policymakers and stakeholders to facilitate translation of research output into practice. DSBR had initiated a pan India 'Socio-Behavioural Research Network" for TB with the participation of different institutes and organisations with an aim to foster multi centric studies relevant to addressing social aspects of TB.

In addition to its research contribution, DSBR is known for its active community outreach towards the vulnerable sections of society that are affected by TB and HIV. DSBR also routinely organises Information, Education and Communications intervention to various sections of society to improve the knowledge, attitude and practices of the community with respect to TB prevention, diagnosis and treatment.

Studies in progress

1. Exploring and understanding the psycho-social factors enabling drug resistant patients to achieve better treatment adherence and completion-A qualitative study in Bengaluru and Hyderabad

Principal Investigator	:	Dr. N Karikalan, Scientist C
Participating Institutes	:	Karnataka Health Promotion Trust (KHPT) /TB Alert
Source of funding	:	USAID through Karnataka Health Promotion Trust (KHPT)
Study period	:	2020-2023
Category	:	TB
Pillar	:	Treat

Background

Treating MDR-TB patient's remains challenging with high loss to follow-up, death, and failure rates. Long duration of treatment, adverse drug reactions, and significant psychological, social, and economic difficulties are faced by MDR-TB patients. But there are few drug-resistant TB patients who complete treatment with high adherence despite challenges. To understand this aspect of the patients who have better adapted to the treatment challenges of MDR-TB, we propose a Positive Deviance (PD) approach, a novel socio- behavioral method to address health and social problems by identifying existing community solutions.

Objectives

1. To explore and understand from the perspectives of MDR-TB patients the enabling, facilitating, and other positive factors that aided them to achieve better treatment adherence and successful treatment completion.
2. To explore and understand from the perspectives of the family members and health care providers of positively deviant MDR-TB patients of the enabling, facilitating, and other positive factors that aided their sick family member to achieve better treatment adherence and successful treatment completion

Methods

This cross-sectional study involves semi-structured interviews (SSIs) and focus group discussions (FGDs). Adult (age 18yrs and above) MDR-TB patients who had completed their treatment within the past one year of study initiation in Hyderabad and Bengaluru city will constitute the study population. The study population will also include family members and health care providers of the MDR-TB patients. Identification of PD patients will be done by the framework: define the problem, determine the presence of positive deviants, and discover uncommon but replicable behaviors and strategies of PDs. Semi-structured qualitative interview guides will be developed specifically for respondents. The emerging themes during the initial phase of analysis will be assessed by the research team and finalized once all data have been coded. Quotes and analytical memos will be reviewed and placed under the appropriate thematic heads. The interviews will be conducted till thematic data saturation is attained.

Study Progress

We have conducted semi structured in-depth interviews among adult DR-TB patient's (7 women, 13 men) who completed shorter treatment regimen (with injections) with maximum treatment adherence (≥ 2 consecutive days of interruption) in India. Patient's family caregivers (14 women, 6 men) and health providers (8 men, 2 women) were also interviewed.

2. An innovative approach for engaging student and women organizations in Tuberculosis case finding and Treatment adherence: A step toward Tuberculosis elimination in Senapati District Manipur.

Principal Investigator	:	Dr. A. Stephen, Scientist C
Participating Institutes	:	Rajendra Institute of Medical Sciences (RIMS), Manipur
Source of funding	:	ICMR Extramural
Study period	:	2023-2024
Category	:	TB
Pillar	:	Detect/Treat/Build

Background

India is heading towards achieving the elimination goal of TB by 2025, however the undiagnosed TB cases still stands a challenge. Further, the tribals in general are highly vulnerable to a number of health risks including TB. For this, the Government of India has come up with National Strategic Plan (NSP) 2017-25 to address this high-risk group and recommended active case finding (ACF) among high-risk groups as a strategy to detect the "missing" TB patients. However, a North-Eastern (NE) state of Manipur has not conducted separate ACF activity, as it requires a lot of manpower to carry out the activities especially to reach hard-to-reach areas as the settlement of the people are widely scattered, especially where tribal people are inhabited. Therefore, a model/demonstration project will be carried out in a tribal dominated, hilly / hard-to-reach Senapati district of Manipur to identify additional human resources at the community level, to improve TB case finding rates, treatment adherence and completion rates by engaging student and women organizations in comparison to routine program strategies.

Objectives

To determine the incremental increase in TB case finding rates, treatment adherence and completion rates by engaging student and women organizations in comparison to routine program strategies.

Methods

The study is being carried out using quasi-experimental pre-post design in the whole district of Senapati, Manipur. The study will be done in 2 phase, preparatory phase and intervention phase. Preparatory phase includes identification of volunteers, training, door to door enumeration and TB awareness campaign (1-3months), Intervention phase include 2 round of TB symptom screening (4^{th} and 10^{th}month) from door to door. Data will be collected using REDCap hosted at ICMR-NIRT. Quarterly TB case notification data will be collected from the baseline period up to the end of the intervention. Trends in PHI/PHCs/CHCs/ DTC specific TB case notifications, adherence and treatment outcome will be analysed.

Study Progress

The project was initiated in February 2023 and 281 volunteers have been trained. 102 TB awareness campaign have been conducted with the volunteers and medical officers of all PHC/CHC/SDH/DTC, student and women organizations. Enumeration has been initiated in 65 villages.

3. Transportation workers lead intervention to improve TB literacy among coworkers and demand generation in the community - A quasi-experimental study to test the effectiveness.

Principal Investigator	:	Mrs Chandra Suresh
Source of funding	:	State TB Cell
Study period	:	2022 to 2024
Category	:	TB
Pillar	:	Build

Background

Public transportation may serve as a potential pathway for TB transmission due to overcrowding and poor ventilation. Thus, there is an unmet need for transportation workers who are at increased risk of airway transmission of infection-for increased awareness and knowledge about TB. On the other hand, public transportation is also used by people from different socioeconomic, demographic, and geographical backgrounds and provides an opportunity for engaging with a large volume of the population. This opportunity for public transportation workers to engage with lakhs of passengers every day could be utilised for demand generation for TB related information among the public.

Objectives

1. To assess the outcomes of transport ambassador lead community engagement strategy in improving TB literacy among co-transportation workers in Chennai
2. To assess the outcomes of transport ambassador lead community engagement strategy in increasing the demand for TB literacy among passengers in Chennai

Methods

A quasi-experimental design with pre and post-test to assess the impact of the intervention (TB-IEC tickets). The study population are Bus Drivers and Conductors. The study is being planned to be carried out in Chennai and the bus commuters.

Study progress

TB -IEC tickers have been developed during the formative phase. Further line listing of the bus depots and sample frame has been completed. The study is ongoing.

Completed studies

S.no	Title of the project	Name of PI Designation	Source of funding	Category/ Pillar
1	Measuring socio-economic risk-benefits and health related quality of life changes associated with tuberculosis disease disclosure	Dr.N.Karikalan, Scientist C	ICSSR-IMPRESS	Build
2	Study on Knowledge, Attitude, Practice towards Tuberculosis (TB) and Feasibility of TB Screening among Public and Private Drivers and Conductors in Tamil Nadu	Dr P. Murugesan, Senior Technical Officer	NIRT intramural	Build

LABORATORY STUDIES

DEPARTMENT OF BACTERIOLOGY

DEPARTMENT OVERVIEW AND MANDATES

The Department of Bacteriology supports the clinical trials and operational research studies carried out at ICMR-NIRT, including setting up drug susceptibility testing for newer anti-TB drugs like Pretomanid, Bedaquiline, and delamanid. The Department also contributes towards TB Prevalence studies namely National TB Prevalence Survey and Tamil Nadu District Prevalence Study. The laboratory is a National Accreditation Board for testing and calibration laboratories (NABL) certificated laboratory.

The Department has established methodologies for newer and repurposed drugs. Molecular validation studies on various in-country kits are being performed. In addition, WGS/TNGS have been harnessed for managing Drug resistant TB patients. Lineage based studies have shown that lineage 1 is common in the Southern part of India and lineage 3 increases as we go towards the North. Effective diagnostic tool for pediatric TB is a challenge. Studies on non-sputum-based diagnostic methods like stool, and urine can be used not only for molecular diagnosis but also for culture-based diagnosis. Utility of the Resuscitation Promoting Factors in detecting the non-replicating persisters and exploring the critical concentrations of anti-TB drugs among *M. tuberculosis* isolates circulating in and around Chennai are being conducted which will be of help in deciphering the pharmacodynamics indices. Our department has initiated a nation-wide DRS by Next generation sequencing technology which will help in resistance prediction and transmission dynamics.

ICMR - NIRT is one of the National Reference Laboratory under the National Tuberculosis Elimination programme (NTEP) and provides technical support for the TB laboratory activities to five states and five Union territories in India for NTEP activities. As part of Supranational National Reference Laboratory (SNRL), NIRT conducts External Quality Assurance (EQA) for culture and DST (Drug susceptibility testing) under the NTEP. This is also extended to SEARO member countries namely Myanmar and Timor Leste. We have also provided support to conduct drug resistance surveillance to Timor Leste. We also provide line probe assay for 1st line and 2nd line anti-tuberculosis drugs and other diagnostic services for Tamilnadu under Programmatic Management of Drug-Resistant TB (PMDT).

Studies in progress

B-1: Prevalence of Resistance to Newer Anti-tubercular Treatment (ATT) drugs in Treatment-Naive Tuberculosis Patients from Tamil Nadu: 2021-2023

Principal Investigator	:	Dr. S Siva Kumar, Scientist D
Participating Institutes	:	Intermediate Refence Laboratory (IRL)'s in Tamil Nadu
Source of funding	:	ICMR Intramural
Study period	:	2021-2023
Category	:	TB
Pillar	:	Detect

Background

Drug resistant TB (DR-TB) is a global public health threat when the world is striving towards TB elimination. Bedaquiline, Delamanid, and Pretomanid are the newer anti-TB drugs for DR-TB patients. Whilst we are adopting policies with the inclusion of newer anti-TB drugs in the treatment guidelines, studies reporting high to moderate levels of resistance to these drugs in treatment naïve patients is worrisome. Hence, early detection of drug resistance and appropriate management is crucial for preventing the transmission of DR-TB.

Objectives

1. To screen for all mutations possibly related to resistance to Bedaquiline, Delamanid, and Pretomanid by whole-genome sequencing (WGS) in the isolates collected from MDR/RR-TB with FQ/SLI resistant DR-TB patients.
2. To determine the Bedaquiline, Delamanid, and Pretomanid MICs for MTB strains isolated from MDR/RR-TB with FQ/SLI resistant DR-TB patients

Methods

Whole-genome sequencing and MGIT DST will be performed in eligible treatment naïve MDR/RR-TB with FQ/SLI resistant, patients to determine resistance if any to the newer and repurposed drugs. The sample size will be 300 MDR/RR-TB with FQ/SLI- resistant patients from Tamil Nadu.

Study progress

A total of 71 sputum samples have been collected from patients under all oral longer and all oral shorter BDQ containing regimens. These sputum samples were cultured to isolate *M.tb*, the same has been stored as an aliquot for further testing. A total of 47 samples of DNA have been extracted by the CTAB method. Phenotypic DST and whole genome sequencing have been performed for 10 samples. The study is ongoing

B-2: Intrinsic lineage specific susceptibility of mycobacterium tuberculosis to pretomanid.

Principal Investigator	:	Dr. S Siva Kumar, Scientist D
Participating Institutes	:	ICMR-National Institute for Research In Tuberculosis(NIRT)
Source of funding	:	ICMR Intramural
Study period	:	2022-2023
Category	:	TB
Pillar	:	Detect

Background

The knowledge base on the mutation leading to resistance to Pretomanid is lacking and the current knowledge on resistance-conferring determinants in *Mycobacterium tuberculosis* is biased toward globally dominant lineages 2 and 4. In contrast, lineages 1 and 3 are predominant in India. We have observed lineage-specific variations in the proportion of isolates with resistance-conferring mutations, with drug resistance more common in lineages 2 and 3. Differences in the intrinsic susceptibility linked to particular genotypes have been reported previously, with intrinsic resistance of *M. bovis* and *M. canettii* to pyrazinamide, *M. bovis* BCG to Cycloserine, and a subgroup of *M. tuberculosis* lineage 4 to capreomycin.

Objective

To delineate the MIC of Pretomanid in different lineages of *Mycobacterium tuberculosis* (MTB) from India. The MTB isolates were collected from the state of Tamil Nadu, Telangana, Andhra Pradesh, Maharashtra, Uttar Pradesh, Gujrat and Delhi,

Methods

A total of 221 MTB isolates with resistance to rifampicin and isoniazid (MDR-TB isolates) were included in the study. All the strains were subjected to Phenotypic DST and whole genome sequencing to predict resistance to Pretomanid through known mutation and lineage prediction.

Study progress

Out of the 221 isolates lineage 1 was predominant, followed by lineage 2, 3 and 4. The MIC classified MTB Lineage into two groups: The lineage1 and other Lineages groups (lineage 2, 3, and 4), The MIC peaked for lineage 1 at 1 µg/ml whereas it peaked at 0.125 for other Lineages group (lineage 2, 3 and 4). This is the first report on MIC of Pretomanid and its association with lineage 1. Further research exploring resistance mechanisms to the nitroimidazoles should be prioritized, since these drugs are part of the all-oral regimens for MDR-TB.

Figure 1: *Mycobacterium tuberculosis* lineage representation of study samples showing diverse *M.tb* strains.

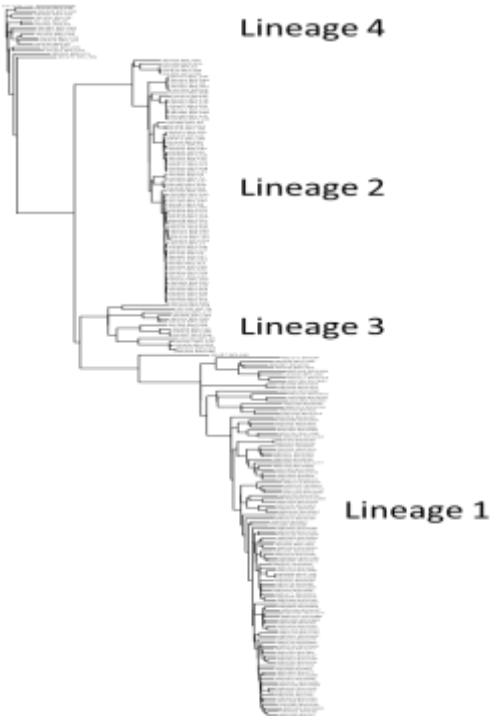
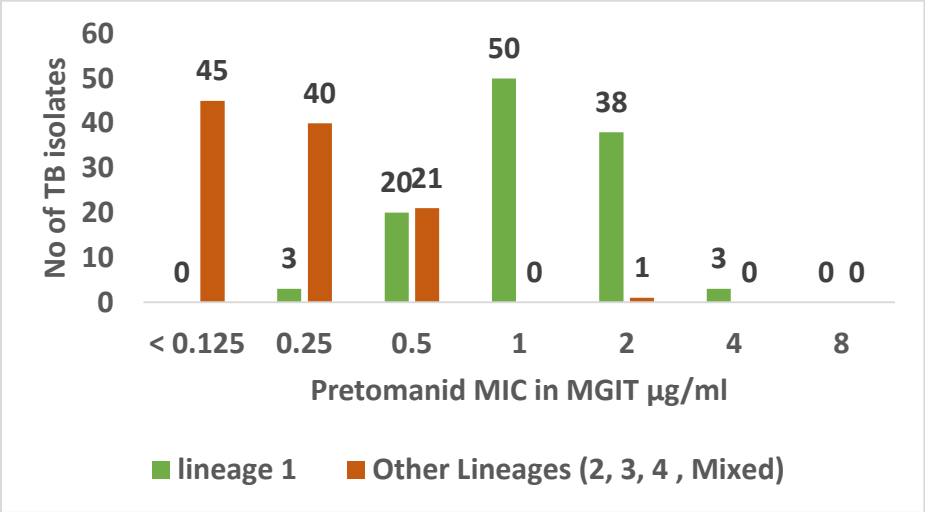


Figure 2: Pretomanid MIC distribution among different lineages of *M.tb*



B-3 Molecular epidemiology of *Mycobacterium tuberculosis* from patients treated under the National TB Elimination Programme (NTEP), India

Principal Investigator	:	Dr. S Siva Kumar, Scientist D
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis(NIRT)
Source of funding	:	ICMR Extramural
Study period	:	2021-2024
Category	:	TB
Pillar	:	Detect

Background

A better understanding of the epidemiology of TB, including molecular typing of Mycobacterium tuberculosis (*M.tb*) strains and their transmission/drug-resistant pattern, is critical for effective TB control. Our rationale is that molecular typing and genotypic characterization of clinical *M.tb* strain can establish a correlation with drug resistance, identify strain predominance, and pave way to understand disease transmission.

Objective

1. Identify and characterize the most prevalent lineage of *M.tb* in various Indian states and their association with mono- and multi- drug resistance to anti - TB drugs.
2. Understanding the dynamics of *M.tb* strain distribution among patients with co-existing Diabetes Mellitus (DM).
3. Evaluate the genotype of non-clustered/orphan *M.tb* strains and determine the evolution of predominant strains through mutation analysis by whole-genome sequencing.
4. Determine the *in vitro* fitness of representative highly transmissible strains from each state, using macrophage phagocytic index and intracellular growth assays, and co-relate the findings with disease transmission in the community.

Methods

The proposed sample size was 1500 M. tb Isolates. Initially, the study sample comprises of comprehensive characterization of 1,200 M.tb strains, which were collected as part of a previous Central TB Division study under the Revised National Tuberculosis Control Programme. The *M.tb* isolates were obtained from a cohort of uniformly newly diagnosed, sputum-positive TB patients and were archived carefully at the host institute (ICMR-NIRT). The patients included in this study were recruited at hospitals in seven different states of India (Tamil Nadu, Karnataka, Delhi, Maharashtra, Madhya Pradesh, Gujarat, and Kerala). Following these two sites were added: IRL Patiala and Bhubaneshwar/IRLPatna with additional 300 samples. All the samples were stored in the repository and were spoligotyped in batches of 40 with a positive and negative control..

Study progress

A total of 1413 M.tb isolates have been extracted and spoligotyping has been performed. Spoligotyping of 211 from Chennai, 130 from Bengaluru, 167 from New Delhi, 129 from Jabalpur, 241 from Kerala, 181 from Ahmadabad, 80 from Punjab, 152 from Bhubaneshwar, and 122 from Wardha were matched with SpolDB4 database.

Figure 1: The figure provides information on the different spoligotype distribution among the Indian cities on to the Indian map. There is a clear demarcation of CAS spoligotype (red) predominant in the north and EAI spoligotype predominant (Blue) in South India.

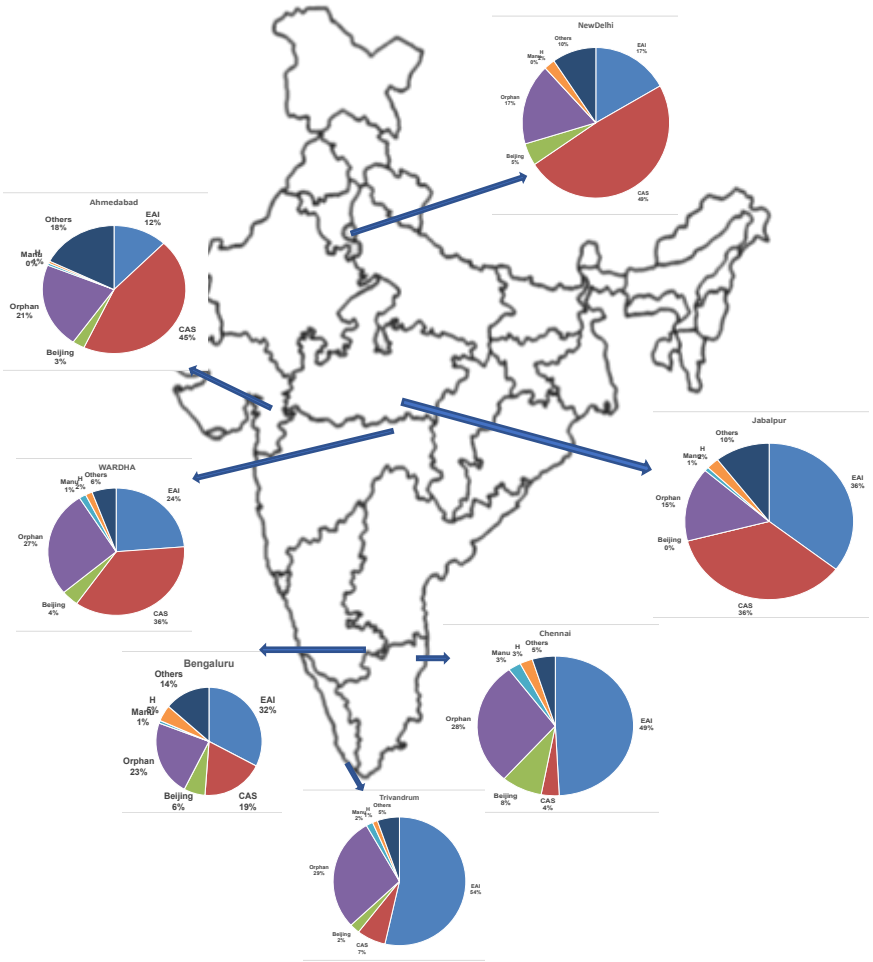
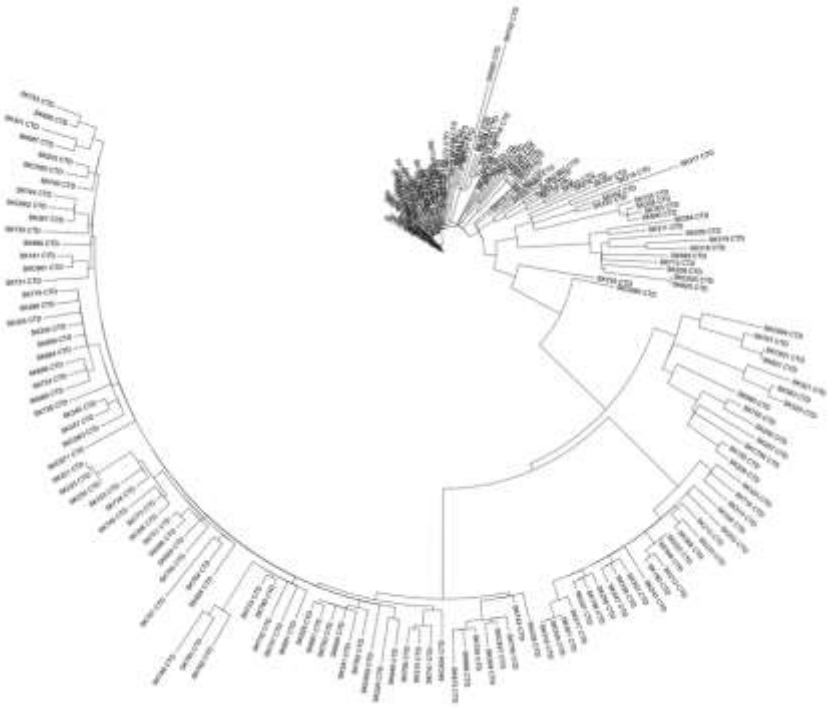
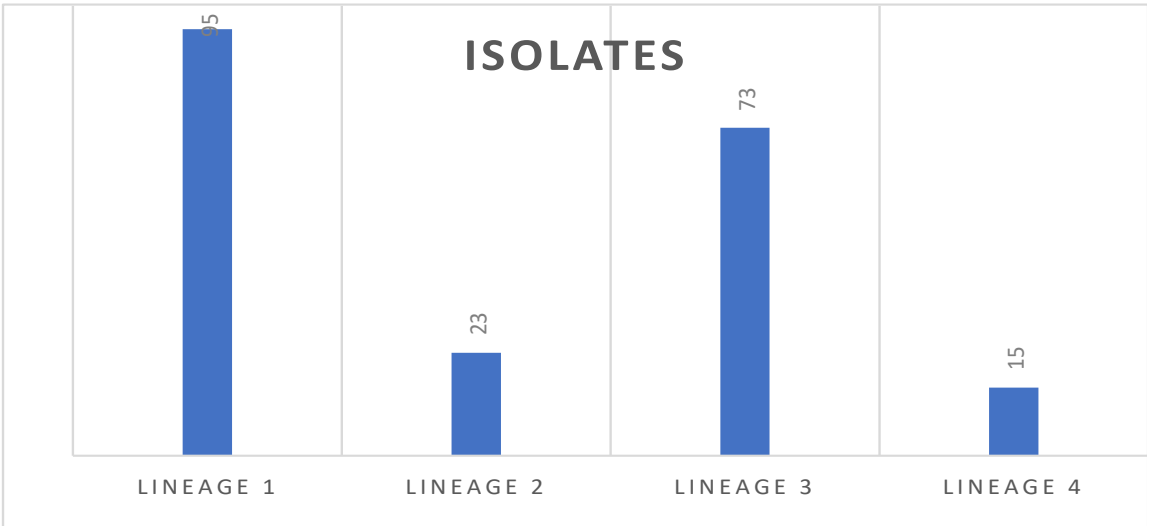


Figure 2 a and b: Phylogenetic tree of 214 M.tb isolates with several clusters and figure 1b displays the lineage prevalent in the study





B-4: Whole Genome Sequencing of MTB Clinical Strains for Determining Drug Resistance and Strain lineage in India: A structured Nationwide approach (Sentinel surveillance of drug resistant tuberculosis in India)

Principal Investigator	:	Dr. S Siva Kumar, Scientist D
Participating Institutes	:	ICMR-National Institute for Research In Tuberculosis(NIRT)
Source of funding	:	Department of Biotechnology (DBT) and ICMR Extramural
Study period	:	2023-2025
Category	:	TB
Pillar	:	Detect

Background

The first ever national anti-tuberculosis drug resistance survey (NDRS) was conducted between 2014-16. The implementation of a surveillance system for drug-resistant TB leads to improved access to timely and appropriate treatment and care. Additionally, it could provide information onoutbreaks, and real-time monitoring of the effectiveness of the programmatic interventions. The inclusion of sequencing technologies in drug resistance surveillance can provide insights into the phylogenetics of the circulating TB strains. It is currently the only approach with the ability to investigate genome-wide targets for multiple first and second-line anti-TB drugs detecting even the rare mutations that could be missed by rapid molecular assays. Additionally, it provides details on species identification, genotyping, detection of mixed populations and hetero resistance in a given sample.

Objective

Primary objectives

- To monitor the proportion and pattern of drug resistance among new and previously treated microbiologically confirmed TB patients in selected districts of India over a period of three years.
- To monitor the pattern and emergence of drug resistance mutations and phenotypic resistance of microbiologically confirmed TB patients in India over a period of three years.

Exploratory objectives

- To describe the genetic traits of circulating strains of M. tuberculosis and outbreaks
- To establish a biorepository of whole genome sequenced *Mycobacterium tuberculosis* isolates.
- To update the Indian Catalogue of *Mycobacterium tuberculosis* mutations and their association with drug resistance

Methods

Total sample size for the high and low burden districts will be 6525 samples from 276 Districts across India. The total period of study will be 4 years. Quarter II of each year will be the sample collection period for the next four years (2022 to 2025). The rest of the quarters will be distributed for training, diagnostic activity, Sequencing, Data Analysis, and reporting each year as appropriate.

Study Progress

The sample collection has been initiated. The samples collected are getting subjected to culture and DNA extraction for whole genome sequencing.

Figure: Distribution of samples across India for the study

B-5: Isolation and Analysis of *Mycobacterium tuberculosis*-Induced-MMPs directly from sputum samples: Inhibitor synthesizing and validation

Principal Investigator	:	Dr. V.N. Azger Dusthackeer, Scientist D Dr. S. Christy Rosaline, Research Associate
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis(NIRT)
Source of funding	:	ICMR Research Associateship
Study period	:	2021-2024
Category	:	TB
Pillar	:	Treat

Background

Lung tissue damage facilitates the dissemination of *M.tuberculosis (M.tb)* Matrix metalloprotease (MMP) which plays an important role in the tissue damage of the lung in TB patients. Other than lung tissue destruction, MMP plays a key role in the formation of granuloma. Tissue inhibitors of matrix metalloproteinases (TIMP) that inhibits MMP activity. The inhibitors TIMPs -1, 2 and 3 facilitate remodeling and repair of lung tissues. These inhibitors are suppressed during *M.tb* infection leading to many side effects in TB patients. Several MMP inhibitors have been identified, but doxycycline is the only inhibitor approved by the Food and Drug Administration. Over the availability of the approved inhibitors for the MMPs the use of the same is not possible due to insufficient safety and efficacy data. Hence more experimental data are required for addressing the issue of severe lung tissue damages among the pulmonary TB patients.

Objectives

- To identify small molecule inhibitors for *M. tb*-induced MMPs using *In silico* virtual screening.
- To analyse the MMP inhibitory activity of lead molecules by *ex-vivo* methods using peripheral blood mononuclear cells.

Methods

- Auto dock was used to screen and shortlist small molecules against MMPs.
- MIC determination by broth micro dilution method and cytotoxicity analysis by rezasurin reduction assay in THP-1 cells for small molecules
- H37RV induced PBMC were treated with small molecule
- RNA were extracted and expression of MMP 1 and 9 were determined by using RT PCR

Study progress

Using *In-silico* based approaches 44 lead molecules from zinc-natural database against MMP was short-listed. Among 44 small molecules 6 were (Meclofenamate sodium (MS), Tazobactam (TZ), Pirfenidone (PF), Diflunisal (DF) Ketoprofen (KP) Bacitracin (BCT) screened against H37Rv strain. The investigation showed that BCT, PF were the least inhibitors active against M. tuberculosis H37RV (MIC 1000 µg/mL). KP,DF and TZ showed potent inhibition (250 µg/mL ,125 µg/mL and 125 µg/mL). MS was the most active compound against MTB (31.25 µg/mL).

Cytotoxicity was determined by using Resazurine assay. Based CC50 of small molecules on THP-1 cells ,BCT ,PF and TZ showed the most toxicity at the concentration of 3000 µg/mL and 375 µg/mL. KP ,MS and DF showed nil toxicity at the concentration of 750 µg/mL,93.75 µg/mL and 375 µg/mL respectively.

Based on the MIC value the small molecules were treated with H37Rv induced PBMC. RNA were extracted in 4 different concept to evaluate MMP-1 and 9 expression. (i) RNA extraction in PBMC alone;(ii) RNA extraction in H37RV induced PBMC after 24 hours incubation;(iii) RNA extraction in H37RV induced PBMC which was treated with small molecules. The 24-hour incubation of PBMC with H37RV revealed MMP-9 expression, which was higher than MMP-1 and was used as the control. PF (Pirfenidone), one of six small compounds, showed suppression of MMP-9 when compared to control. The other compounds did not exhibit any appreciable inhibition.

B-6: Multicentre trial to assess the performance of centralized assay solutions for detection of MTB and resistance to Rifampicin and Isoniazid.

Principal Investigator	:	Dr. R. Priya, Scientist C
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis(NIRT)
Source of funding	:	Foundation for Innovative New Diagnostics (FIND),India
Study period	:	2022 -2023
Category	:	TB
Pillar	:	Detect

Background

The development of rapid molecular diagnostic tests for the identification of Mycobacterium tuberculosis (MTB) and TB drug resistance is a research priority. While GeneXpert and Truenat are used at point of care level, several novel assays have been recently developed. One of these assays is the Fluorotype MTBDR V2 which is commercialized by Hain LifeScience. The MTBDR V2 assay was highly comparable to LPA for the detection of resistance to rifampicin and isoniazid irrespective of sputum smear grade, and also showed a high accuracy for the identification of mutations in rpoB, katG and inhA promoter region.

Objectives

Primary objectives

1. Estimate diagnostic accuracy of Fluorotype MTBDR V2 assay for MTB detection for smear positive and smear-negative TB, including Xpert MTB/RIF (or ultra) as a comparator and culture as the reference standard
2. Estimate diagnostic accuracy of Fluorotype MTBDR V2 assay for resistance detection (RIF/INH) with sequencing and phenotypic DST as the reference standard.

Secondary objectives

1. Estimate diagnostic accuracy of Fluorotype MTBDR V2 assay for MTB detection by subgroup (sputum processing method, site, HIV status and TB history) including Xpert MTB/RIF (or ultra) as a comparator and culture as the reference standard.
2. Assess operational characteristics, including invalid and indeterminate rate, throughput and ease of use.

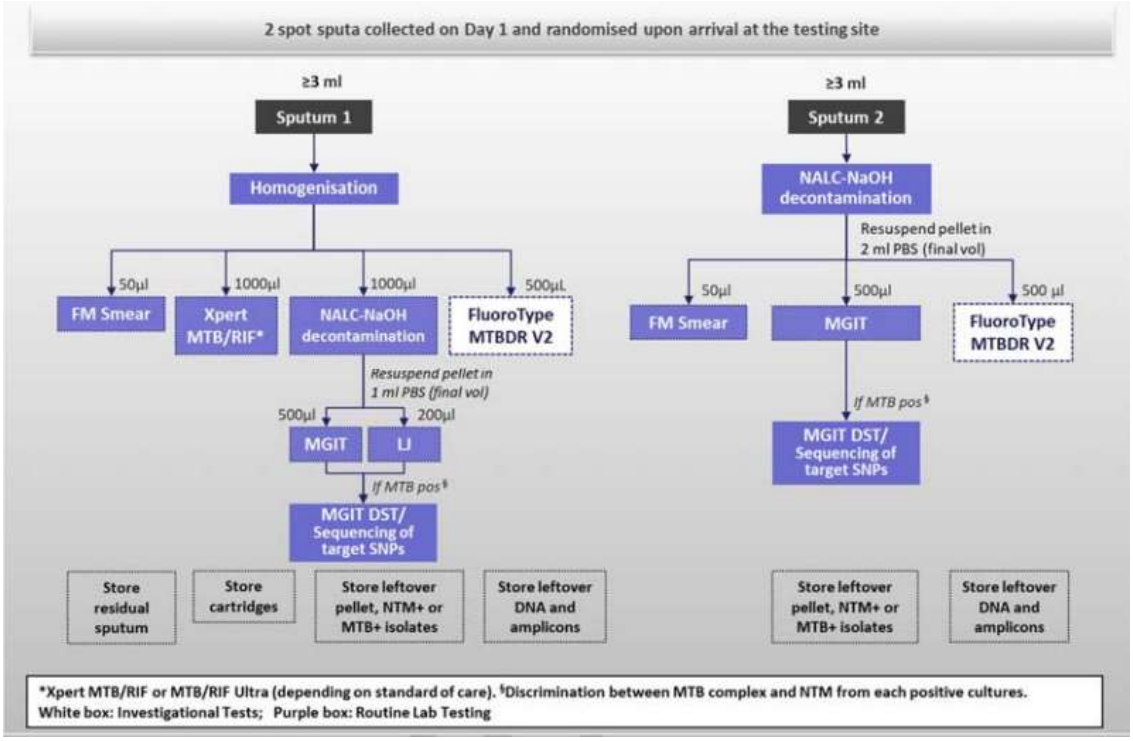
Methods

The Fluorotype MTBDR assay uses non-symmetric PCR (previously described as Linear After the Exponential (LATE) PCR), together with sets of Lights-On/Lights-Off probes. DNA is extracted using the GenoXtract96 instrument from NALC-decontaminated specimens. Briefly, NALC-decontaminated specimens are inactivated with the Inactivation Reagent Set (Hain LifeScience) and transferred to the GenoXtract96 instrument. This fully automated instrument does DNA extraction from clinical specimens and cultured isolates, prepares the PCR mix plates and transfers the extracted DNA to the PCR plate. PCR and detection are then done in the FluoroCycler XT. Result interpretation is done by the FluoroSoftware XT-IVD.

Study progress

A total of 340 patients were recruited for the study. Laboratory procedures are completed and the data analysis is ongoing.

Figure: Laboratory procedure to assess the performance of centralized assay solutions for detection of MTB and resistance to Rifampicin and Isoniazid.



B-7: Characterisation of *M. abscessus, M.kansasii, M.avium- intracellulare Complex* - the most common NTM species isolated from presumptive TB patients

Principal Investigator	:	Dr. R. Priya, Scientist C
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis(NIRT)
Source of funding	:	ICMR Intramural
Study period	:	2022 -2025
Category	:	TB
Pillar	:	Detect

Background

Non tuberculosis mycobacteria (NTM) are increasingly recognized as causative agents of opportunistic infection in humans. In general, *Mycobacterium tuberculosis* (MTB) and NTM infections have identical clinical symptoms leading to misdiagnosis of disease. Patients not responding to treatment, as most of the NTM being resistant to antibiotics and ATT (anti-tuberculosis therapy), instances of them being identified as multi drug resistant TB is common. Appropriate identification methods for NTM and MTB are need of the hour. In this study, we aim to identify NTM isolated from presumptive TB patients and further characterize them by genotypic and phenotypic methods.

Objectives

Primary objective

To identify the pathogenic non-tuberculous mycobacteria causing symptomatic pulmonary disease

Secondary objective

1. To characterize the most common species *M.abscessus, M.kansasii,* and *MAC* isolates using different molecular methods.
2. To determine the drug resistance pattern of the isolates using different phenotypic and genotypic methods.

Methods

The positive MGIT/LJ cultures will be tested with ICT (Immunochromatography) test involving MPT64Ag to differentiate MTB and NTM. DNA from NTM cultures will be extracted with Genolyse Extraction kit. Speciation of growth from two positive cultures per patient will be done using Genotype *Mycobacterium* CM/AS kit. In addition, PCR RFLP will be carried out on the species for further subtyping. Genotypic and phenotypic drug resistance testing will be carried out by NTM-DR kit and broth microdilution method respectively.

Study progress

A total of 79 isolates have been subjected to characterisation methods and sequencing. The study is ongoing.

B-8: Assessing the utility of different biological samples (Urine, stool, and respiratory specimens) for pediatric pulmonary TB detection – a cross sectional study

Principal Investigator	:	Dr. R. Priya, Scientist C
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT), Maulana Azad Medical College (MAMC), Regional Medical Research Centre (RMRC)
Source of funding	:	ICMR Intramural
Study period	:	2022 -2025
Category	:	TB
Pillar	:	Detect

Background

Prompt diagnosis of pulmonary tuberculosis (PTB) remains challenging in children because it is highly difficult to obtain the expectorated samples from them. The poor reliability of current pediatric diagnostics has made clinicians rely entirely on medical history, clinical symptoms, and chest radiography for TB treatment. Therefore, there is an urgent need for the development of diagnostic methods using non-sputum-based specimens that would be cutting edge for the diagnosis of childhood tuberculosis. In this study, we aim to detect TB in different biological samples (respiratory samples, urine and stool) collected from the children with presumptive TB and to compare the yield of MTB detected.

Objectives

Primary objective

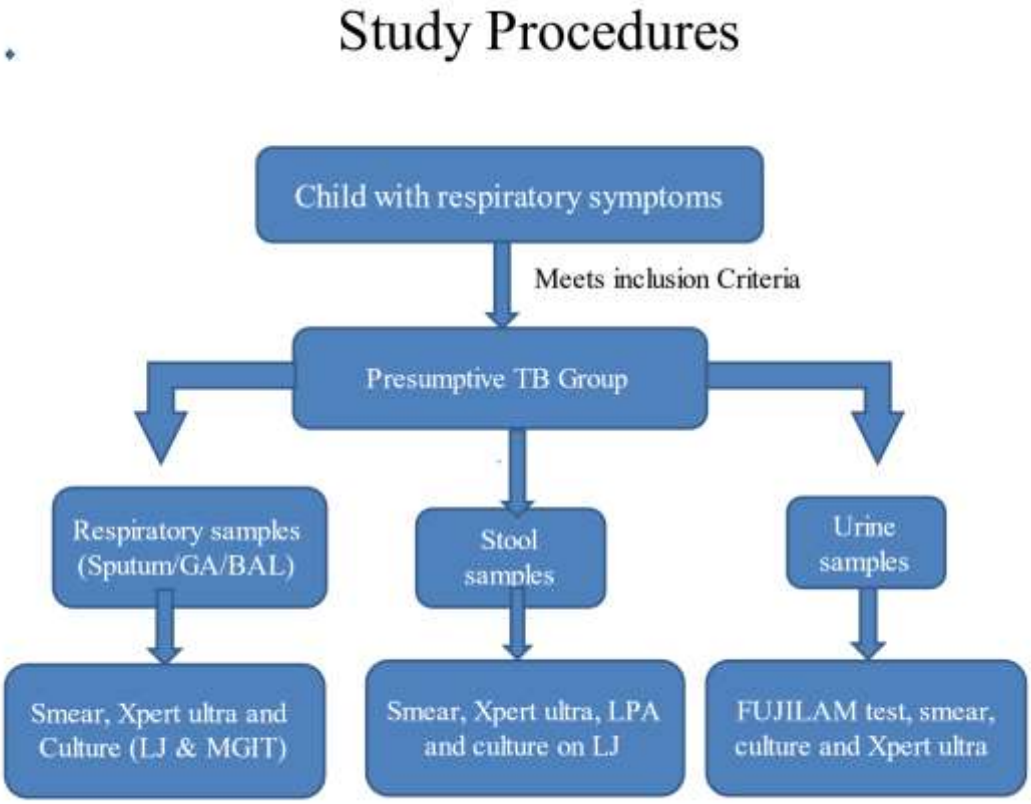
To evaluate the comparative yield of MTB, detected from easily available biological samples such as stool and urine in comparison to respiratory samples.

Secondary objectives

1. To determine the diagnostic accuracy of molecular detection of MTB detection in stool processed by an in-house standardized protocol.
2. To determine the utility of SILVAMP FUJILAM test in urine samples for pediatric TB diagnosis.

Methods

Expectorated or induced sputum specimens, urine, and stool will be collected from eligible children. Further investigations on these specimens will be conducted at NIRT as depicted in the figure below.



Study progress

A total of 103 children have been recruited so far and their biological samples were subjected to MTB detection procedure.

Completed studies

S.no	Title of the project	Name of PI Designation	Source of funding	Category/Pillar
1	A proof-of-concept study to evaluate diagnostic performance of TATA MD CHECK KshayANTH MTB and KshayANTH MDR TB (Rif+INH) for the detection of Tuberculosis with drug resistance in stored samples.	Dr.S.Siva Kumar, Scientist D	ICMR-Intramural	TB/Detect
2	A proof-of-concept study to evaluate diagnostic performance of TATA MD CHECK MTB MDR (Rif+INH) Real-Time PCR test for the detection of Tuberculosis with drug resistance in stored samples	Dr.S.Siva Kumar, Scientist D	ICMR-Intramural	TB/Detect
3	To evaluate the sensitivity and specificity of the PathoDetect^{TM} MTB and PathoDetect^{TM} MTB RIF and INH drug resistance kit for detection of *Mycobacterium tuberculosis* in TB suspects and M.Tb drug resistance in MDR suspects as compared to the gold standard.	Dr.V.N. Azger Dusthackeer, Scientist D	MYLAB	TB/Detect
4	Role of Membrane proteins responsible for drug efflux mechanisms in *Mycobacterium tuberculosis*	Dr.V.N. Azger Dusthackeer, Scientist D	ICMR Research Associateship	TB/Detect
5	Performance evaluation of *mfloDx® MDR-TB* and *mfloDx® MDR-TB* plus test for the detection of *M. tuberculosis* and its drug resistance from sputum samples	Dr. R. Priya Scientist C	Empe Diagnostics Pvt. ltd	TB/Detect
6	Feasibility of using Trueprep extracted DNA for Line Probe Assay testing in National Tuberculosis Elimination Program	Dr. R. Priya Scientist C	USAID	Category: TB Pillar: Detect

DEPARTMENT OF IMMUNOLOGY

DEPARTMENT OVERVIEW AND MANDATES

The Department of Immunology focuses on the biological, immunological and molecular aspects of mycobacterial infections. The department is involved in studies on basic pathogenic mechanisms that may lead to better tuberculosis (TB) diagnostic tools, development of vaccines and other immune interventions for the prevention and control of infection and disease. The department has adopted a multidisciplinary approach which includes clinical Immunology, Molecular biology, genomics and proteomics together with molecular epidemiology to explore immunology of TB.

Immunologic studies focus on genetic regulation of the immune response, the role of both HLA and non-HLA polymorphisms, and cellular immune responses in TB. We also try to understand the molecular mechanisms of infection and diseases, by extensive transcriptomic studies, along with the specific roles of mycobacterial antigens and their interactions with monocytes and other soluble immune components. More recently, the department has added facility for Next Generation Sequencing of mycobacterial clinical isolates and performing research activities towards understanding the drug resistance, transmission dynamics and identification of novel mutations driving resistance to the anti TB drugs. Apart from these, the department is also focusses on understanding the Zoonotic and reverse zoonotic transmission of tuberculosis between human and cattle.

Studies in progress

1. Accurate, Rapid, Robust & Economical Diagnostic Technologies for Tuberculosis (ARREST-TB)

Principal Investigator	:	Dr. K. R. Uma Devi, Scientist F
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis(NIRT), Government Hospital of Thoracic Medicine (GHTM), Greater Chennai Corporation
Source of funding	:	Department of Biotechnology (DBT)
Study period	:	2020-2023
Category	:	TB
Pillar	:	Detect

Background

Tuberculosis (TB) is under-reported due to poor access to appropriate diagnosis, as most of the current 'gold standard' diagnostic tools are expensive and ill adapted to resource-limited settings. Although improvements have been realized in the diagnosis TB, an estimated 75% of such cases are still not identified. This is largely due to the fact that many countries are still reliant on sputum smear microscopy as their primary analysis methodology as other diagnostic tests are simply unaffordable. To accelerate and steer product development, the WHO has identified current unmet needs and defined target product profiles to guide global investments in research, based on their impacts.

Objectives

1. Develop low-cost optical device and molecular probes to achieve 'no-wash', rapid detection of Mycobacterium tuberculosis in sputum samples.
2. Develop and validate novel molecular diagnostics for the detection of Mycobacterium tuberculosis complex and multidrug-resistant TB, with seamless data interpretation, collation and 'real-time' reporting.
3. Develop assays for detection of TB-specific microRNAs: Develop assays that will allow rapid detection of microRNAs as early biomarkers.

Methods

(a) Develop molecular probes and portable optical devices for improved 'triage'- The collaborators will be developing molecular probes that will be tested in the presumptive sputum samples and the results will be compared with the current staining method.

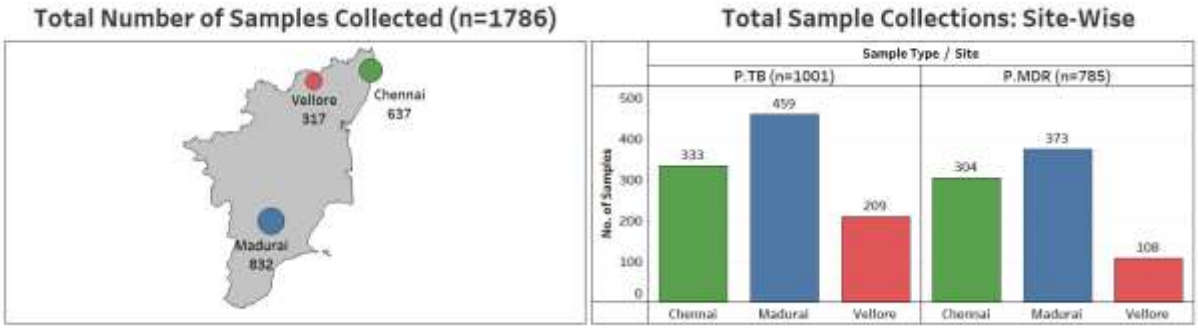
(b) The collaborators have developed an innovative DNA analysis approach through the application of Dynamic Chemistry, (herein referred as DestiNA technology) with a cheap/flexible spin-tube colorimetric platform that can be easily deployed in the field, allowing real-time, accurate and cost-effective detection of nucleic acids using DestiNA technology. The provide readout of the multiplexed assay to allow detection/diagnosis of Mycobacterium tuberculosis complex infection and/or multidrug resistant TB.

(c) We will develop an innovative assay for TB-specific microRNAs detection directly from blood samples, by using DestiNA technology which has been integrated with a Single Photon Avalanche Diode (SPAD) detector from Optoi that allows direct microRNA detection without the need for RNA extraction and amplification and provides a bench-top solution for clinical use. The DestiNA-Optoi device will now be used to develop assays for quantification of the baseline expression levels of known TB-related microRNAs

(in healthy individuals) and elevated levels in latent and active TB cases, thus providing a point-of-care device that has the potential to determine the risk of progression from latent to active TB, as well as enable monitoring of treatment outcomes. 6ml of blood will be collected from contacts of TB Patients. IGRA Testing by QuantiFERON-TB-Gold Assay will be performed and those who are IGRA Positive will be considered as LTBI (Latent Tuberculosis Infection) and the IGRA Negative will be considered as healthy house hold contact of TB Patients for the study.

Study progress

A) Evaluation of stain and device (100 sputum samples)



Validation of 'no- wash' stain has been completed for nineteen probes. One of the merocyanine probes have been selected for it specificity of staining MTB.

b) Evaluation of spin tubes for detection of TB 1001 MTB samples and 785 P. MDR-TB have been collected. Comparator tests has been completed for all received samples. First version of spin tube has been developed. Awaiting the spin tube from collaborators for further testing and completing the study.

c) Develop assays for detection of TB-specific microRNAs

235 sample have been collected from household contacts and IGRA testing has been completed for these samples (133 positive, 98 negative and 4 indeterminate) samples. 100 blood samples have been collected from AFB positive patients and serum has been separated and stored at -80 O C. Totally 72 Follow-up samples (after completion of treatment at six months) have been collected. The miRNA reagents are awaited from the collaborators for testing on the Optoi Device developed by the collaborators for detecting the TB specific miRNAs.

2. Attenuated Mycobacteria-based vaccine against tuberculosis with a novel strategy for T cell priming

Principal Investigator	:	Dr. K. R. Uma Devi, Scientist F Ms. J S V Soundarya (SRF-ICMR)
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR Intramural
Study period	:	2017-2024
Category	:	TB
Pillar	:	Prevent

Background

The currently available BCG vaccine has shown to have varying efficacy in adult populations in different parts of the world. Therefore, in the current scenario, the development of new vaccine candidates is a priority. rBCG co-expressing Ag85A-ESAT6 fusion protein of M.tb elicited more long-lasting and stronger Th 1 type cellular responses in BALB/c mice. In the present study, additional modifications will be carried out in BCG to provide an enhanced immune response by a two-prong approach. First approach is to add an additional deletion of ChoD or Tgs4 to $mc^2$6206 and BCG and second is to provide targeted delivery of T cell-specific mycobacterial antigens to the Dendritic cells using these knock-out strains.

Objectives

1. Construction of rAMtb (Recombinant attenuated mycobacterium tuberculosis) and rABCG (Recombinant attenuated BCG) by deletions in either of two genes, Rv3409c (ChoD) or Rv3088 (Tgs4) in attenuated M.tb (mc2 6206) and in the identical homologues in BCG (Mb3443c and Mb3115) expressing CFP10 and/or ESAT 6.
2. Construction of fused CFP10 and/or ESAT6 to Dec205 scFv, for secretion (Antigen 85 signal sequence) from the mycobacterium for enhanced highest frequency TB-specific T cells.
3. To test the efficacy of the constructed rAMtb or rABCG for their immunogenicity and to compare their efficacy with that of BCG.

Methods

a) Cloning of the fusion protein insert into Mycobacterial shuttle vectors and confirmation of the same through restriction digestion.
b) Electroporation of the confirmed plasmids into *M.smegmatis* and *M.bovis* BCG.
c) Selection of clones and growth, Protein extraction, SDS and confirmation of the protein expression in western blot.
d) Survival studies of *rM.smegmatis* in Thp 1 cell lines at 4-time points (4 hrs, 24 hrs, 48hrs and 72hrs) along with controls.
e) Testing of the vaccine candidates for immunogenicity in C57BL/6 mice and FACS analysis of the splenocytes and PBMC for T-cell profiling.

Study progress

Designing and construction of recombinant plasmids with inserts has been achieved. The recombinant plasmids transformed in *E.coli* were screened. Recombinant *M.smegmatis* and BCG strains have been constructed after electroporation. Western blot confirmation of the expression of the fusion protein in *M.smegmatis* has been achieved. Recombinant *M.smegmatis* harboring eGFP along with fusion protein has been constructed. PCR confirmation and western blot confirmation of recombinant BCG strains have been achieved. Survival studies of the recombinant *M.smegmatis* strains conducted in Thp1 cell lines have shown that there is no significant difference in the survival rate of the recombinant strains when compared to the wild type.

3. CRISPR Mediated platform for diagnosis and rapid detection of drug resistance pattern in *Mycobacterium Tuberculosis*.

Principal Investigator	:	Dr. K. R. Uma Devi, Scientist F Mr. P. Venkatesan (SRF–Lady Tata Memorial Trust Fellowship)
Participating Institutes	:	ICMR- National Institute for Research in Tuberculosis (NIRT), Government Hospital of Thoracic Medicine (GHTM).
Source of funding	:	ICMR Intramural
Study period	:	2018-2023
Category	:	TB
Pillar	:	Detect

Background

The available gold standard culture techniques for TB diagnosis have several drawbacks, and therefore there is an urgent requirement for a more precise and reliable diagnosis method for TB. Currently, several nucleic acid-based amplification techniques, such as the Xpert MTB/RIF assay and Line Probe Assay, are also available to diagnose and detect the drug resistant pattern of pulmonary clinical specimens. These techniques, however, are limited in identifying drug resistance patterns for a few drugs. In this context, it is important to develop tools using newer technologies like CRISPR based tools for diagnosis and detection of drug resistance in *Mycobacterium tuberculosis* with less turnaround time and high sensitivity and specificity.

Objectives

1. To develop CRISPR mediated programming platform for detection and identification of drug resistance in *Mycobacterium tuberculosis.*
2. To evaluate the performance of developed CRISPR Cas13a detection tool in clinical isolates of *Mycobacterium tuberculosis.*
3. To evaluate the performance of developed CRISPR Cas13a detection tool in biological specimens of *Mycobacterium tuberculosis.*

Methods

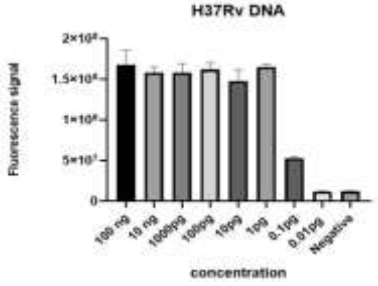
Step 1: Expression and Purification of Cas13a: The Cas13a bacterial expression system was purchased from Addgene. This Cas13a bacterial expression vector was transformed in to Rosetta competent cells for expression of protein. All subsequent steps of protein purification were performed according to Gootenberg et al., 2017 with slight modifications.

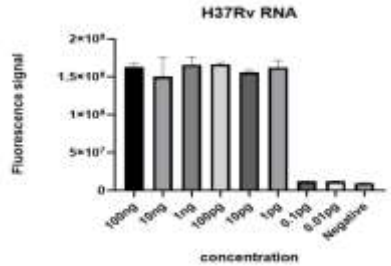
Step 2: CRISPR RNA PREPARATION [crRNA Preparation]: The CRISPR RNA for MTB detection and drug resistance was designed by us and the construct was ordered as DNA (integrated with appended T7 promoter sequence). Using Hiscribe T7 quick high yield RNA synthesis Kit(NEB), crRNA was synthesized from the template then purified using Monarch RNA purification kit(NEB).

Step 3: DNA and RNA extraction: The DNA and RNA extraction from the respective samples was carried out as per optimised protocol and the samples were subjected to Cas13a assay.

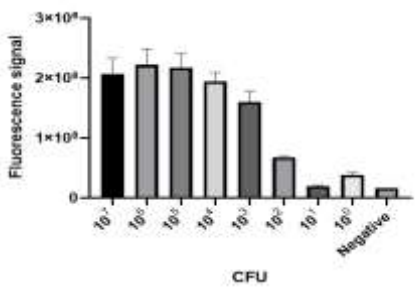
Step 4: Collateral detection assay: Detection assay was performed for both detection in target nucleic acid with the purified Cas13a, crRNA, quenched fluorescent RNA reporter [RNAse alert V2 Thermo scientific]. The reaction was allowed to proceed for 1 to 3 hours at 37^0C on a fluorescent plate reader.

Evaluation of LOD in Concentration

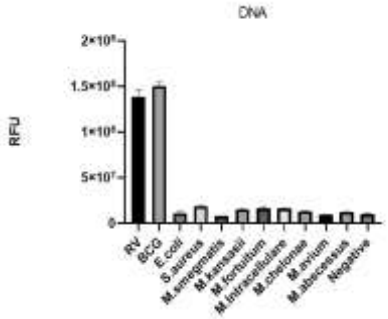




Evaluation of LOD in CFU



Evaluation of Specificity



Study progress

We determined the analytical sensitivity of the CRISPR-Cas13 MTB detection tool using H37Rv DNA and RNA as the template for the assay. We found that the CRISPR-Cas13 MTB detection assay could detect 0.1 pg of MTB DNA and 1pg of MTB RNA. When further evaluating the LOD in CFU, the results showed that, the CRISPR-Cas13 MTB detection tool detecting the LOD of 100 CFU/ml. In addition, we evaluated the specificity of CRISPR-Cas13 MTB assay using nucleic acid templates extracted from various pathogens, including H37Rv,BCG, non-tuberculous mycobacteria(NTM), and non-mycobacteria strains. The analytical specificity of CRISPR-Cas13 MTB test established in our experiment was 100% in both DNA and RNA.

4. Molecular Analysis of Monocyte Subsets from Humans Infected with *Mycobacterium tuberculosis*

Principal Investigator	:	Dr. Ramalingam B, Scientist E
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis(NIRT), Greater Chennai Corporation (GCC)
Source of funding	:	DBT Ramalingaswami Fellowship
Study period	:	2022-2023
Category	:	TB
Pillar	:	Detect

Background

Transcriptomic studies of peripheral blood mononuclear cells (PBMC) revealed the immune protective and defective functional behaviour of monocytes against TB. In addition, monocyte abundance with differential gene expression was observed between latent and active TB and those genes are found to be associated with inflammatory responses. However, PBMCs often confound the transcriptome data due to the mixed expression of heterogenous cell population. Hence, studying the single cells particularly monocytes is essential as they are the precursor of macrophages and the prominent innate cell in PBMCs with marked immune function during *mycobacterium tuberculosis* infection.

Objective

1. To study the transcriptome profiles from sorted monocytes and to identify the differentially expressed genes across the TB spectrum.
2. To identify the most promising candidate biomarker genes, together with its pathway networks by comparing active TB patients and healthy subjects.

Methods

FACS sorted monocytes (HLA-DR+ CD14+ CD16+), (N-32) were subjected to Illumina RNA sequencing, representing four groups [healthy individuals (HC), latently infected (LTB), drug sensitive TB (DS-TB) and single or multi-drug resistant TB (DR-TB)] with 8 samples each. Differentially regulated mRNAs and their targeted pathways were identified using DESeq2 and GSEA signature.

Study Progress

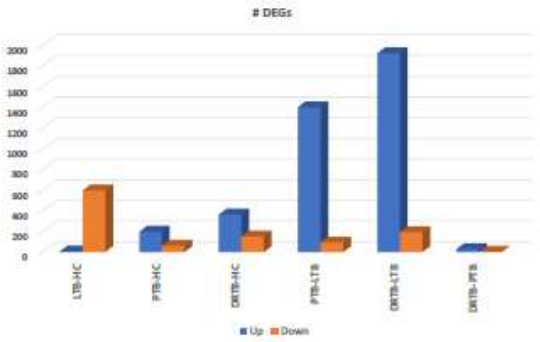
We identified 5019 differentially expressed genes across the various study group comparison. TB specific targeted pathways identified for the differentially regulated miRNAs between DS-TB and DR-TB are Th1, Th2 and Th17 differentiation, T-cell receptor signaling and co-stimulatory signaling, cytokine signaling, IL-2 signaling, Interferon type-1 signaling, Inflammatory response, B-cell receptor signalling, PD-1 signalling, FCER1 mediated Ca+2 mobilization, natural killer cell mediated cytotoxicity and apoptosis.

Figure: Differentially expressed genes of sorted monocytes through RNA sequencing analysis. A) No. of differentially expressed genes (DEG) (upregulated and downregulated) across LTB vs HC, DS-TB vs HC, DR-TB vs HC, DS-TB vs LTB, DR-TB vs LTB and DR-TB vs DS-TB represented in table and graph; B) Hierarchical clustering of DEGs and samples and C) Principal component analysis of the normalized mRNA expression across the study samples of HC, LTB, DS-TB and DR-TB groups

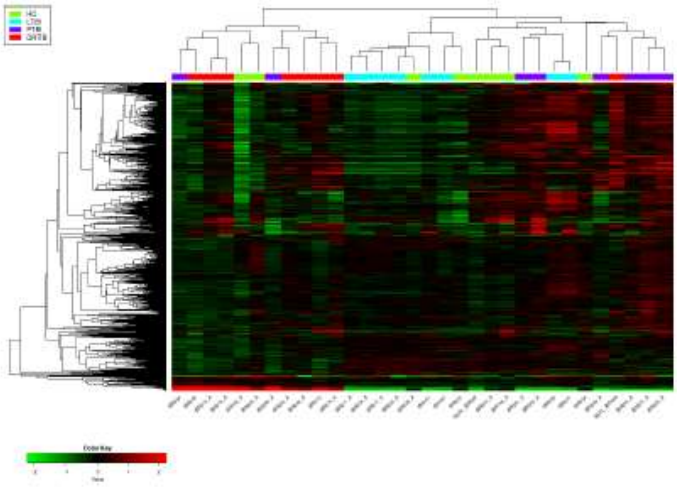
A No of Differentially Expressed Genes across various study group comparisons

Comparisons	DE Genes	Up	Down
LTB-HC	604	8	596
DS-TB-HC	259	197	62
DR-TB-HC	514	363	151
DS-TB-LTB	1494	1401	93
DR-TB-LTB	2114	1922	192
DR-TB-DS-TB	34	30	4

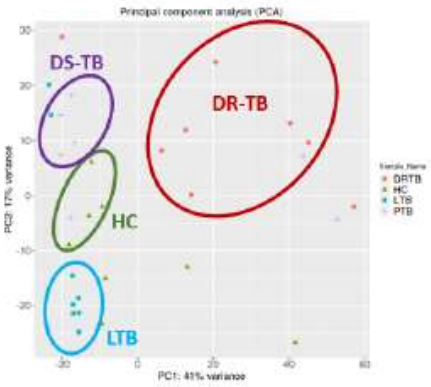
FC >= 2; padj <=0.05



B Hierarchical clustering



C Principal Component Analysis



5. CYP27b1 gene promoter polymorphisms in pulmonary tuberculosis

Principal Investigator	:	Dr. Ramalingam B, Scientist E Mr. Harishanker M, Technical Officer C
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis, (NIRT)
Source of funding	:	ICMR Intramural
Study period	:	2022-2023
Category	:	TB
Pillar	:	Prevent

Background

Vitamin D deficiency has been reported in the association of tuberculosis in different ethnic populations. It has been reported that inadequate levels may suppress the human cathelicidin antimicrobial peptide (hCAP18) and associated with increased susceptibility to infections. Several evidence have highlighted the importance of mutations in vitamin D-regulating genes for vitamin D status. *Cyp27b1* gene encodes 1α-hydroxylase enzyme which synthesize active form of vitamin D_3. Polymorphisms in this gene associated with vitamin D deficiency and TB outcome.

Objectives

1. To find out allele and genotype frequencies of Cyp27b1 -1077, -1260 and -1918 promoter polymorphisms in 100 healthy controls (HCs) and 100 pulmonary tuberculosis (PTB) patients.
2. To find out the association of gene variants with vitamin D deficiency by correlating with vitamin D levels.

Methods

Genomic DNA was isolated from portion of whole blood by a simple salting out procedure. Genotyping was performed by polymerase chain reaction followed by restriction fragment length polymorphism (PCR-RFLP) method from isolated genomic DNA of HCs and PTB patients. Vitamin D levels were estimated by ELISA method.

Study progress

The heterozygous genotype -1077 CG" found higher frequency in HCs and PTB patients. -1077 GG genotype found higher frequency in PTB patients and associated with trend towards susceptibility while "CC" genotype found higher frequency in HCs and associated with trend towards protection.

In -1260 promoter polymorphism, genotype "AC" found higher frequency in HCs and PTB patients. -1260 'AA' genotype found higher frequency in PTB patents and associated with trend towards susceptibility to tuberculosis. In -1918 polymorphism genotype "CC" found higher frequency in HCs and PTB patients.

In -1077 and -1260 promoter polymorphisms 25 samples needs to be done.

In -1918, 50 samples need to be done in both the study groups.

Table shows number of subjects studied and genotype details using PCR-RFLP method

Cyp27b1 Promoter SNPs	So far studied		PCR size in base pair (bp)	Restriction enzyme	Genotypes	Restricted fragment length in base pair(bp)
	HCs	PTB				
-1077(C/G)	75	75	666	*TaqI*	CC CT GG	436bp 436+182+48bp 182+48bp
-1260 (A/C)	75	75	666	*TfiI*	AA AG CC	423bp 423+177+66bp 177+66bp
-1918(C/T)	50	50	164	Tsp509I	CC CT TT	164bp 164+145+19bp 145+19bp

6. Identification of *Mycobacterium tuberculosis* complex (MTBC) organisms in the lymphnode samples of slaughtered cattle in Chennai

Principal Investigator	:	Dr. P. Kannan, Scientist E
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis NIRT), Tamil Nadu Veterinary and Animal Sciences University (TANUVAS)
Source of funding	:	ICMR Extramural
Study period	:	2019-2023
Category	:	TB
Pillar	:	Detect

Background

Bovine tuberculosis (bTB) is a significant concern due to its severe impact on both economic losses and public health. *Mycobacterium tuberculosis* and *Mycobacterium bovis* are the primary causative agents in humans and cattle, respectively. India has seen an increasing incidence of reverse zoonosis, where *M. tuberculosis* affects cattle. Diagnosing bTB involves various tests on live animals and post-mortem examinations. However, post-mortem inspections may miss early cases without visible lesions, lesions in unexamined organs, or those mistaken for other infections. Slaughterhouse examinations only occur when visible lesions are present, and it's been reported that bacilli can survive in cattle's lymph nodes without clinical symptoms or visible lesions, resembling latent infection in humans.

Objective

To isolate, identify and understand the MTBC organisms from the lymph node samples of slaughtered cattle with and without visible lesions.

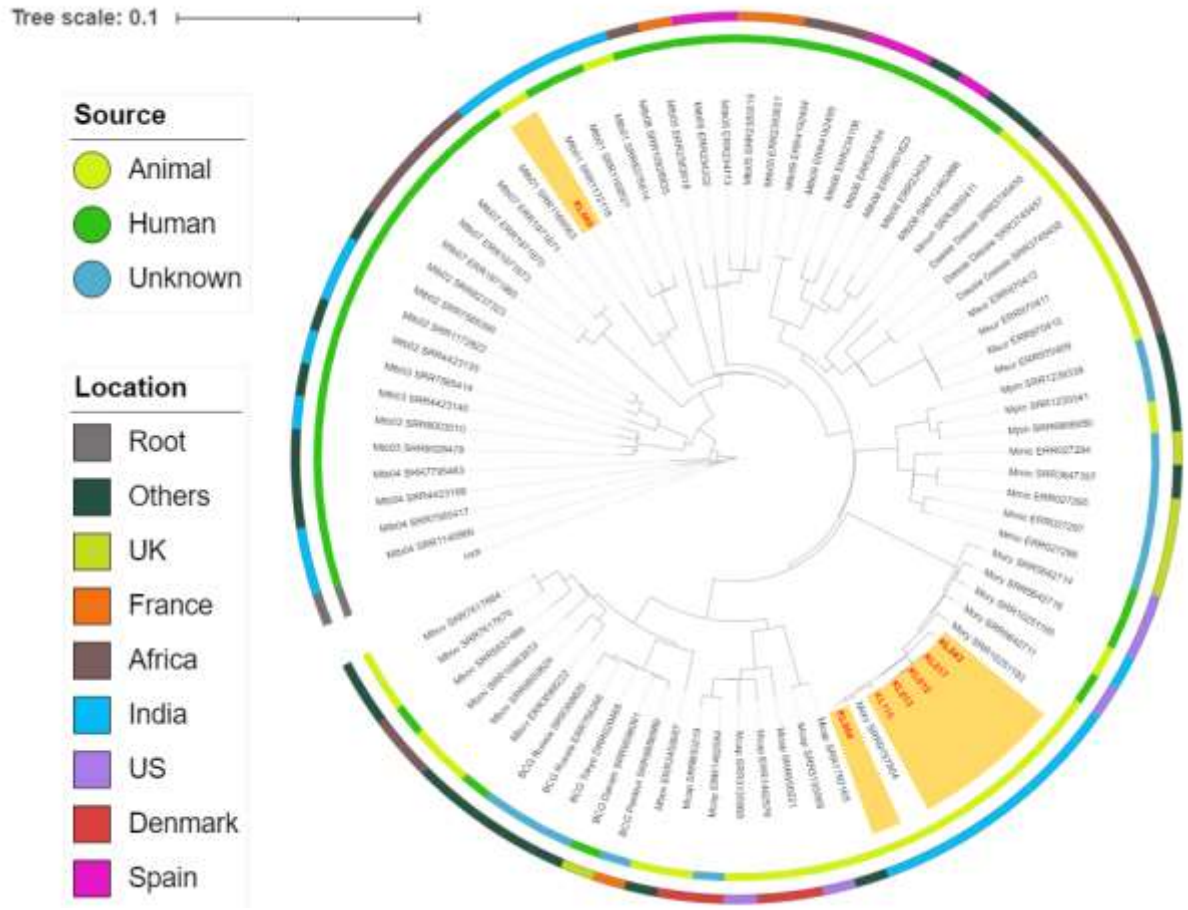
Methods

In this cross-sectional study, the lymph node samples were collected from slaughtered cattle with or without visible lesions, decontaminated and inoculated into a liquid and solid medium for MTBC isolation. The MTBC isolated were tested for drug susceptibility (DST) for the first-line anti-TB drugs. DNA extracted from the cultured isolates was subject to PCR (MPT64 gene), spoligotyping and Whole genome sequencing (WGS) to identify the genetic relatedness of the MTBC.

Study progress

A total of 534 samples have been collected from 500 animals from the Perambur slaughterhouse in Chennai. Fourteen samples out of the 534 samples have been identified to belong to MTBC by phenotypic methods (colony morphology, microscopy) and using an immunochromatographic ICT test. PCR revealed that all isolates belonged to MTBC. Spoligotyping pattern exhibited the spoligotype 587 (ST587) as compared against the SpolDB4 database corresponding to *M. orygis* for 6 of the MTBC isolates. Whole genome sequencing (WGS) confirmed that the six isolates were *M. orygis* and identified one isolate as *M. tuberculosis*. WGS for 7 more samples is under process. Apart from this, 102 non-tuberculous mycobacteria have been identified in this study.

Figure: Whole genome sequence-based maximum-likelihood-based phylogeny of representative human-adapted and animal-adapted MTBC lineages showing placement of the MTBC isolates recovered from cattle during slaughter in Chennai, India. The tree is unrooted and branch lengths are shown to be proportional to nucleotide substitutions between taxa. The isolates from this study are highlighted in yellow.



7. Study on Mutations Associated with Pyrazinamide Resistance in *Mycobacterium tuberculosis*

Principal Investigator	:	Dr. P. Kannan, Scientist E Ms. R. Ananthi (ICMR-SRF)
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR Extramural
Study period	:	2019-2023
Category	:	TB
Pillar	:	Detect

Background

Pyrazinamide (PZA) has a unique role in current anti-TB regimens, and its application in Pyrazinamide resistant (PZA^R) patients leads to treatment failure. Thus, understanding PZA^R patterns would improve treatment management. This study investigated diagnostic performance of phenotypic and genotypic methods for detecting prevalence of PZA^R from presumptive drug resistance TB patients.

Objectives

To understand the Pyrazinamide resistance in *Mycobacterium tuberculosis* strain isolated from presumptive drug resistant patients from Chennai.

Methods

We assessed DST among 401 *Mycobacterium tuberculosis* isolates from Chennai, India, collected during 2017-2018. We investigated phenotype by Wayne's and reduced inoculum MGIT960-DST, genotype by Sanger sequencing. The discrepancies were resolved using whole genome sequencing (WGS) to investigate WHO-listed variants and novel gene mutations. PZA^R was confirmed by performing PZA-DST at various concentrations (50, 100, 200 µg/ml).

Study progress

Among 401 clinical isolates, 38 (9.5%) isolates were found resistant to PZA. Sensitivity and specificity of PZA MGIT-DST and Wayne's method were 100% and 91.2%, respectively. In Wayne's method, 8.4% showed discrepancy with MGIT and 0.5% with Sanger sequencing. Of 11.7% PZAR, 3.2% had *pncA* mutations, and 8.5% had unknown mechanisms associated with PZAR detected by WGS. WGS data revealed four novel gene mutations with different polymorphisms in *mas, glpK, and lprG*. Sixteen variable mutations were found in the mentioned four newly reported genes, and two isolates had individual mutations in *mas* and *glpK* genes with wildtype *pncA*.

Table: Gene mutations and its association with PZA resistance

Genes associated with PZA^R	**Low level PZA^R 50ug/ml**	**Standard concentration of PZA 100ug/ml**	**Strongest association to PZA^R 200ug/ml**	**Total no of Isolates**
pncA	R	R	R	2
pncA+mas	R	R	R	2
pncA+fadD2	R	R	R	1
pncA+clpC1+mas	R	R	R	4
pncA+clpC1+mas+fadD2	R	R	R	1
pncA+clpC1+mas+glpK+gpsl+fadD2	R	R	R	1
panD+clpC1	R	R	R	1
panD+clpC1 +mas	R	R	R	1
panD+clpC1+mas+glpK+gpsl+fadD2	R	R	R	1
glpK	R	R	*S*	1
Mas	R	R	*S*	1
clpC1+mas+glpK+gpsl+fadD2	R	R	R	5
clpC1+mas+glpK+fadD2	R	R	R	1
clpC1+mas+glpK+fadD2+lprG	R	R	R	1
clpC1+mas	R	R	R	1
clpC1+mas+glpK+gpsl+fadD2	R	R	*S*	5
clpC1+mas	R	R	*S*	4
clpC1+mas+glpK+gpsl+fadD2	R	*S*	*S*	2
clpC1+mas	R	*S*	*S*	1
clpC1+mas+fadD2	R	*S*	*S*	2
Total				**38**

Table Descriptions: R – Resistant; S- Sensitive; *pncA*- Pyrazinamidase*; panD*- Aspartate decarboxylase*; clpC1*- caseinolytic protease complex ClpP*; glpK*- Glycerol kinese*; gpsI*- guanosine pentaphosphate synthetase*; mas*- Mycocerosic acid synthase*; fadD2*- Fatty acid CoA ligase; *and lprG*- Lipoprotein.

8. Protecting and improving public health globally: Building laboratory, surveillance and workforce capacity to detect, respond to and prevent drug resistant tuberculosis in India.

Principal Investigator	:	Dr. K. R. Uma Devi, Scientist F
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT), Central TB Division (CTD).
Source of funding	:	US Centers for Disease Control and Prevention, Atlanta
Study period	:	2015-2023
Category	:	TB
Pillar	:	Build, Detect and Prevent

Background

Mycobacterium tuberculosis (MTB) is the ancient causative agent of tuberculosis (TB), a disease that is presently a serious global public health concern. The prevalence of TB in the nation is the highest in the globe. Even though various developments have made tuberculosis easily detectable and treatable, the illness is still progressing due to the advent and ongoing spread of drug-resistant MTB, which endangers disease control efforts and causes TB cases that are more difficult to diagnose and treat.

Objectives

The proposed activities of this project is to build capacity to prevent, detect, respond to, and control the growing problem of DR-TB in India.

Methodology

- Establish primary solid culture at NIRT in 4 LJ slopes for: 1) NGS; 2) 12 drug DST in MGIT; 3) 12 drug DST on Sensititre plate; 4) Archive specimen
- Perform Whole genome sequencing
- Perform 12 drug DST via MGIT (Gold standard)
- Assess sensitivity and specificity for detection of known markers of genotypic drug resistance using NGS versus DST via MGIT (MGIT is gold standard).
- Assess strain diversity and clustering using existing pipelines
- Assess for unknown markers of resistance by comparing to international databases
- Assess sensitivity and specificity for detection of phenotypic drug resistance of DST on MGIT (MGIT is gold standard) and NGS with Sensititer assay.

Study progress

- The proposed activities had enabled us to build capacity to perform Next Generation Sequencing facility with MiSeq
- A National catalogue for drug resistance associated mutations for a panel of 14 first- and second-line anti TB drugs with confidence grading is developed and released.
- WGS and pDST for 13 drugs performed for 2226 eligible strains.
- The Sensititre plate assay is completed for 938 strains.
- The National mutation catalogue has been developed and released on June 2022 and uploaded on NIRT website for public access.
- Distinct clusters of Lineage 2 preXDR strains have been identified indicating recent transmission in two of the states in the country.

9. Immunomodulation of Serum Vitamin D levels combined with circulatory proteins towards a prognostic biomarker for pulmonary tuberculosis

Principal Investigator	:	Dr. Ramalingam B, Scientist E Dr Subash Babu, Scientific Director ICER
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT)
Source of funding	:	Department of Biotechnology DBT)/ International Centre for Excellence in Research (ICER).
Study period	:	2020-2023
Category	:	TB
Pillar		Detect

Background

The molecular mechanism for control of inflammation towards infection is dependent on a set of micronutrients, particularly the trace elements, with that of the inflammatory cytokines are being regulated each other through feed-forward loops. These Trace elements, particularly, iron, Zinc, copper and selenium have an immunomodulatory effect towards controlling the infection and inflammation process. Deficiency of these metals in any form any form, i.e., malnutrition, can lead to nutritionally acquired immunodeficiency syndrome, by all means, it can increase an individual's susceptibility to progression of infection and to disease. Here, in this study, the circulatory levels of the trace elements and micronutrients in the TB patients and the correlation between them and the other inflammatory molecules, vitamin D has been carried out , which has not been accurately estimated by any study yet.

Objectives

To estimate the levels of circulating trace elements and to correlate with the other soluble inflammatory proteins and vitamin D towards immunomodulation among pulmonary TB patients, during and after the treatment.

Methods

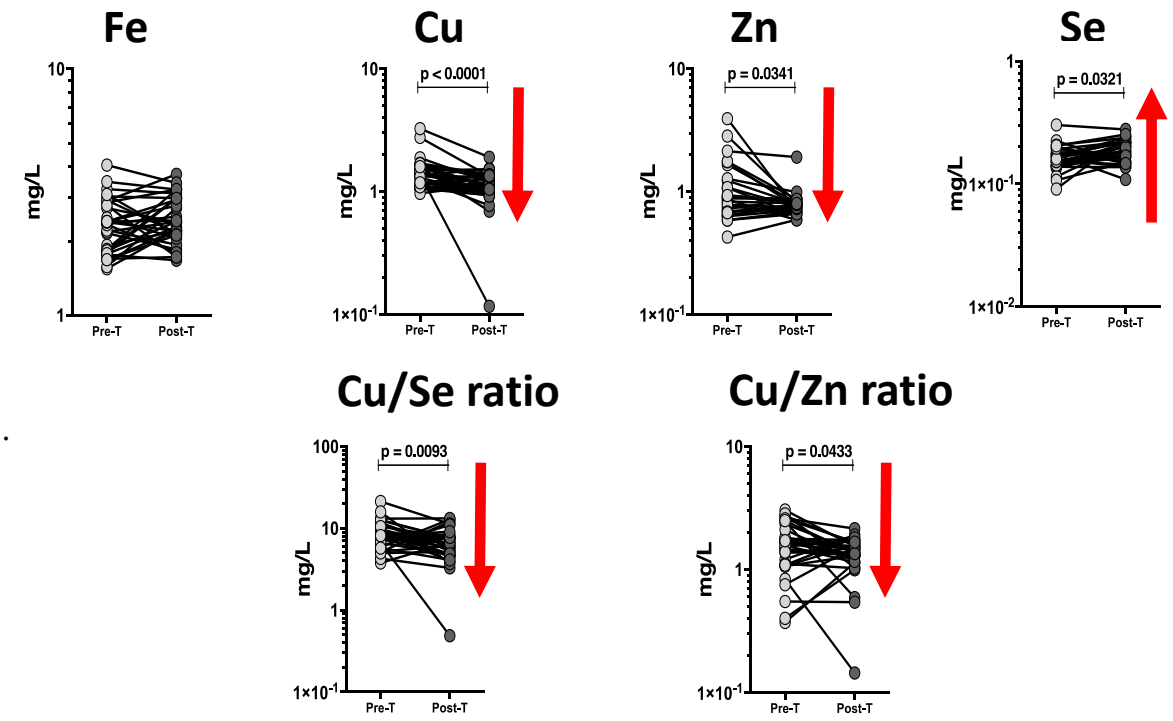
Plasma samples were collected from (1) Pulmonary Tuberculosis (PTB) patients at two time points: baseline and after 6 months of anti-TB treatment (ATT), (2) latently Mtb infected (IFN-γ+) participants, and (3) healthy controls. The PTB patients (n=32) were microscopically sputum smear-positive for Mtb at the time of diagnosis and X-ray positive for TB disease. The LTB group (n=32) was positive for interferon-gamma (IFN-γ) test when diagnosed by 3rd generation QuantiFERON-TB Gold assay. The non-LTB group (n=32) was negative for the IFN-γ test and not symptomatic for TB. Plasma trace element levels and vitamin D were estimated and were correlated with other soluble key inflammatory proteins, together with other demographic data and soluble key inflammatory mediators in TB disease.

Study progress

We could observe a significant increase in Se levels after ATT among PTB patients, when compared to the baseline time point. Se negatively correlated with TNFα, IL-17A and Vitamin D.

Concentrations of circulating Cu and Zn levels were found to be significantly decreased at the end of 6 months of treatment, when compared to the baseline timepoint. The Cu/Se and Cu/Zn ratios also showed a significant reduction in PTB at post-ATT timepoint when compared to the pre-ATT timepoint. Among the trace elements, Cu showed correlation with several pro- and anti-inflammatory cytokines. It showed a significant positive correlation with IL-2, IFNg, TNFα, IL-17A, IL-8, G-CSF, IL-4, IL-5, IL-10, IL-27, resistin and negative correlation with IL-37 and adiponectin. Where as Zn showed positive correlation with IL-27.

Figure 1: Altered plasma levels of trace elements upon treatment of PTB



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10. Insights into the genomic adaptations of *Mycobacterium tuberculosis* (MTBC) species in cattle

Principal Investigator	:	Dr. P. Kannan, Scientist E Dr Ahmed Kabir Refaya, ICMR-RA
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR Extramural
Study period	:	2021-2024
Category	:	TB
Pillar		Detect

Background

The key role of Mobile genetic elements or insertion sequences (IS*6110*) is exclusively found in *Mycobacterium tuberculosis* complex (MTBC) and this feature makes it a valuable diagnostic tool. There are not many studies that have examined the biological implications of IS*6110* and its role in host specificity. We propose to determine the genetic characteristics that have evolved among the MTBC isolates which might contribute to its host adaptation by a comprehensive comparative analysis of the genomes along with gene expression and macrophage infection studies.

Objective

To determine the genetic characteristics (IS*6110*, SNPs, and InDels), Gene expression studies, pathway enrichment analysis of these genes leading to host adaptation, IS*6110* transposition and its distribution between various lineages of the animal-adapted MTBC strains by manifesting the use of Whole genome sequencing (WGS).

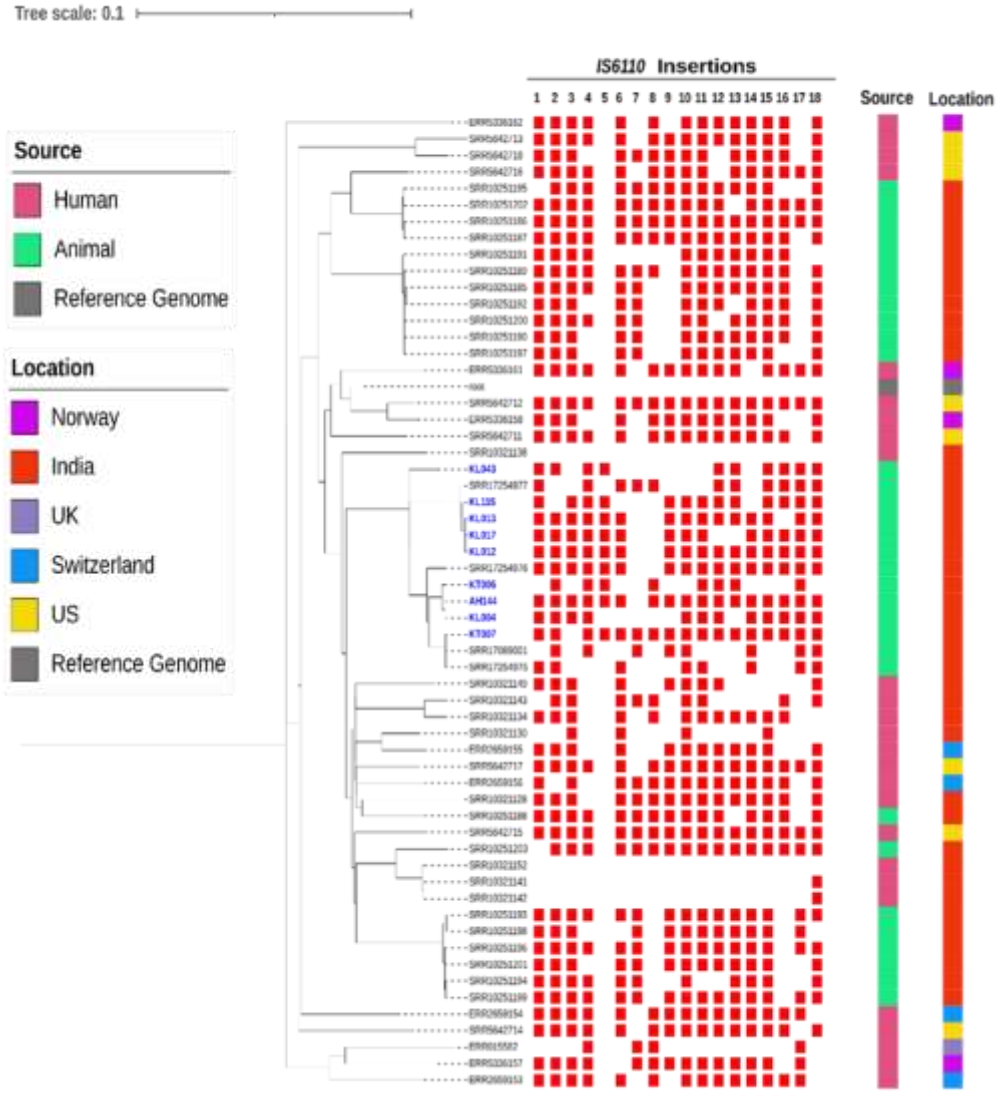
Methods

WGS data generated were mapped with *M. tuberculosis* and *M. orygis* reference genomes and analysis was done in the vSNP pipeline. ISMapper was used to localize the IS*6110* insertions in the genome and were further compared with 48 other *M. orygis* genomes downloaded from NCBI. The identified genes were functionally annotated with DAVID and a phylogenetic generated in vSNP was annotated using iTOL.

Study progress

We identified 4 *M. tuberculosis* isolates of which one was resistant to isoniazid and rifampicin and 9 *M. orygis* isolates. One isolate was identified as a mixed sample comprised of ~80% *M. tuberculosis* and ~20% *M. orygis.* SNP difference among *M. tuberculosis* cluster ranged from 9 to 454 SNPs and between 0 to 107 SNPs in the *M.orygis* cluster. Intergenic insertions of IS*6110* were found in genes such as *espA, ephA* among *M. tuberculosis* isolates and Rv2337, *MoeW, TrxB* and *kdtB* among the *M. orygis* isolates. Comparative analysis identified 61 genes to possess IS*6110* insertions among which 33 genes were involved in biological process (BP), 19 in Cellular component (CC) and 9 in Molecular Function (MF). The KEGG pathway analysis predicted 3 genes *rocA, pip* & Rv1188 to play an important role in arginine & proline metabolism.

Figure: Heat map showing the presence or absence of IS*6110* in 59 *M. orygis* genomes. Red squares show the presence of IS*6110* in a specific site. The source and the geographic location of the isolates are represented in the respective bands. The study isolates are labeled in Blue.



11. Identification of Bovine tuberculosis specific proteins by the Immunoproteomic approach

Principal Investigator	: Dr. P. Kannan, Scientist E
Participating Institutes	: ICMR-National Institute for Research in Tuberculosis (NIRT)
Source of funding	: ICMR Intramural
Study period	: 2022-2024
Category	: TB
Pillar	: Detect

Background

Bovine tuberculosis (bTB) is a major health and economic issue. *Mycobacterium tuberculosis* and *M. bovis* cause most human and animal TB. The major diagnostic test for bovine tuberculosis is the TST. In this test, animals receive intradermal *M. bovis* pure protein derivative (PPD). Bovine PPD is a poorly characterised protein, lipid, and carbohydrate combination. Environmental Mycobacterial species share certain Bovine PPD components. It sometimes causes false positives. In order to uncover bovine tuberculosis-specific antigens, we propose to analyse the immune response of the culture filtrate proteome of *Mycobacterium tuberculosis* of bovine origin isolated from prior NIRT studies. These methods will detect new bovine TB antigens. This helps produce a more sensitive bovine TB blood test.

Objectives

1. Separation of culture filtrate proteins of the *Mycobacterium tuberculosis* by Iso Electrofocussing (IEF) and Second-dimensional separation of IEF separated fractions by SDS-PAGE followed by whole gel elution
2. Immunologic characterization of the separated culture filtrate proteins in the bovine blood sample and Proteomic characterization of the Immuno dominant proteins by Mass spectrometry analysis

Methods

Mycobacterium tuberculosis strain from infected cattle recovered from glycerol stocks was sub-cultured on Lowenstein-Jensen media at 37^0C. Independent colonies formed after 21 days was transferred and incubated in 10ml Sautons minimum media at 37^0c for three weeks. After incubation, 10ml culture was transferred to 100ml Sautons media. BHI agar was tested for contamination and incubated at 37^0c for three weeks. Culture filtrate Protein (CFP) was collected by aseptically transferring the culture to 1 litre new Sautons media and incubating at 370c for 45 days. After incubation, the liquid culture was centrifuged at 4000g and 40c for 10 min to collect the CFP in a sterile vial. Pellets were stored at -800c.

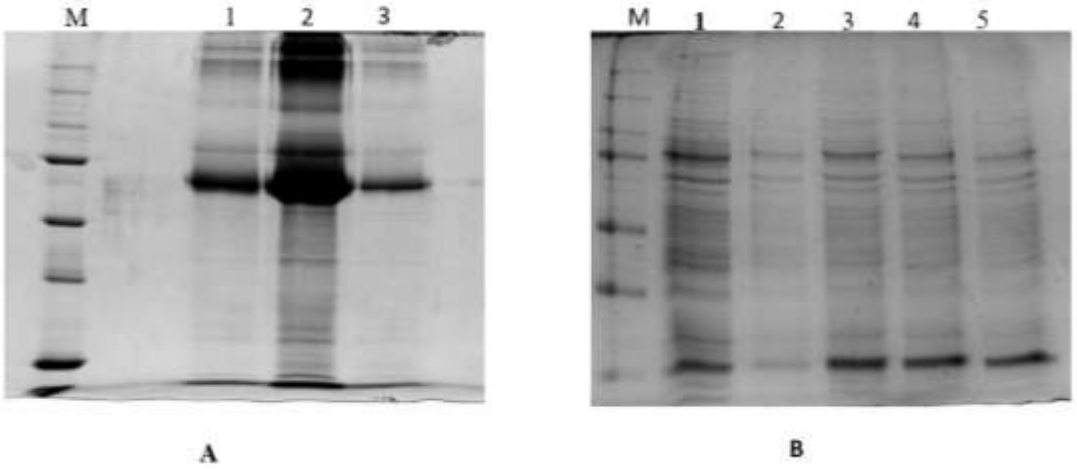
The CFP was filtered through a 0.22µm sterile cup and concentrated using a semi-automated protein concentrator. As per manufacturer directions, the protein concentration was measured using Pierce™ BCA Protein Assay Kit (Sigma). Standardised culture pellet lysis to extract whole-cell protein after not getting the expected protein concentration.

Study progress

The total concentration of CFP extracted from *Mycobacterium tuberculosis* culture was 300mg (less than one gram). The culture lysate of *Mycobacterium tuberculosis* was initiated to get the required concentration of protein (Figure).

Fig A: Culture Filtrate Protein of *Mycobacterium tuberculosis* in three batches (M-Marker, Lane1- First batch extracted culture filtrate protein, Lane 2- Second batch extracted culture filtrate protein and Lane 3- Third batch culture filtrate protein).

Fig B: Culture Lysate Protein of *Mycobacterium tuberculosis* on SDS PAGE and stained with Coomassie brilliant blue- M-Marker, Lane 1 & 2 - Culture lysate protein extracted at 37°C & 85°C by bead beating cycles 8, Lane 3, 4 & 5- Culture lysate protein extracted at 37°C by bead beating cycles 4, 8 &12.13.



12. Screening for the presence of *Mycobacterium tuberculosis* complex (MTBC) organisms in wild ungulates (spotted deer and blackbuck) and their environment in Chennai-an explorative study

Principal Investigator	:	Dr. P. Kannan, Scientist E
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT), Madras Vetenary College.
Source of funding	:	ICMR Intramural
Study period	:	2022-2025
Category	:	TB
Pillar	:	Detect

Background

Wildlife tuberculosis (wTB) is an understudied area in India, a country with a high TB burden and significant zoonotic risk. To achieve the End TB goal with a One Health approach, it's crucial to investigate wTB incidence and the *Mycobacterium tuberculosis* complex (MTBC) in wildlife. Guindy National Park in Chennai, India, home to spotted deer, sambar deer, and endangered blackbuck, provides a unique setting. We plan to collect and test fecal pellets and post-mortem samples from these animals, along with soil and water samples from their environment, to detect MTBC presence, shedding light on wTB dynamics.

Objectives

To explore the presence of MTBC organisms in the faecal, and post mortem samples from free ranging blackbuck and spotted deer as well as soil water samples in their natural environment at the Guindy national park and adjoining areas in Chennai.

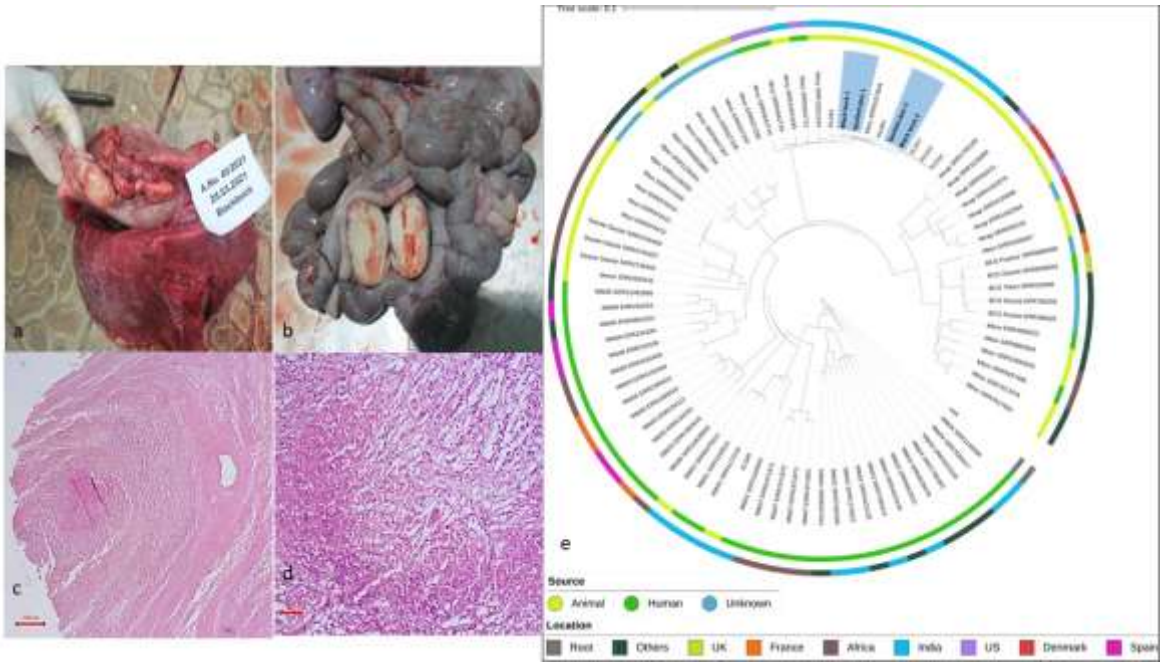
Methods

An exploratory study was conducted at Chennai's Guindy National Park, collecting faecal samples from black bucks and spotted deer, along with post-mortem lung and lymph node samples from wild ungulates whenever available. For faecal, soil, and water samples, MTBC isolation is performed following positive PCR detection of the MPT64 gene, characteristic of MTBC. Post-mortem lung and lymph node samples are decontaminated and inoculated into both liquid and solid media for MTBC isolation. Drug susceptibility testing (DST) is conducted and whole genome sequencing (WGS) is employed to determine MTBC genetic relatedness. Additionally, histopathological analysis is carried out on tissue sections.

Study progress

From Guindy National Park, 70 faecal pellets were collected. GeneXpertUltra and Line Probe Assay (LPA) on 14 samples confirmed MTBC presence in 7 of which one isolate was isoniazid-resistant, and another was resistant to both rifampicin and isoniazid, (collected from cohabiting black bucks). Nine tissue samples were collected (4 black bucks, 4 spotted deer, 1 sambar deer). Culture methods detected MTBC in 3 black bucks, 2 spotted deer, and 1 sambar deer. Except for one sambar deer and one black buck, all cultured isolates were identified as *M. orygis* through PCR, spoligotyping (ST587), WGS, and RD analysis (RD7 to RD10, RDOryx_1, RDOryx_4, RD12Oryx, RD301, RD315 deletions). These isolates clustered with global *M. orygis* isolates in phylogenetic analysis, with SNP differences of 20-153 SNPs, indicating no in-herd transmission. All cultured isolates were drug-sensitive; histopathology revealed Stage III granuloma formation in positive tissue samples.

Fig (a). Macroscopic lesions observed in the lungs of a black buck sample.
Fig (b). Calcified lesion in mesenteric lymph node of black buck.
Fig (c). Stage III granuloma with central necrotic core surrounded by macrophages and lymphocytes.
Fig (d): Giant cells, lymphocytes and macrophages present in the granuloma.
Fig (e): Interpretative phylogenetic tree combining four study isolates (labelled blue) along with 74 MTBC sequences downloaded from NCBI SRA. The outer band and inner band represent the isolates' source and' geographic location respectively.



13. Characterization of immune responses against SARS-CoV-2 and variants of concern in SARS-CoV-2 naturally infected and COVID-19 vaccinated individuals

Principal Investigator	: Dr. N. Pavan Kumar, Scientist D
Participating Institutes	: Greater Chennai Corporation(GCC)
Source of funding	: ICMR Ad Hoc Extramural
Study period	: 2022-2024
Category	: COVID-19

Background

The emergence of SARS-CoV-2 variants harbouring mutations in the spike (S) protein has raised concern about potential immune escape. Immunological memory is established by an initial priming of the immune system, either by natural infection or vaccination. SARS-CoV-2 infections may induce lasting immunological memory, although the different components of the adaptive immune system exhibit distinct kinetics.

Objectives

1. Characterization of humoral immune response in naturally infected and vaccinated individuals
2. Characterization of immune protection in naturally infected and vaccinated individuals

Methods

This is a prospective Cohort study. Study population included the following: COVID-19 vaccinated individuals (Covaxin or Covishield) after completion of two doses of vaccine, COVID-19 naturally infected individuals with 15-30 days post PCR confirmation, who had either asymptomatic, mild or severe disease. From the collected samples PBMC cells, serum and plasma were cryopreserved. SARS-CoV-2 specific IgG (S) and neutralizing antibodies for wild type and for other emerging variants were estimated during pre and post vaccination time points. Flowcytometry ex-vivo immunonphenotypying (memory T cells, monocytes and B cells) and Invitro whole blood cell cultures were performed upon stimulating with the peptide pools of PepTivator SARS-CoV-2 Prot_S1 and PepTivator SARS-CoV-2 Prot_S.

Study progress

Till date 146 baseline and 111 follow-up samples were collected from Covaxin or Covishield Vaccinated or naturally infected individuals. COVID-19 vaccination induced enhanced SARS-CoV-2 IgG and neutralizing antibody against SARS-CoV-2 viral variants. Frequencies of memory T cells and B cells were in significantly elevated frequencies with two-fold increase among vaccinated population in comparison to COVID-19 infection.

14. Immune response to precautionary third dose of COVISHIELD/COVAXIN among healthy adult population: an ICMR Cohort study, India

Principal Investigator	: Dr. N. Pavan Kumar, Scientist D
Participating Institutes	: ICMR Institutes all over India
Source of funding	: ICMR Ad Hoc Extramural
Study period	: 2022-2024
Category	: COVID-19

Background

COVID-19 cases was rising rapidly in countries where Omicron VOC has been reported, indicating its high transmissibility. India's COVID-19 vaccination programme had proposed to initiate additional third dose for healthcare and frontline workers and individuals aged above 60 years with comorbidities. Limited studies from India have documented dynamics of immune response of additional third dose of COVISHIELD/COVAXIN vaccine using homologous regimen.

Objectives

1. To characterise SARS-CoV-2 specific humoral and cellular immune response after homologous precautionary third dose of COVISHIELD/COVAXIN vaccine at different time points.
2. To estimate the incidence of SARS -CoV-2 symptomatic infection post third dose of COVID-19 vaccine.

Methods

This prospective cohort study will be conducted among fully vaccinated (i. e. who have received two doses) individuals working in different ICMR institutes in India. From the enrolled study participants, SARS-CoV-2 specific IgG (S) and neutralizing antibodies for wild type were estimated. From the Collected samples Invitro cell cultures are undergoing stimulation with the peptide pools of PepTivator SARS-CoV-2 Prot_S1, PepTivator SARS-CoV-2 Prot_M, omicron variant and delta variants. A panel of multifunction T cells, memory T cells and immune activation markers were estimated.

Study progress

Till date 44 blood samples were collected from COVID-19 vaccinated individuals. Additionally, 32 samples from ICMR-NIE were collected for Cell Mediated Immune Responses analysis.

Completed studies

S.no	Title of the project	Name of PI Designation	Source of funding	Category/ Pillar
1.	A cross sectional study of the systems immunology and viral diversity of SARS-CoV2 infection, COVID-19 disease and Multisystem Inflammatory Syndrome in children	Dr. N. Pavan Kumar, Scientist C	NIRT-ICER	COVID-19
2.	Characterization and Durability of COVID-19 vaccine induced immune responses in healthcare/frontline workers	Dr. N. Pavan Kumar Scientist C	ICMR	COVID-19
3.	Identification of the latent tuberculosis specific marker by the immunoproteomic analysis of the cell wall and membrane proteins of M. tuberculosis.	Dr.K.R.Uma Devi Scientist F & HOD	DST-SERB	TB/Detect
4.	Dereplication guided bio-prospecting of cyclic lipopeptides from marine *Bacillus* sp. for inhibition of *Mycobacterium tuberculosis*	Dr.P.Kannan/ Dr Sagarika Scientist E	DST	TB/Detect
5.	Identification of tuberculosis specific biomarkers in children by the proteomic analysis of urine	Dr.D.Anbarasu Technical Officer B	DHR-ICMR	TB/Detect

DEPARTMENT OF BIOCHEMISTRY

DEPARTMENT OVERVIEW AND MANDATES

Department of Biochemistry provides laboratory support to various clinical trials and basic research activities of ICMR-NIRT, through the Clinical Biochemistry Laboratory (CBL). The analytical services rendered by the CBL during the year 2022-23 accounts for approximately 4000 externally quality assured high-quality clinical chemistry reports generated for various in-house requirements. The Laboratory Information Management System (LIMS) that is meant to encompass and document the pre and post analysis processes, report generation and distribution has significantly improved the turnaround time (TAT) of clinical chemistry reports and the clinical care management of study participants. The CBL is in the process of getting accredited with the National Accreditation Board for Testing and Calibration Laboratories (*NABL*).

The basic research activities of the department are focused towards strengthening the 'Treat' and 'Detect' pillars of NTEP. We have initiated research studies on nanodelivery approaches for therapeutic application and identification of adjuvant therapeutic leads from natural compounds. Studied also initiated on point of care diagnostic tools for their potential use in high-risk populations. The future research focus of the department would be on biomarker discovery through omics approaches using cutting edge techniques like LC/MS/MS.

Studies in progress

1. Development and Characterization of a Novel Nanopeptide System for Therapeutic Application in Residual Lung Injury caused by Pulmonary Tuberculosis

Principal Investigator	:	Dr N Saravanan, Scientist E Dr N Usha Rani, ICMR-RA
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT), Chennai & CSIR-Central Leather Research Institute(CSIR-CLRI),Chennai
Source of funding	:	ICMR Extramural
Study period	:	2021-2024
Category	:	TB
Pillar	:	Treat

Background

The hyper inflammation occurred due to chronic tuberculosis (TB) infection and biochemical changes caused by anti-tubercular therapy (anti-TB) drugs, leading to severe residual lung injury which is a common risk factor for TB reinfection post cure. Host directed therapies gain importance in the management of irreversible lung tissue damage which is caused due to the excessive inflammation during TB disease. Functional nanomaterials with intrinsic immunomodulatory properties are preferred choice in targeting the excessive inflammation in the lungs while delivering anti-TB drugs. Carnosine (β-alanyl-L-histidine) is a natural dipeptide, which is shown to have anti-inflammatory, antioxidant, and wound healing properties. This dipeptide could be self-assembled into nanostructures by modulating the pH, ionic strength and using a cross-linker. The self-assembled nanostructure can be used as a nanocarrier for drug delivery applications in TB.

Objectives

1. To develop and characterize a novel nano delivery system using carnosine as a bioactive molecule for therapeutic application.
2. To investigate the therapeutic potential in, *in vitro* experimental infection system of pulmonary tuberculosis.
3. To investigate the therapeutic potential in, *in vivo* experimental infection system of pulmonary tuberculosis.

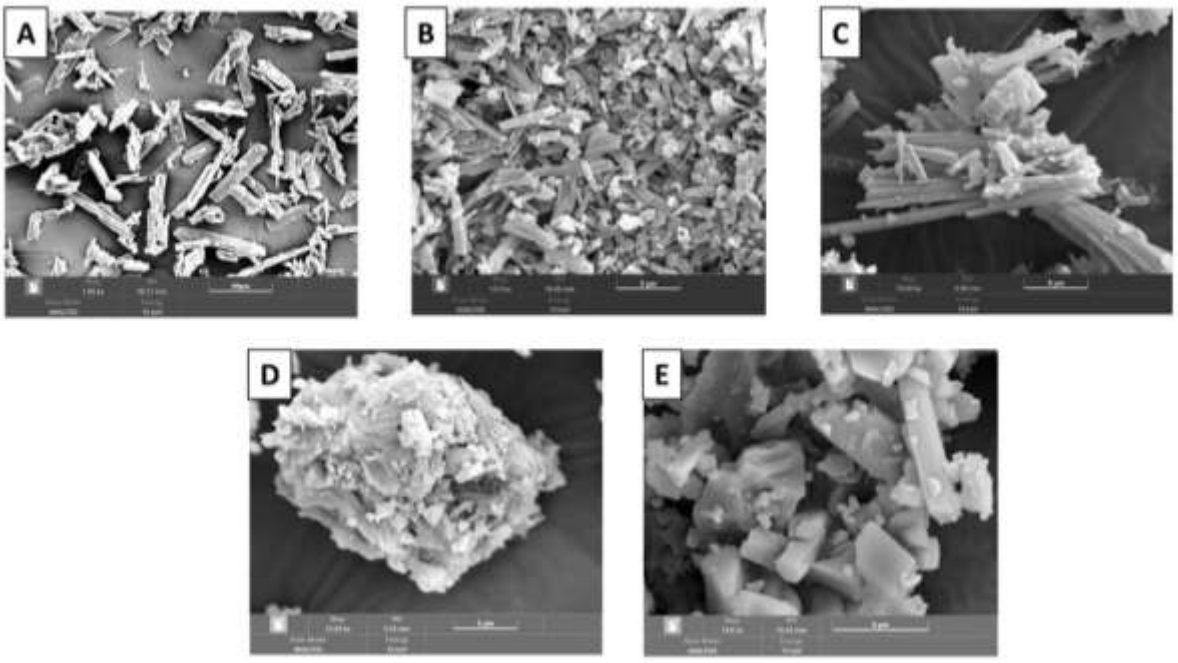
Methods

In the current study, the team has planned to develop a carnosine peptide nanostructure and explore its effects on the initial intense pro-inflammatory response, immune homeostasis, and excessive inflammation that causes residual lung injury during pulmonary tuberculosis. To achieve the preliminary objective, the team has employed multiscale self-assembly approaches and developed functional nanostructures from native carnosine dipeptide oligomers using hydrothermal process, and further nanocomposites were prepared individually with Rifampicin, Isoniazid, Pyrazinamide and Ethambutol. The immunomodulatory and anti-inflammatory effects of the carnosine nanosystem *in vitro* experiments will be conducted. To comprehend the biological functions of the developed nanosystem, experimental studies will be performed in *in vivo* models.

Study progress

As a first part of the study, the development and characterization of carnosine nanostructure have been completed. In continuation, the carnosine- anti-TB drug nanoclusters were prepared and subjected for the biophysical characterization experiments such as hydrophobicity, surface tension, morphology and mesoporosity etc., using sophisticated techniques. In the Figure, the scanning electron microscopic images of carnosine-anti-TB drug nanocomposites are presented. The drug release experiments indicated that the conjugation of carnosine-anti-TB drug exhibit a sustained release profile compared to free drugs. The developed carnosine-anti-TB drug nanocomposites were very stable at physiological states and they are uniform in size. Thus, the carnosine-anti-TB drug nanocomposites made through a simple, cost-effective process prompt further experimentations in the *in vitro* and *in vivo* experimental systems.

Figure: Morphological analysis of hydrothermally processed carnosine anti-TB drug nanocomposites prepared in the ratio of 1:1[A-Native Carnosine (Scale- 50 µm), B-Carnosine-Rifampicin (C-R) (Scale- 5 µm), C-Carnosine-Isoniazid (C-H) (Scale- 5 µm), D-Carnosine-Pyrazinamide (C-Z) (Scale- 5 µm) and E- Carnosine-Ethambutol (C-E) (Scale-5 µm)]



2. Evaluation and characterization of potential therapeutic leads from the AYUSH system of medicine for adjuvant therapy during anti-tuberculosis treatment.

Principal Investigator	:	Dr N Saravanan, Scientist E
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT) National Institute of Siddha (NIS)/Central Council for Research in Siddha (CCRS), Chennai, Vellore Institute of Technology (VIT), Vellore
Study period	:	2019-2024
Category	:	TB
Pillar	:	Treat

Background

TB infection leads to altered inflammatory homeostasis in the lung and results in the progression of latent infection to active disease. In people undergoing anti-TB treatment, the adverse drug reaction caused in the host and the altered inflammatory homeostasis may reflect poor adherence to treatment, poor treatment outcome and acquired drug resistance. Therefore, the exploration of antimycobacterial compounds from natural sources should be in the interest of (i) promoting the immunity of the host to achieve optimal clearance of *Mycobacterium tuberculosis (Mtb)*, (ii) to aid pulmonary health to withstand the necrotic effects of *Mtb* infection and to (iii) preserve liver function during treatment to avoid anti-tubercular drugs (ATT) drugs induced adverse effects.

Objectives

(a) Identify and characterize natural and herbal compounds which are
   (i) antimycobacterial,
   (ii) immunomodulatory
   (iii) hepatoprotective
   (iv) pulmonary protective
   (iv) and compounds that promote weight gain using analytical and *in silico* approaches.
(b) Validate their medicinal properties using *in vitro* studies
(c) To investigate their safety and toxicity as an adjuvant using *in vivo* models.

Methods

The individual list of natural compounds for their (i) Antimycobacterial, (ii) Immunomodulatory, (iii) Hepato-protective and (iv) Pulmonary-protective effects will be identified based on scientific evidence and literature in Siddha and Ayurveda. Novel formulations will be prepared based on the expertise of a siddha practitioners and the *in vitro* and *in vivo* studies will be conducted on the indices of antimycobacterial effects and drug toxicity. Promising formulations will be identified and further investigated for their effects on quality of life.

Study progress

The team has conducted virtual screening for potential antimycobacterial compounds from fifteen phytonutrients/ phytochemicals for their efficiency of binding with the active targets of first-line (INH, RIF, PZA, and EMB) and second-line (Fluoroquinolones, Bedaquiline and Capreomycin) ATT in collaboration with the Medical and Biological Computing Laboratory, School of Biosciences and Technology, Vellore Institute of Technology (VIT), Vellore and the preliminary data is published. Utility of these compounds will be further explored while preparing the formulations before exploring their beneficial effects through *in vitro* and *in vivo* experiments.

DEPARTMENT OF CLINICAL PHARMACOLOGY

DEPARTMENT OVERVIEW AND MANDATES

The primary mandate of the department is to undertake the pharmacokinetic profiling of anti-tuberculosis drugs, anti-diabetic and anti-retroviral drugs in clinical trials of ICMR-NIRT and other studies conducted by various organizations, across the country. The focus is to develop new, simple and novel HPLC-based methods for measuring newer anti-TB, anti-viral and anti-diabetic drugs. Studies to understand the role of body composition & fat mass, and transcriptomes of drug metabolizing enzymes in influencing the pharmacokinetic properties of anti-TB drugs and treatment outcome are being done. The department undertakes core-research in the area of drug-drug interactions and drug-nutrient interactions on treatment outcome.

The department renders service and support to therapeutic drug monitoring (TDM) of anti-TB drugs for patients undergoing treatment at various government research institutes, organizations and Hospitals at the state and national level. The department is a member of the External Quality Assessment Scheme (EQAS) - Dutch Foundation for Quality Assessment in Medical Laboratories-(SKML Netherlands) for proficiency testing of anti-TB drugs.

Studies in progress

1. Bioavailability of fixed dose combination of first line anti-TB drugs in patients with pulmonary tuberculosis

Principal Investigator	:	S.M.Jeyakumar, Scientist F
Participating Institutes	:	Govt. Hospital for Thoracic Medicine, Tambaram Institute of Child Health, Chennai
Source of funding	:	ICMR Intramural
Study period	:	2020-2023
Category	:	TB
Pillar	:	Treat

Background

Fixed dose combination (FDC) of drugs is one of the methods to improve compliance and reduce errors. The rationale of FDC is that the presence of all these drugs combined in one tablet can facilitate dosage calculation, prevent prescribing errors, increases patient's acceptance and decreases pill burden. In India, FDC's are recommended for TB patients under the National Tuberculosis Elimination Programme (NTEP) during daily treatment both in intensive and continuation phase. There are four weight bands for adult TB patients receiving INH, RMP, PZA and EMB (75/150/400/275mg) and 6 weight bands for children receiving dispersible FDC's (50/75/150/100) in addition to streptomycin for 2 months in the intensive phase. No study to date has assessed the combined use of the three drugs (FDC's) for TB treatment in different weight bands, both in adults and children, which is of great clinical relevance.

Objectives

To assess the bioavailability of RMP, INH and PZA when administered as FDC in adults and children with pulmonary TB treated in the NTEP in India.

Methods

This is an observational and bioavailability study, carried out at the Institute for Child Health, Egmore for children and at Government Hospital for Thoracic Medicine, Tambaram for adults. As per the sample size, 12 patients each receiving treatment under 5 different weight bands in adults and 6 different weight bands in children, will be included according to the inclusion criteria, i) newly diagnosed pulmonary TB patients (both adult and children) as per the NTEP guidelines, ii) willing for blood draws and iii) adult patients or parent/guardian of pediatric patients willing to give written informed consent.

On the day for PK evaluation, eligible patients will be requested to report at the hospital in the morning under fasting condition. A sample of blood (2.5ml) will be collected in a heparinised vacutainer tube, followed by administration of anti-TB medications. Blood samples (2.5 ml equivalent to half teaspoon) will be collected at 2, 4, 6, 8 and 12 hours in heparinised vacutainer tubes after drug administration. Plasma RMP, INH and PZA levels will be measured by validated HPLC methods.

Study progress

The patient recruitment of four weight bands in the adult category is completed. Recruitment is in the progress for weight band >75kg in adults, and for all the weight bands in children.

2. Pharmacokinetics of linezolid when administered with other second line anti-TB drugs in MDR-TB/Pre-XDR-TB Patients

Principal Investigator	:	S.M.Jeyakumar, Scientist F
Participating Institutes	:	Govt. Hospital for Thoracic Medicine, Tambaram Govt. Stanley Medical College Hospital, Chennai
Source of funding	:	ICMR Intramural
Study period	:	2020-2023
Category	:	TB
Pillar	:	Treat

Background

Drug-resistant TB (DR-TB) is more difficult to treat than drug-sensitive TB (DS-TB) and the treatment options are very limited. Addition of linezolid (LZD) in the treatment regimen of DR-TB has been associated with improved treatment outcome with reduction of mortality among MDR-TB and Pre-XDR TB patients. However, limited information is available on the pharmacokinetics of second-line drugs used in the treatment regimen of MDR-TB and Pre-XDR TB, particularly in the Indian context. Therefore, here we plan to undertake a pharmacokinetic study of LZD and other second-line anti-TB drugs used in the treatment of MDR-TB and Pre-XDR TB.

Objectives

1. To develop and validate methods for the estimation of linezolid (LZD) in plasma and saliva by HPLC.
2. To study the pharmacokinetics of LZD and other second-line anti-TB drugs in adult patients with multi-drug resistant (MDR) and pre-extensive drug resistant (pre-XDR) TB patients

Methodology

This prospective study will involve adult MDR-TB and pre-XDR-TB patients aged $\geq$18 years, based on the following Inclusion criteria: i) Bacteriologically confirmed ii) Treatment regimen containing LZD along with other second line drugs for minimum period of 15 days, iii) Willing to give informed written consent. Patients who are HIV-seropositive, moribund, pregnant, lactating, having chronic diarrhoea, liver and renal abnormalities will be excluded.

On the day for PK evaluation, study participants will be requested to report at the hospital in the morning under fasting condition. A sample of blood (5mL) will be collected in a heparinised vacutainer tube, followed by administration of anti-TB medications. Blood samples (5mL) will be collected at 2, 4, 6, 8 and 12 hours in heparinised vacutainer tubes after drug administration. Similarly, saliva (5 ml) will be collected from these patients at each time point of blood collection.

Study progress

A new method was developed for the measurement of plasma LZD by HPLC and the methodology was published. Currently, we have initiated the process for standardization for saliva LZD by HPLC method.

Completed studies

S.no	Title of the project	Name of PI Designation	Source of funding	Category/ Pillar
1	Pharmacokinetics of second-line anti-TB drugs in children and adolescents with MDR TB	S.M.Jeyakumar, Scientist E	ICMR-ITRC	TB/Treat

DEPARTMENT OF VIROLOGY AND BIOTECHNOLOGY

DEPARTMENT OVERVIEW AND MANDATES

The Department of Virology and Biotechnology plays a key role in providing high quality diagnostic services to support various studies and clinical trials of the Institute including serological testing for a panel of infections like HIV, Hepatitis B & C, Syphilis, HSV, CMV and Toxoplasma. Other laboratory services include CD4 count, HIV-1 viral load, HIV-1 TNA PCR and HIV-1 drug resistance testing. The department has a long record of successful participation in some of the best External Quality Assurance programs for the diagnostic services it provides.

The Molecular Diagnostics Division of the Department serves as a Regional Reference Lab (RRL) for the National AIDS Control Organization (NACO) for molecular diagnosis of HIV infection for the National Early Infant Diagnosis (EID) Program and HIV-1 viral load testing for the National Antiretroviral Therapy (ART) Program. The Department also serves as the Central TB Biorepository for the RePORT India Consortium and Regional Biorepository for the National HIV Cohort study (COHRPICA). The Department also has a medical college level Viral Research and Diagnostic Lab (VRDL) and implements the first and only in-country PT program for isolation and cryopreservation of peripheral blood mononuclear cells (PBMC) for immunological studies.

The scientific programs of the department are organized into TB, TB/HIV, HIV and COVID-19 research. The major focus of research includes identification of biomarkers for progression from latent TB infection to active TB disease, evaluation of novel diagnostics and biomarkers for diverse states of *Mycobacterium tuberculosis (Mtb)* infection and disease. Determining the role of TB-induced immunosenescence on accelerated onset of aging-associated comorbidities and increased risk of death among cured TB patients is being undertaken. Delineating neutrophil-mediated immune responses in patients with pulmonary TB and other co-infections/co-morbidities are being studied. Estimating the prevalence of transmitted and acquired drug resistance in a cohort of newly diagnosed HIV positive individuals started on first line antiretroviral treatment as per the revised WHO guidelines and development of simple and affordable HIV drug resistance testing strategies are undertaken.

Studies in progress

1. Identification of biomarkers for predicting progression from Latent Tuberculosis Infection to Active Tuberculosis disease

Principal Investigator	:	Dr Luke Elizabeth Hanna, Scientist F
Research Scholar	:	Ms. Evangeline Ann Daniel
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT), B. J. Medical College (BJMC) - Pune, Johns Hopkins - Baltimore
Source of funding	:	ICMR Adhoc
Study period	:	2022-2024
Category	:	TB
Pillar	:	Detect

Background

Majority of *M. tuberculosis*-infected individuals remain healthy, implying that immune responses in individuals that control infection (latent infection) differ from responses in those who develop TB disease within few years following infection. This suggests that correlates of TB progression do exist. Identification of these predictors would play a crucial role in the early identification of individuals with the highest immediate risk of progression to active TB, so that they can be targeted for prophylactic intervention.

Objectives

1. Multiplexed cytokine analysis of non-induced (Nil) and induced (TB Ag-stimulated) plasma (QuantiFERON supernatant) of TB progressors and non-progressors.
2. MicroRNA profiling of non-induced and induced plasma of TB progressors and non-progressors.
3. Untargeted metabolite profiling of non-induced and induced plasma of TB progressors and non-progressors

Methods

Progressors were defined as healthy household contacts (HHCs) of index TB cases who developed TB disease during a 2-year follow-up period and non-progressors were defined as HHCs who did not develop TB during the entire follow-up period. Multiplexed cytokine analysis was performed using the Luminex platform, miRNA profiling was performed using the Nanostring technique and high throughput metabolomics profiling was performed using high resolution Sciex Q-TRAP mass spectrometry.

Study progress

The study identified several analytes that were significantly different between the progressors and non-progressors in samples collected at least 6 months prior to TB breakdown (Figure 1). ROC analysis identified six biomarkers, *viz.* interferon-γ inducible protein (IP)-10, chemokine ligand (CCL)-19, interferon (IFN)-γ, interleukin (IL)-1ra, CCL3, and granulocyte-macrophage colony-stimulating factor (GM-CSF) as the most promising predictive markers, with area under the curve (AUC) ≥90.

Figure 1: Levels of significantly different analytes between the progressor, non-progressor & TB groups

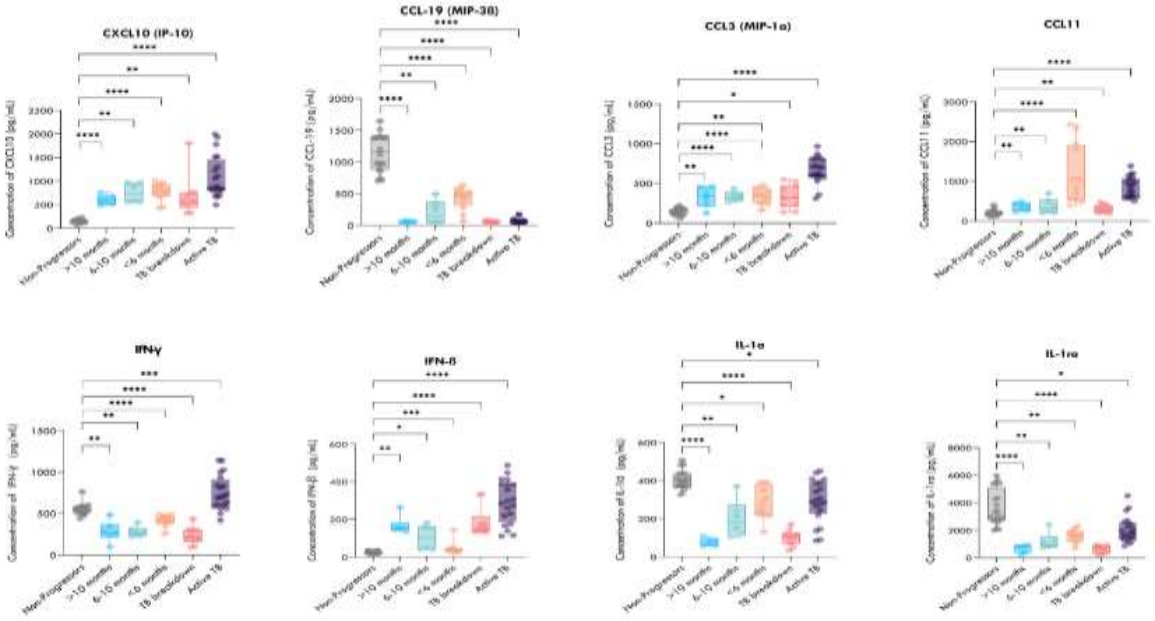
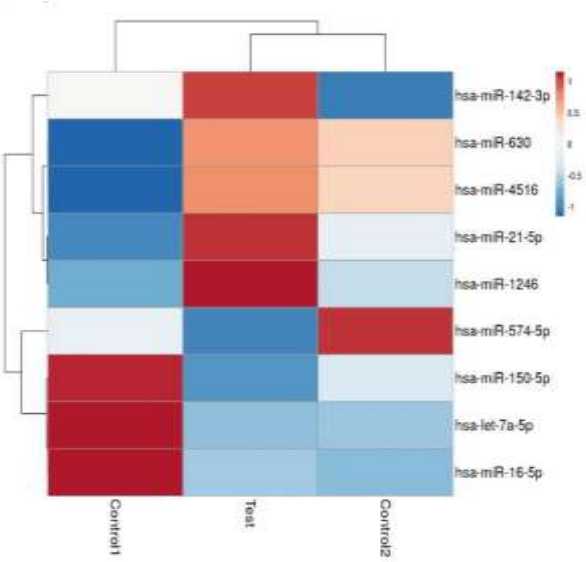


Figure 5. Median levels of analytes (pg/mL) in *Mtb* antigen-stimulated QuantiFERON supernatants of progressors, non-progressors and active TB groups: Progressors were further stratified based on time duration to TB activation. The above analytes were statistically significant at all time points studied, between the progressor and non-progressor groups. Significant differences between groups were calculated using Kruskal–Wallis test coupled with Dunn's correction for multiple comparison and expressed as: * ($P < .05$), ** ($P < .01$), *** ($P < .001$), **** ($P < .0001$). Abbreviations: CCL, chemokine ligand; CXCL, chemokine (C-X-C motif) ligand; IFN, interferon; IL, interleukin; MIP, macrophage inflammatory protein *Mtb*, *Mycobacterium tuberculosis*; TB, tuberculosis.

We also identified a distinct panel of 5 miRNAs, *viz.* hsa-miR-223-3p, hsa-miR-451a, hsa-miR-92a-3p, hsa-miR-423-5p and hsa-miR-29a-3p that could identify HHCs with a high risk of developing active TB (Figure 2).

Figure 2: Heat map showing differential expression of the top 5 miRNAs in progressors vs. non-progressors



We also shortlisted 5 top metabolites that were distinctly different between the progressor and non-progressor groups in the high through metabolomics analysis (data not shown). Further validation of the identified protein, miRNA and metabolites biomarkers in an independent cohort would endorse their potential as predictive biomarkers for TB.

2. Role of neutrophils and Neutrophil Extracellular Traps (NETS) in the pathogenesis of Pulmonary Tuberculosis (PTB) and Corona Virus Disease (COVID 19) co-infection

Principal Investigator	:	Dr. Nancy Hilda J, Scientist D
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR Intramural
Study period	:	2021-2024
Category	:	TB/COVID
Pillar	:	Detect

Background

Neutrophil Extracellular Traps (NETs) consist of extracellular DNA strands and granular enzymes which can trap microbes and partly kill them. On the one hand they act as a first line of defense against microorganisms and on the other hand as a contributor to the pathogenesis of various illnesses, including TB and COVID-19. The present study was aimed to investigate the influential role of recent SARS CoV-2 infection on NET formation in TB. Levels of NET markers like citrullinated Histone (C3 Histone), myeloperoxidase (MPO) and elastase, which are involved in NET formation and degradation and form the indices of NETs, were estimated in plasma.

Objective

To estimate the influence of recent COVID 19 infections on NET formation during TB disease by measuring levels of NET markers in the disease groups

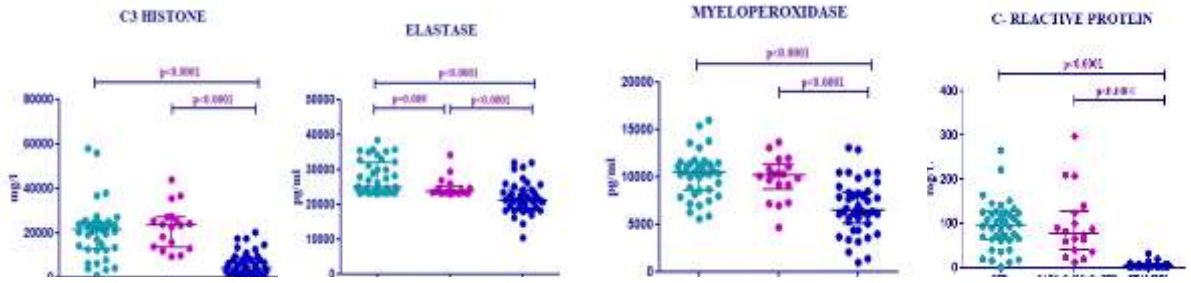
Methods

We recruited 40 newly diagnosed pulmonary tuberculosis (PTB) patients (without a history of known COVID-19 and/or vaccination), 43 healthy volunteers and 18 newly diagnosed PTB patients with a documented history of past COVID-19 (detectable levels of SARS CoV-2 IgG). Plasma was separated from whole blood and stored at -80^{0}C until use. ELISA was performed using commercial ELISA kits for citrullinated histone (C3 Histone), myeloperoxidase and elastase in plasma. C-reactive protein (CRP) levels were also measured in plasma. Mann Whitney U test was performed to compute statistical significance. P<0.05 was considered to be statistically significant.

Study progress

Significantly higher levels of C3 histone, elastase, MPO and CRP were found in both PTB and SARS CoV-2 IgG +ve PTB groups as compared to healthy controls (Figure).

Figure: Levels of citrullinated histone, elastase, myeloperoxidase and C - reactive protein in circulation of the study groups



3. Role of persistent immune activation and systemic inflammation on accelerated immune senescence and increased mortality in successfully treated and cured TB patients

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR Adhoc
Study period	:	2022-2025
Category	:	TB
Pillar	:	Detect

Background

Although TB is a treatable and curable disease, several studies have shown significantly higher rates of mortality in successfully treated and cured TB patients than in the general population. A number of experimental studies have demonstrated heightened levels of immune activation in TB patients, which declines with anti-TB treatment but does not normalize to levels seen in healthy controls even after complete microbiological sterilization and cure.

Objectives

i. To evaluate levels of systemic inflammation by measuring soluble inflammatory molecules in plasma.
ii. To analyse the extent of immune activation by assessing soluble and cellular markers of activation.
iii. To evaluate immunological senescence by measuring the expression of senescence markers on immune cells.
iv. To examine alterations in the frequency of CD4 and CD8 memory cell subsets.
v. To evaluate the cytotoxic potential of terminally differentiated immune cells.
vi. To assess the extent of mitochondrial dysfunction and telomerase activity in immune cells

Methods

This is a case-control laboratory study with one time point analysis. Cured TB cases (Group 1) and healthy controls who are asymptomatic with no past history of TB (Group 2) were approached to participate in this study. Both the groups were matched for age, sex and life style (smoking, alcohol and substance use) . Participants underwent detailed clinical, radiological and lab investigations to rule out active TB. Data on the socio-demographic profile, life style and habits, past history of TB, history of other medical conditions, medications taken, etc. were collected from the participants using a questionnaire and 15 ml of venous blood was drawn.

The blood was used for routine haematological, biochemical and serological investigations including CBC, random blood sugar HbA1C, lipid profile, LFT and RFT. HIV, Hepatitis B & Hepatitis C. IGRA was performed for all Group 2 participants. The remaining blood was used for immunological evaluations plasma biomarkers and cytokines, surface markers on immune cells, apoptosis and Beta-galactosidase production) and molecular tests (telomere length, telomerase activity and mitochondrial dysfunction). The study is ongoing. Table provides a summary of the samples collected and processed for this study during the reporting period.

Table: Number of specimens received, processed and stored

Specimen Type	Plasma	Serum	Whole blood	PBMC
Group 1	111	37	37	67
Group 2	165	52	52	100

4. Comparing the performance of T-SPOT and TB-Feron tests for detection of latent tuberculosis infection (LTBI)

Principal Investigator	:	Mr. Anbalagan S, Technical Officer C
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR Intramural
Study period	:	2022-2023
Category	:	TB
Pillar	:	Detect

Background

Detection of latent tuberculosis infection (LTBI) in high-risk individuals followed by appropriate treatment could be instrumental in reducing TB burden. The Interferon Gamma Release Assays (IGRA) have higher specificity than the tuberculin skin test (TST), and are therefore a more effective option for diagnosis of latent infection. The present study is aimed at comparing the performance of two IGRA based kits, the T-SPOT.TB test and the Standard E TB-Feron ELISA test with the currently used QuantiFERON-TB Gold Plus assay (QFT-Plus). In a subset of individuals, the new skin test C-Tb will also be compared against QFT-Plus.

Objectives

i. To compare the performance of T-SPOT.TB test and QFT-Plus
ii. To compare the performance of Standard E TB FERON test QFT-Plus
iii. To compare the performance of C-Tb test and QFT-Plus
iv. To determine the diagnostic accuracy measures of T-SPOT.TB, Standard E TB-Feron assay in detecting LTBI

Methods

The study population includes healthy household contacts of smear-positive TB patients (n=100; 70 adults and 30 pediatric), healthy TB healthcare workers (n=50), immunocompromised/HIV+ individuals (n=50) and community controls (n=80). Twelve millilitres of blood was collected into labelled lithium heparin blood collection tubes (T-SPOT.TB) and QFT-Plus blood collection tubes. All assays were performed according to the manufacturer's instructions. C-Tb was administered intradermally and the induration was read after 48 h up to 72 h by measuring the size of the induration (mm).The sensitivity, specificity, PPV, NPV, LR+, LR- and diagnostic efficiency will be calculated using statistical software. Agreement between tests will be assessed by estimating Cohen's κ coefficient

Study progress

Pilot testing of T-SPOT was done. Pilot comparison was also undertaken between C-Tb and QFT-Plus. Participant recruitment is ongoing.

5. **Study of virologic response and HIV drug resistance (pre-treatment and acquired) in adults initiating antiretroviral therapy in a representative population from Chennai, Tamil Nadu**

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT), Government Hospital of Thoracic Medicine (GHTM)
Source of funding	:	ICMR Intramural
Study period	:	2021-2025
Category	:	HIV

Background

WHO recommended dolutegravir (DTG) based first-line regimen (TLD/tenofovir disoproxil, lamivudine and dolutegravir) was adapted by India's National ART program in 2020. As the use of DTG-based first-line ART is being scaled up, it becomes important to conduct periodic pre-treatment drug resistance surveys to document any signals of increase in pre-treatment resistance to INSTI or NRTI (nucleoside reverse transcriptase inhibitor) class of drugs that may affect population level treatment outcomes. This study aims to estimate the prevalence of drug resistance in a representative adult population in Tamil Nadu newly initiated on ART, with the objective to inform effectiveness of first-line therapy at the regional level.

Objectives

i. To determine the prevalence of drug resistance in treatment-naive individuals among adults initiating first line antiretroviral treatment (Pre-treatment Drug Resistance)
ii. To document virological suppression and drug resistance in adults receiving ART for 12 (±3) months (Acquired Drug Resistance)
iii. To investigate association between viral failure and drug resistance with specific ART regimen, adherence patterns, and other demographic and clinical factors.

Methods

This is a prospective observational study that enrols newly diagnosed HIV infected adults who are about to initiate ART and follows them up for one year to determine their response to treatment in terms of virological suppression and emergence of drug resistance. Four millilitres of whole blood were collected from the participants at baseline (prior to initiation of ART) and after 12months of ART. HIV-1 viral load test was performed using the Abbott-m2000 system. HIV drug resistance genotyping (Sanger sequencing of HIV-1 protease, integrase and reverse transcriptase genes) was performed on samples with viral load >1000 copies/ml using a standardized in-house assay on the 3500 genetic analyser (Applied Biosystems, Foster City, California, USA).The sequences were assembled and analysed by using Seqscape software V2.6 (Applied Biosystems). Drug resistance was interpreted with the standard HIV Stanford algorithm.

Study progress

Eighty-four HIV-1 infected ART naïve participants were screened and enrolled. HIV Drug resistance genotyping has been completed for 36 participants.

6. Development of a simple and affordable assay for screening of Dolutegravir (DTG) resistance in HIV-1 infected persons

Principal Investigator	:	S. Manohar Nesa Kumar, Technical officer A
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR Intramural
Study period	:	2022-2024
Category	:	HIV
Pillar	:	Detect

Background

Drug resistance mutations (DRMs) are often associated with reduced virological response to antiretroviral drugs (ARVs). In the current national ART program, HIV drug resistance genotyping is not routinely offered due to the following reasons: lack of Sanger/NGS sequencing facilities infrastructure in the country, high cost, etc. To circumvent these challenges, a method known as "targeted genotyping" has been developed that captures only drug specific mutations by a modified real time-PCR technique. The existing "targeted genotyping" method

reported in the literature can detect major mutations that are specific markers for (N)NRTI–based regimen. However, there is no method available to detect drug resistance mutations to the integrase inhibitor drug, dolutegravir (DTG) that has recently been included in the country's National ART program as a first line drug. This study aims to design and develop a rapid HIV drug resistance assay based on real time PCR technology that can be implemented in the ART programme settings. The proposed assay can identify key drug resistance mutations at 4 positions in HIV-1 integrase gene that can lead to reduced susceptibility to the INSTI class of drugs including, Doultegravir.

Objectives

i. To develop a real time PCR based assay for detection and identification of HIV-1 drug resistance at four important drug resistance associated codons that are markers of various HIV-1 integrase class of inhibitors including Dolutegravir.
ii. To design primers and probes and carry out standardisation experiments
iii. To evaluate the performance of the qualified primers and probes set in the initial standardisation further using synthetic templates and NGS characterised drug resistant EQAPOL QC panel samples

Methods

We designed 4 sets of primers and probes for drug resistance mutation (DRM)-specific amplification and detection. The 5' end of the target specific DRM primers were incorporated with degenerate bases representative of nucleotide variability up to 95%-99% consensus coverage and 3' termini overlap with the probe binding site (except for the DRM codon) having fixed sequences in specific positions that match with the probe-sequences (adaptor sequences). We used subtype C majority alleles as probe sequence; however, the unique "pan-probe" design approach employed by us also covers non-subtype C sequences. Thus, the DRM specific mutagenic primers will also target other alleles encountered in multiple subtypes. Five stored EQAPOL panel samples having moderate viral load copies were selected for initial standardization experiments. These samples have been genotyped for HIV Drug resistance by Sanger sequencing for VQA proficiency testing and the return results gave good agreement. A nested PCR approach was standardised with conventional gradient PCR. Validation will be performed on EQAPOL drug resistant virus panel that has been requested from Duke University.

Study progress

Design of primers and probes has been completed. Initial standardisation experiments using conventional gradient PCR with various primer concentrations and temperatures, and specificity checks have been completed. Further confirmation was done using real time PCR sybr green method. A material transfer agreement (MTA) has been signed between NIRT-ICMR and Duke University for the import of EQAPOL genetic diversity and EQAPOL drug resistant virus panels for carrying out the validation of the newly developed assay.

7. Impact of HIV infection and antiretroviral therapy on premature onset of aging-associated disorders

Principal Investigator	:	Dr. A. Nusrath Unissa
Mentor	:	Dr. Luke Elizabeth Hanna, Dr. Murugavel KG
Participating Institutes	:	ICMR-National Institute for Research in Tuberculosis (NIRT), YR Gaitonde Centre for AIDS Research and Education (YRG CARE)
Source of funding	:	ICMR Intramural
Study period	:	2019-2023
Category	:	HIV

Background

There is emerging evidence to suggest the long-term effects of HIV infection and/or antiretroviral medication on increased risk of inflammaging and premature onset of metabolic disorders in HIV infected persons. Recent studies have identified increased levels of inflammatory proteins and metabolites that are associated with metabolic conditions in HIV-infected individuals on long term ART. The present study aims to correlate alterations in immunological, hematological, metabolite, and cellular profile with risk factors for aging associated co-morbidities like cardiovascular disease (CVD), cancer, diabetes mellitus (DM), liver and kidney diseases.

Objectives

i. To identify abnormalities in immunological, hematological and biochemical parameters in HIV-infected individuals on long term suppressive ART
ii. To correlate cellular and immunological abnormalities with biochemical markers indicative of risk for CVD, DM, liver and kidney diseases

Methods

During the reporting period, 18 participants (3 HIV-infected on ART participants and 15 HIV-infected treatment- naïve) were recruited to the study. Blood samples were collected from recruited participants and used for routine lab analyses (HIV-1 viral load, CD4 count, complete blood count, LFT, RFT, RBS and Lipid profile). PBMC were analyzed for expression of immunosenescence, memory, differentiation and cytotoxicity markers using flow cytometry. Multiplex ELISA was performed for measuring levels of cytokine and peptide biomarkers associated with organ dysfunction. Telomere length was measured using qRT-PCR.

Study progress

Comparative analysis of ART-naïve and treated HIV+ individuals showed significant differences in leucocyte, platelets and mean platelet levels. Abnormalities in biochemical parameters including perturbation in lipid components were observed, signifying dyslipidemia leading to increased risk for cardiovascular disorders. Alteration in several metabolic signatures suggests the probable occurrence of metabolic syndrome, altered liver and renal functions. Significant difference was seen in bilirubin levels between HIV naïve and treated individuals. Besides, a significant difference was seen in telomere length of PBMC as well as CD8+ T cells of HIV-infected individuals as compared to healthy controls. The study is ongoing.

8. Construction and characterization of Infectious Molecular Clones (IMCs) of Transmitted/Founder (TF) HIV-1 viruses

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Research Scholar	:	Mr. Aanand Sonowane
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR Intramural
Study period	:	2018-2023
Category	:	HIV

Background

Understanding the unique characteristics of the HIV-1 variants that are capable of successfully establishing new infection in a human host (Transmitted/Founder or TF viruses) will pave way for the explicit design of an effective vaccine against HIV. Infectious molecular clones of TF viruses would serve as invaluable tools for this analysis.

Objectives

i. To construct full-length infectious molecular clones (IMCs) of Transmitted/Founder (TF) virus from recently infected HIV positive individuals
ii. To compare the phenotypic characteristics of the TF viruses with that of chronic (CC) viruses
iii. To investigate the mechanisms involved in the transmission of the viruses across the mucosal barrier using an *in vitro* cell culture model

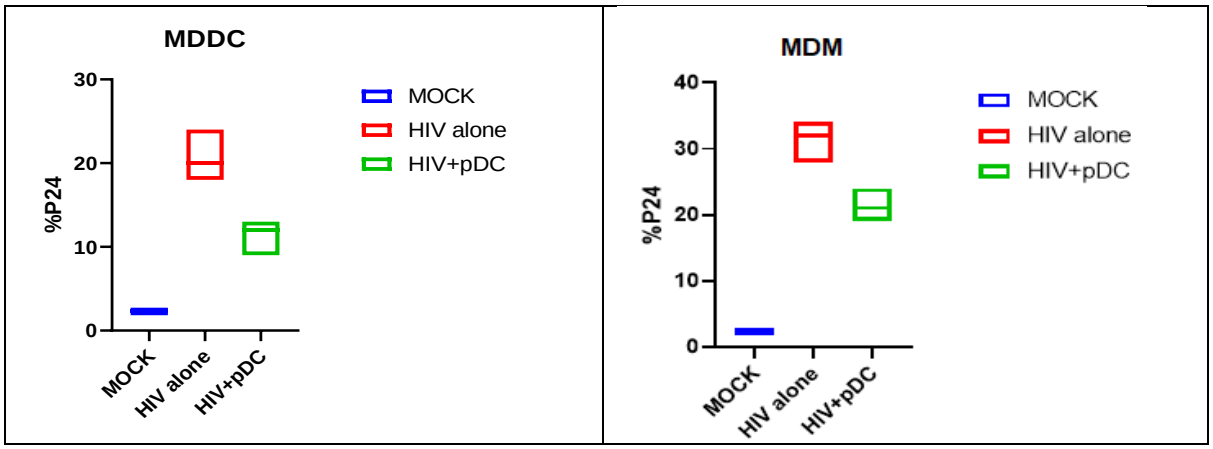
Methods

We constructed IMCs from two recently infected HIV positive individuals and characterized the clones for their biological properties including infectivity, replication kinetics, co-receptor use, sensitivity to broadly neutralizing antibodies, resistance to innate immune factors, etc. To investigate the initial interaction of the virus with innate immune cells and the role of pDCs in early infection, we infected monocyte derived macrophages (MDMs) and monocyte-derived dendritic cells (MDDCs) with the TF and CC viruses in the presence and absence of plasmacytoid dendritic cells (pDCs) and compared infection levels at 5 days post-infection (dpi).

Study progress

We found that co-culture with pDCs resulted in a significant decrease in the percentage of HIV p24 positive (HIV-infected) cells in both MDDCs and MDMs (Figure). Additionally, the number of virions per cell was reduced in the presence of pDCs. Importantly, no p24-positive pDCs were detected at higher multiplicities of infection (MOIs). These observations indicate that pDCs significantly inhibit productive HIV infection and subsequent spread in MDDCs and MDMs.

Figure : Mean percentage of HIV-1 p24^{+} MDDCs (n = 16) and MDMs (n = 16)



9. Introduction and characterization of point mutations in *gag* gene of HIV-1using Adenosine Deaminase acting on RNA (ADAR)

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Research Scholar		Mr. Balakumaran S, SRF
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR Intramural
Study period	:	2021-2024
Category	:	HIV

Background

HIV uses the host machinery to translate its mRNA, and any alteration in the codon would lead to the production of an incomplete/non-functional protein and a non-infectious virus. Adenosine deaminase acting on dsRNA (ADAR) is a ubiquitously expressed enzyme that deaminates adenosine to inosine in double stranded pre-mRNA in humans. The aim of the present study is to investigate the gene editing activity of ADAR-1 in inhibiting HIV-1 protein synthesis.

Objectives

i. To construct an ADAR-1 p150 guide RNA cassette
ii. To analyse the gene editing efficiency of the cassette
iii. To investigate the impact of ADAR-based gene editing on inhibition of HIV protein (Gag) synthesis

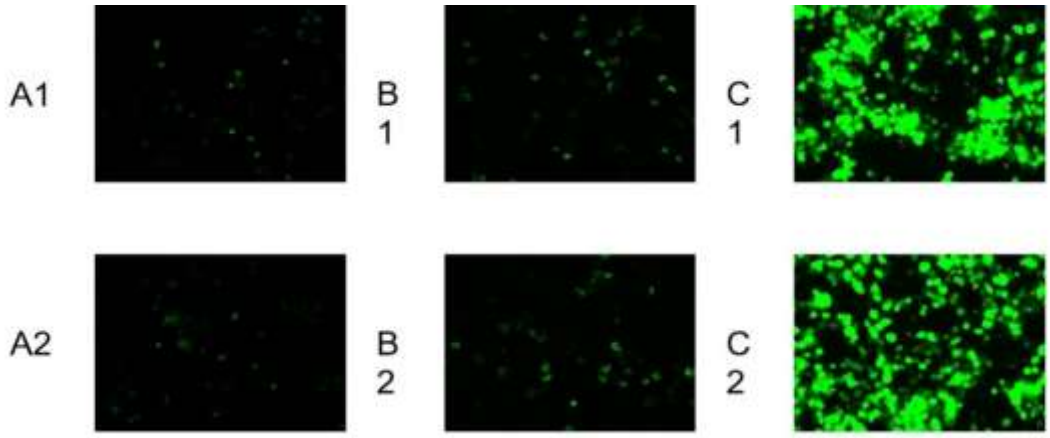
Methods

A single cassette containing guide RNA (gRNA) was constructed by cloning the GluR-B recruiter sequence and a ~50 bp target homologous sequence. Cloning of gRNA was carried out using the Block-it U6 entry vector kit, following the manufacturer's instructions. The constructed clone was confirmed through restriction digestion and Sanger sequencing. The constructed ADAR-1 guide RNA cassette is being tested for gene editing efficiency in HIV culture.

Study progress

Standardization of co-transfection protocol and pre-mRNA editing experiments are ongoing (Figure).

Figure: Co-transfection efficiency verified through GFP expression



A- pmGFPADAR-p150 [300ng] + pNL4-3 [300ng] + gagpLentiguide puro [1.5ug]
B- pmGFPADAR-p150 [300ng] + pNL4-3 [300ng]
C- pmGFP [300ng] + pNL4-3 [300ng] + gagpLentiguide puro [1.5ug]

A1 & A2, B1 & B2 represent successful transfection of pmGFPADARp150 isoform and C1 & C2 represent successful transfection of pmGFP control.

10. HIV-1 transmission pairs: genetic variability and clinical implications

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR Intramural
Study period	:	2022-2023
Category	:	HIV

Background

The failure of HIV vaccine trials is largely due to the high degree of genetic variability observed between HIV genomes. When HIV is transmitted from an infected donor, the transmitted viral population is extremely diverse. However, only a single or very few viruses called transmitted/founder virus successfully establish infection in the recipient. Prior investigation suggests that this selection depends largely on the sequence of the HIV-1 *env*. Further, the *env* sequence also determines the course of disease in the recipient. This study aims to identify key mutations in the *env* gene of HIV-1 transmission pairs (transmitting partner and infected spouse) and analyze the clinical impact of these mutations.

Objectives

i. To amplify the envelope gene of HIV from the plasma samples of transmission pairs with varying levels of neutralization ability
ii. To generate *env* clones and deduce the genetic and phenotypic characteristics of the *env* clones derived from transmission pairs

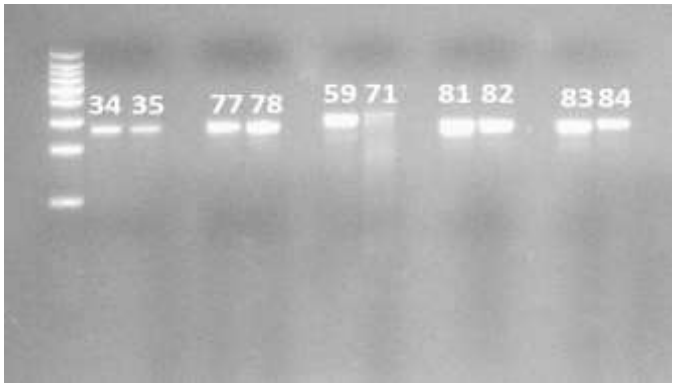
Methods

Viral RNA was extracted from the plasma of transmission pairs and reverse transcribed into cDNA. The HIV-1 *env* gene was amplified using semi-nested PCR. Cloning and characterization work are in progress.

Study progress

The *env* gene of five transmission pairs were amplified by nested PCR (Figure). The amplified products were around 2.5-3kb. Cloning and sequencing are currently under progress. Positive clones will be characterized for their genotypic and phenotypic characteristics.

Figure : Amplified HIV-1 *env* from transmission pairs



11. Understanding the role of Interferon Stimulated Genes (ISGs) in the establishment/ maintenance of latency in HIV and HIV-TB infection

Principal Investigator	:	Dr. Divyadarshini A
Mentor	:	Dr. Luke Elizabeth Hanna, Scientist F
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR – RA fellowship
Study period	:	2022-2025
Category	:	TB/HIV

Background

Interferon stimulated genes (ISGs) can efficiently repress the active viral replication during the acute stage of infection. Down regulation of these genes by HIV can modulate these genes expression through viral proteins thereby causing defects in immunosurveillance. HIV LTR proviral expression and ISG expression is regulated by chromatin remodelling histone acetyl transferasae (HATs) and histone deacetylases (HDACs) with the aid of transcription factors and repressor molecules. We hypothesize that down regulation of ISGs promotes HIV latency by promoting HDAC recruitment at the HIV LTR promoter. Epigenetic modulation of ISGs induced by IFNs through chromatin remodelling is also reported in *Mycobacterium tuberculosis* and is thought to play a role in contributing to intracellular persistence of the bacteria. Therefore, it becomes essential to investigate the down regulated ISGs induced by IFNs that promote HIV latency and favor MTB persistence.

Objectives

i. To identify critical ISGs induced by Type I/Type II IFNs involved in mediating HIV-1 latency
ii. To establish the role of the identified ISGs in HIV-1 latency by demonstrating latency reversal through knock down of the ISGs
iii. To investigate the epigenetic mechanisms involved in the establishment/ maintenance of viral latency
iv. To correlate the level of epigenetic modifications in target gene expression with the size of the viral reservoir in HIV and HIV-*M. tuberculosis* co-infected persons

Methods

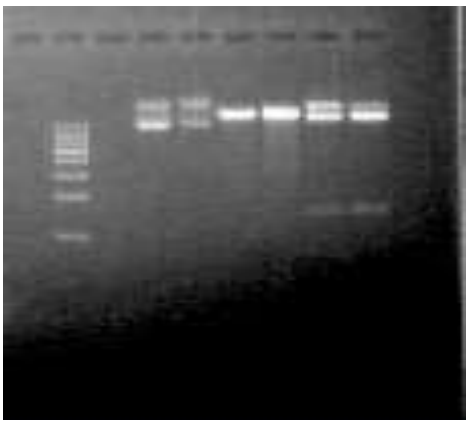
The methods employed for the study include generation of HIV latent cell model using the dual reporter lentiviral plasmid in CD4+ cells, identification of ISGs involved in HIV latency using transcriptomics analysis, studying the latency reversal potency of IFN induced ISGs using knock-out experiments, analysing the epigenetic changes associated with differences in ISG expression and comparing the ISG profile between HIV and HIV-TB patients.

Study progress

HIV GKO, a dual reporter virus plasmid, was purchased from Addgene and used for the identification of productively infected cells as double positive cells (DP - GFP+ and mKo2+) cells and latently infected cells as single mKo2 positive cells (GFP- mko2+). HIV GKO plasmid was isolated and confirmed using restriction digestion with the unique cutter Bam HI producing a 13.5 kb fragment and a dual cutter Spe I producing two fragments of 12 Kb and 1.2 Kb. After confirmation, the plasmids were co-transfected into 293T cells using FUGENE transfection kit. After 48 hours, medium from each well was aspirated and centrifuged to obtain the virus supernatant. The virus supernatant was aliquoted and stored at -80 degree until use after estimating the TCID50 value.

PBMC were freshly isolated from whole blood using density gradient centrifugation. CD4 T cells were enriched using the Rosette Sep TM Human CD8 depletion cocktail protocol. The isolated CD4 cells were activated with PHA at the concentration of 5-10 µg/ml for 48 hours. The activated CD4 cells were used to establish the *in vitro* latency model.

Figure : Agarose gel electrophoresis of RE digested HIV GKO plasmid



Lane 2: 1 Kb plus ladder
Lane 4 & 5: HIV GKO uncut plasmid
Lane 6 & 7: BamHI digested linear fragment of 13kb
Lane 7 & 8: SpeI digested fragment size of 12 kb and 1.2 kb. Residual undigested plasmid above the 12kb fragment.

12. Molecular and immune profiling in adults affected with COVID-19 disease

Principal Investigator	:	Dr. Sudhakar N, Scientist C
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT), Government Corona Hospital (GCH), Guindy, Chennai
Source of funding	:	ICMR Intramural
Study period	:	2020-2023
Category	:	COVID-19

Background

Angiotensin converting enzyme 2 (ACE2) is an entry receptor for the binding of SARS CoV-2 to the host cells. After entry into host cells, viral entry is facilitated by activation of the viral spike glycoprotein and cleavage of the c-terminal portion of ACE2 by serine protease TMPRSS2 and FURIN that are readily expressed in lung tissue. The proposed study aims to study the significance of ACE-2 and TMPRSS-2 gene expression in COVID-19 affected adults and studying the varying immune responses in mild, moderate and severe SARS CoV-2 infected adults.

Objectives

i. To determine the expression of ACE-2 and TMPRSS-2 gene in nasal epithelial cells and peripheral blood mononuclear cells and measure circulating levels of ACE2 in COVID-19 infected individuals.
ii. To investigate immune dysregulation and to assess the magnitude of cytokine and chemokine response in COVID-19 infected adults with varying disease severity.
iii. To quantify the viral load in COVID-19 affected adults and to correlate it with the immune response and clinical outcome.

Methods

This is a prospective study carried out among COVID-19 infected adults. All enrolled participants were tested for complete blood count, LFT, RFT, C-reactive protein (CRP) and LDH levels in blood. ACE-2 and TMPRSS-2 gene expression in epithelial cells from nasal swabs and PBMC was determined using real-time RT-PCR. Levels of cytokines and chemokines were estimated using a multiplex assay on the Luminex platform.

Study progress
We compared the Ct value of ORF1ab gene between COVID-19 cases with mild, moderate, and severe disease. It was observed that during the first and second waves of the pandemic, there was a significant difference in Ct values between the moderate (p value = 0.003) and mild groups (p value = 0.023) but no significant difference in the severe group. However, the Ct value of severe COVID-19 cases with type 2 diabetes was significantly different from that of the non-diabetic subgroup (p value < 0.05). This suggests that Ct value by itself does not have a role in aiding severity stratification among patients with COVID-19 since the viral dynamics and Ct value may vary with the emerging variants that occur in different waves of the pandemic. We also observed a significant difference in expression of ACE-2 gene in nasal swabs of moderate/severe COVID-19 compared to mild COVID-19. On the other hand, there was no significant difference in the levels of expression of TMPRSS2 gene. The study is in progress.

13. Evaluation of immunogenicity of ChAdOx1 nCoV-19 (Covishield) vaccine in adults with Diabetes

Principal Investigator	:	Dr. P. L. Natarajan, Scientist C
Participating Institutes	:	Rajiv Gandhi Govt. General Hospital, ICMR-National Insitute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR Intramural
Study period	:	2021-2023
Category	:	COVID-19

Background
Diabetic individuals infected with SARS-CoV-2 are known to have a significantly higher risk for hospitalisation, intensive care unit admission, intubation and death. The severity of COVID-19 disease intensifies in patients with hyperglycemia probably through, poor innate immunity, altered B cell populations and impaired ability of activated B cells to respond to new antigens. It is well known that neutralizing antibodies (Nabs) are of central importance in protecting the body against acute viral infections. Impaired anti-SARS-CoV-2 antibody response in non-severe COVID-19 patients with diabetes mellitus has been reported. Hence this study was taken up to compare the immunogenicity of Covishield SARS-CoV-2 vaccine between persons with and without diabetes.

Objective
To compare the kinetics of anti-spike IgG antibody and neutralising antibody responses to Covishield vaccine in persons with and without diabetes.

Methods
After recording basic demographic profile, vital signs, and the types of diabetes, a prime-boost regimen of Covishield vaccine with two doses was given 12 weeks apart by the staff of RGGGH. Venous blood samples were collected at baseline, 14 days, 28 days after the prime (first) dose, at the time of booster, one month, 3 months and 6 months post-booster, and at the time of development of COVID-19. Anti-spike IgG antibody levels and neutralising antibody responses to SARS-CoV-2 were measured in the samples and compared between the groups at each of the different time points.

Study progress
Currently the recruitment of participants has been completed. The follow-up is ongoing. The samples are being stored for all immunological analyses.

Completed studies

S.no	Title of the project	Name of PI Designation	Source of funding	Category
1	Structural analysis and molecular dynamics simulation studies of HIV-1 antisense protein predict its potential role in HIV replication and pathogenesis	Dr. Luke Elizabeth Hanna, Scientist F Dr. Umashankar V, Scientist E	Nil	HIV

DEPARTMENT OF STATISTICS

DEPARTMENT OVERVIEW AND MANDATES

Department of Statistics plays a significant role in study planning, sample selection, data management, interpretation, and reporting of medical research studies. The department works in collaboration with other departments and offers expertise in various statistical methods. The department is involved in curriculum development and also undertakes its own independent research projects in statistics and modelling. Our department holds expertise in linear, nonlinear, and longitudinal modelling; latent variable modelling, clinical trial and experimental design; survival analysis; categorical data analysis; causal inference; TB, HIV and Cancer disease modelling; Markov modelling; multi-level modelling; computational biology and bioinformatics; machine learning algorithms and data mining; GIS based spatial modelling and Bayesian methodology. The department aims to advance the statistical discipline by training students in methodological research and its application, conducting collaborative interdisciplinary research in the fields of public health and medicine, and by contributing to the academic, research and professional committees.

Studies in progress

1. Latent class analysis of Health-related quality of life of TB patients during and post treatment in a longitudinal design

Principal Investigator	:	Dr. M. Vasantha, Technical Officer C
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT)
Source of funding	:	ICMR -Adhoc
Study period	:	2020 – 2023
Category	:	TB
Pillar	:	Treat

Background

Health Related Quality of Life (HRQoL) is a multidimensional concept that is evaluated by different latent constructs such as physical function, health status, mental status and social relationships. The use of Bayesian Structural Equation Model (BSEM) to evaluate the impact of TB on quantitative measures of self-reported HRQoL of TB patients in a longitudinal design has not been studied. In the current study, the study aimed to assess the self-reported multidimensional and structural relationship of HRQoL of TB patients including multidrug resistant (MDR), extensively drug resistant (XDR) TB patients using BSEM model.

Objective

To assess the self-reported multidimensional and structural relationship of HRQoL of TB patient including MDR and XDR TB patients treated under National TB Elimination program at different time points (at the initiation, at the end of intensive phase, at the end of treatment, and after three months of completion of treatment) using BSEM.

Methodology

This prospective longitudinal study is being conducted in multiple TB Units (TU) from rural, Tiruvallur district and multiple TUs from urban Chennai in Tamil Nadu, south India. New Pulmonary TB patients, MDR and XDR TB patients who are diagnosed and registered for treatment under NTEP in Chennai and Tiruvallur districts of Tamil Nadu constitute the study population.

Study Progress

A total of 315 TB patients were screened for the study. Among the 315 patients, 226 (72%) were interviewed at the initiation of treatment. Of the 226, a total of 194, 166 and 140 have been interviewed at the end of intensive phase of treatment, end of treatment and after 3 months of completion of treatment respectively. The study is on-going.

2. Development and Validation of Artificial Intelligence Tool for Screening/Detection of Pulmonary TB and other lung diseases using Chest X-rays

Principal Investigator	:	Dr. C. Ponnuraja, Scientist F
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis NIRT
Source of funding	:	ICMR -Adhoc
Study period	:	2022 – 2023
Category	:	TB
Pillar	:	Detect

Background

Effective and timely TB screening at the peripheral health sector level and in remote India remains a constant issue for the health sector. Artificial Intelligence **(**AI) tools that can mimic human like thought processing, reasoning and self -correction abilities. AI technologies include training of tool and deep learning. Deep learning is a particular kind of machine learning that achieves great power and flexibility by learning to represent the world as nested hierarchy of concepts, with each concept defined in relation to simpler concepts, and more abstract representations computed in terms of less abstract ones. Hence, development of an AI Tool for Screening/Detection of Pulmonary TB and other lung diseases using Chest X-rays is the need to bridge the diagnostic gap and facilitate appropriate management. The project aims to develop a computer-aided detection (CAD) system for using chest x-rays for peripheral settings and under national Program for screening and diagnosing TB and other lung diseases.

Objectives

- To develop a computer assisted screening system to differentiate clinically normal chest x ray from clinically abnormal types.
- To develop a computer aided detection system that enables auto differentiation of TB from other chest diseases/ other lung diseases using X-rays
- To further develop the computer aided detection system for auto identification of various presentation of pulmonary tuberculosis.

Methodology

Phase 1: Development of tool: (learning and training)

Milestone 1: Initial proposal would consist of the use of retrospective validated data for development of the tool to differentiate between normal from abnormal chest x ray and then segregate the X-rays with suspected TB lesions. The data would consist of X-ray images: The participating Institutes would collect the images along with the clinical diagnosis and results of diagnostic test (gold standard). The images would be annotated by the experts for the demarcation of the lesion clearly indicating the diseased area(s) on the X-ray image. The data would be uploaded on ICMR portal and Institute of Plasma Research would access the data through the ICMR Portal and use the images for training of AI tool. There would a central annotation team who would reconfirm the annotation done by site before the images are shared with IPR.

Milestone 2 (Objective 2 and 3): This milestone would be undertaken wherein an algorithm would be built that would detect TB and differentiate from other non-tuberculous diseases and other lung diseases. The AI tool would also detect TB with great accuracy including differentiation of all possible presentation of TB. The annotated images would be obtained, along with clinical information and diagnosis confirmed via gold standard method and uploaded on ICMR portal via software. The assessment of the performance would be done on test data set in terms of sensitivity and specificity of the artificial intelligence tool.

Impact Assessment Progress: Evaluation of the progress (technical progress) for use of AI Tool for automated detection of TB in India. The feasibility study would be conducted in peripheral areas for Implementation, accuracy and use of AI tool in peripheral settings. The AI Tool for automated detection of TB projects would be provided to the collaborating partners in the future.

Study progress

According to the protocol, 6500 x-ray images distributed among the several categories have to be included. We have collected retrospective images from the NIRT clinical trials and the national TB prevalence research. We are now pre-processing the images to unify the size, clarity, and quality, and some of them have been tagged using the ICMR's list of labels. All the pre-processed and annotated images have been uploaded into the AI portal with the complete patient as well as the image profile. It is in progress.

Completed studies

S.no	Title of the project	Name of PI Designation	Source of funding	Category/ Pillar
1	Development of a Database of Clinical Study X-rays at NIRT, Chennai	Dr C Ponnuraja C, Scientist F	ICMR	TB/Build
2	ICMR-IPR Project of AI tool for Survey X-rays: Phase-I X-Rays Annotation at NIRT, Chennai	Dr C Ponnuraja, Scientist F	IPR (Institute of Plasma Research)	TB/Detect
3	A Monte Carlo Simulation approach to compare binary regression models for clinical trials	Dr Adhin Bhaskar, Scientist C	Nil	Build

DEPARTMENT OF EPIDEMIOLOGY

DEPARTMENT OVERVIEW AND MANDATES

The Department of Epidemiology conducts studies to estimate the burden of TB by using surveys, modelling techniques, performs Monitoring and Evaluation of TB control in the country. It also conducts Implementation research in TB focusing on for National TB Programme priorities. The department also works on capacity building for students on TB epidemiology by various seminars and internship programs. The Department supports the State and National TB programs by providing Technical Support in the area of TB Epidemiology.The Department conducted the world's largest TB Prevalence Survey in India from 2019 to 2021. The National TB Prevalence Survey was conducted by the Department in collaboration with Central TB Division and World Health Organization. The survey has provided the TB prevalence for the country as well as TB prevalence of various states/ state group. This will help in monitoring the END TB activities in the country.

Studies in progress

1. Scaling up short course TB preventive regimen containing Isoniazid and Rifapentine given once-weekly for three months (3HP) among household contacts of sputum positive pulmonary TB patients in India: A demonstration project

Principal Investigator	:	Dr G. Prathiksha, Scientist C
Participating Institutes	:	National Institute of Tuberculosis and Respiratory Diseases NITRD), Regional Medical Research Centre RMRC) Bhubaneshwar, National Institute of Tuberculosis and Respiratory Diseases and TB Elimation Programme of Tamil Nadu,Karnataka, Gujarat, Pondicherry and Andaman
Source of funding	:	ICMR Extramural
Study period	:	2022 -2026
Category	:	TB
Pillar	:	Prevent

Background

Household contacts of TB patients are at a high risk of TB infection and disease due to prolonged and proximal exposure to source TB case. The National Tuberculosis Elimination Programme (NTEP) of India recommends TPT for Household contacts of bacteriologically positive pulmonary TB patients. The TB preventive therapy guidelines of India, 2021 also recommends 3HP as an alternative to 6 months of isoniazid monotherapy.

Objectives

Primary objective

To determine the feasibility of providing 3HP preventive therapy to household contacts of bacteriologically positive pulmonary TB patients under program settings.

Secondary objective

To describe the pattern of adverse drug reactions to 3HP preventive therapy and its management under program settings.

Methods

This is a multi-centric prospective demonstration study where Household contacts of sputum positive pulmonary TB patients above 2 years of age are administered short course TB preventive regimen containing Isoniazid and Rifapentine given once-weekly for three months (3HP) after ruling out active TB under programmatic conditions. Focus Group Discussions (FGD) will be conducted among participants and health Care workers to understand the barriers and facilitators for 3HP implementation and ADRs will be captured using a treatment card for 3 HP.

Study progress

We have completed enrolment of 4696 participants for the study. The initial findings from few FGDs show that there is a hesitancy among household contacts to take TPT and the completion rate of TPT with 3 HP is high compared to 6H.

Completed studies

S.no	Title of the project	Name of PI Designation	Source of funding	Category /Pillar
1	District wise prevalence of microbiologically confirmed pulmonary tuberculosis in Tamil Nadu	Dr Prathiksha Scientist C	NHM, Tamil Nadu	TB / Detect
2.	Evaluation of information slip method in case finding among contacts of Tuberculosis cases at household and community under programme settings in Tamil Nadu.	Dr Prathiksha Scientist C	DHR	TB / Detect

DEPARTMENT OF HEALTH ECONOMICS

DEPARTMENT OVERVIEW AND MANDATES

Health Economics is a growing academic and research discipline in India. The importance of health economics is being increasingly recognized in public health and health research settings at the government and non-governmental levels. More complex research, development and diagnostic capabilities are leading to higher healthcare costs, healthcare budgets are stretched at state and central level so that health economics is now foundational and integral to healthcare decision making at every level. With this background for the first time under ICMR a separate Department of Health Economics was established in ICMR-NIRT, Chennai in on 4th July 2018. The mandate of Department of Health Economics is to conduct research on economic aspects of diseases with special focus to tuberculosis. In addition, scientist and staff of the department will provide their technical support on application of economic tools in their research to generate health economics evidence to make decisions relating to drugs, devices, treatment pathways and preventative health intervention strategies. One of the key mandates of Department of Health Economics is to build the capacity for health economic research and practice in the country through various training, workshops and capacity building programme. Research on cost-effectiveness of new drugs, devices, treatment pathways, and preventative health intervention strategies is conducted. Health Technology Assessment is undertaken to prioritize national health spending-on various health technologies.

Establishment of Regional Resource Centre for Health Technology Assessment in India (HTA-In)

Principal Investigator	:	Dr. M Muniyandi, Scientist E
Source of funding	:	DHR, MoHFW, New Delhi
Study period	:	2018-2026
Category	:	TB/NON TB
Pillar	:	Treat

Background:

Ministry of Health and Family Welfare (MoHFW), Department of Health Research (DHR) had set up a system for the evaluation of appropriateness and cost effectiveness of the available and new health technologies in India as part of the research governance mandate of the DHR. The purpose of HTA-In is to design and institutionalise HTA that embodies modern best international practice which features transparent, inclusive, fair and evidence based decisions. These HTA evidences would serve as an important tool in prioritising national health spending on various health technologies such as devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of life. In this context HTA-In would make recommendations to the government of India after suitable HTA of medical technologies, interventions and procedures for introduction / procurement in India.

Objectives

1. To inform Government health department officials about undertaking public health programs (e.g. immunization, screening, and environmental protection programs).
2. To inform research agencies about evidence gaps and unmet health needs.
3. To inform hospitals, health care networks, purchasing organizations, other health care organizations, and help in decisions regarding technology acquisition and management.
4. To inform clinicians and patients about the appropriate use of health care interventions for a particular patient's clinical needs and circumstances.

ICMR-NIRT Activities

1. To provide necessary input and technical support to DHR for developing a policy perspective for HTA for use in public health programs in the country.
2. To promote introduction and assessment of new and existing health technologies in the system and will provide support for adoption of health technologies.
3. This resource centre will undertake HTA in terms of medical effectiveness, cost effectiveness, appropriateness, efficacy, safety, psychological, social, ethical, organizational and economic aspects.
4. To build capacity in the country towards Health Technology Assessment.
5. To support evaluation of health technologies for industry through DHR for products that may enter public health domain.

Study Progress

For this project we have been working closely with Government of Tamil Nadu and Government of India. Based on their demands and priorities we received different topics for Health Technology Assessment. So far, we developed six proposals developed and three HTA studies competed. Three completed study reports were approved by Technical Advisory Committee of DHR, New Delhi. Based on the study findings the policy brief was submitted to DHR for approval. In addition to that for capacity building we conducted a systematic review and meta-analysis workshop.

Completed studies

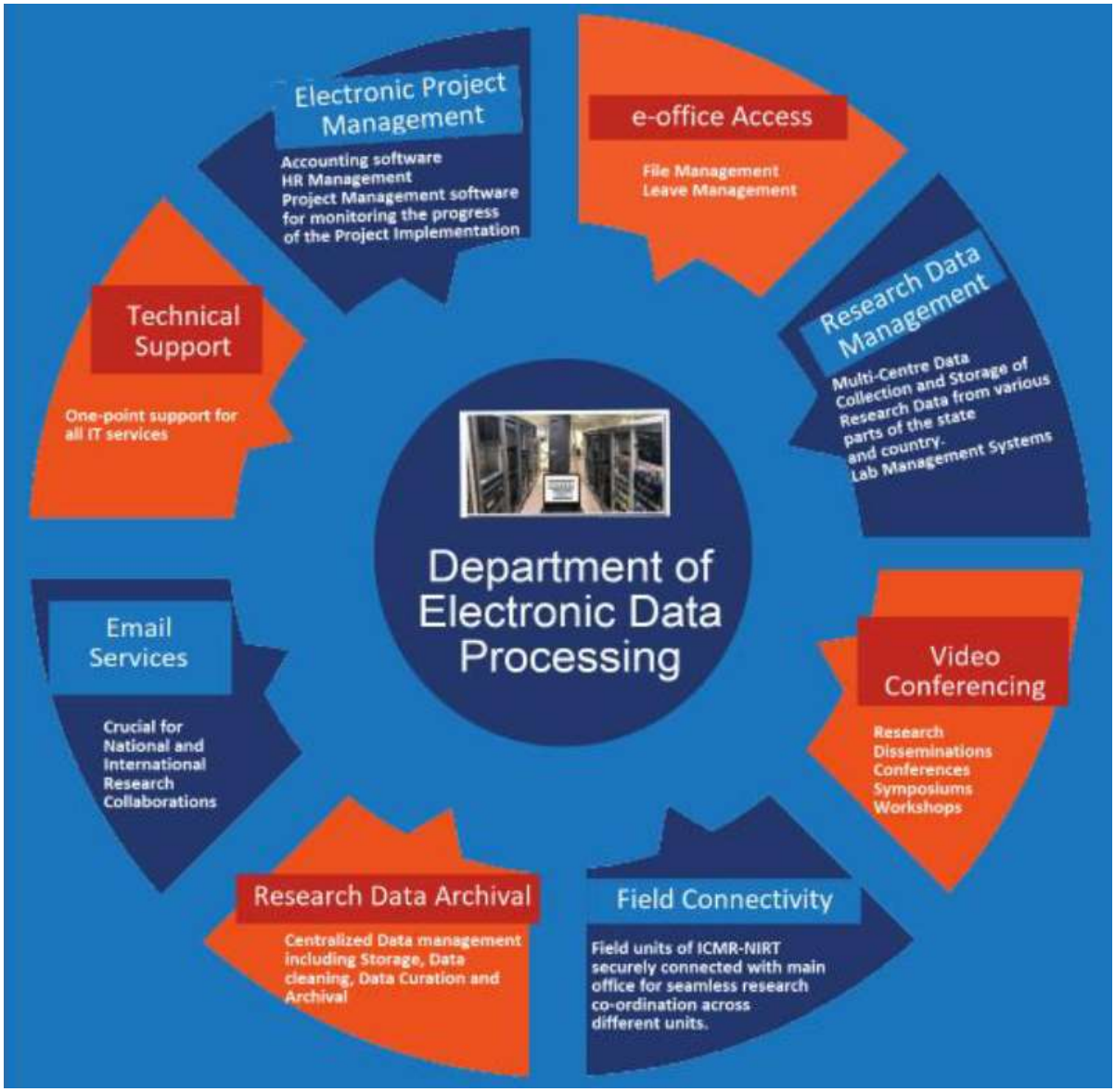
S.no	Title of the project	Name of PI Designation	Source of funding	Category /Pillar
1	The Evaluation of a standard treatment regimen of anti-tuberculosis drugs for patients with MDR-TB Stage II (STREAM II) – Health Economics Component	Dr. M Muniyandi, Scientist E	Liverpool School of Tropical Medicine, UK	TB / Treat
2.	The Potential Impact of COVID-19 Pandemic on Tuberculosis Epidemic	Dr. M Muniyandi, Scientist E	Operational Research Programme	TB / Detect

DEPARTMENT OF ELECTRONIC DATA PROCESSING

DEPARTMENT OVERVIEW AND MANDATES

The ICMR-NIRT Electronic Data Processing division is a core supporter of research relating to IT and data processing. It plays two major roles within the organization: 1. Maintains IT equipment and network services and provides troubleshooting services whenever required. 2. Online server-based data collection /verification support for the research undertaken in the epidemiological unit, clinical division, laboratory, and other operational research studies. The department also plays a key role in the conduct of Epidemiological surveys.

ICMR-National Institute for Research in Tuberculosis pioneers the TB Research system to view digital transformation become more user-friendly through National Knowledge Network (NKN) facility. NIRT maintains digital technology that is of international standards with a 200 TB storage capacity through 100 Mbps NKN connectivity. It has physical and VM servers to provide more than 30 projects with real-time server-based data collection using hand held devices like mobile phones and tablets. It has been providing more than 500 net points to NIRT users functioning from four campuses in Chennai, Tiruvallur, Madurai, and Vellore. Thiruvallur and Madurai have been facilitated Radio Frequency mode net connectivity with internal LAN feasibility.


Electronic Project Management
Accounting software
HR Management
Project Management software for monitoring the progress of the Project Implementation
e-office Access
File Management
Leave Management
Research Data Management
Multi-Centre Data Collection and Storage of Research Data from various parts of the state and country.
Lab Management Systems
Technical Support
One-point support for all IT services
Department of Electronic Data Processing
Email Services
Crucial for National and International Research Collaborations
Video Conferencing
Research
Disseminations
Conferences
Symposiums
Workshops
Research Data Archival
Centralized Data management including Storage, Data cleaning, Data Curation and Archival
Field Connectivity
Field units of ICMR-NIRT securely connected with main office for seamless research co-ordination across different units.

Data Centre at Thiruvallur

The upcoming Data Centre has 5 servers and 1 PB storage on the NIRT-Tiruvallur campus with proposed 1 Gbps NKN connectivity.

The mission of the data centre at Thiruvallur

- Provide *state-of-the-art* IT infrastructure to the researchers in NIRT for it to reach its vision to be a centre of excellence in TB research
- To become a hub for IT infrastructure and data management support for TB research in the country
- Become a core facility for training on data management in TB research in the country

E-Mail migration to NIC

The permanent staff of the NIRT icmr.gov.in e-mail accounts have been migrated successfully to NIC. As part of the mail migration staff email ids have been changed into icmr.gov.in in the 1) employee self-service 2) SFACTS grant management and 3) employee information management system portals.

REDCap

REDCap is a secure web application for building and managing online surveys and databases. While REDCap can be used to collect virtually any type of data, it is specifically geared to support online or offline data capture for research studies and operations. NIRT has obtained license under the REDCap consortium and has become functional from August, 2018.

IT, infrastructure and Data management

EDP provides REDCap services for clinical, laboratory, and epidemiological studies. Currently, there are 14 ongoing projects with 144 active users. It assists the NIRT administration with e-governance portals like e-Procurement, eMarketing, and e-Office. Maintenance of Bacteriology Lab Automation Software and Project Monitoring Portal, creation of a local database for storing Epidemiology survey data is being done. The Division facilitated e-office access to Vellore staff using NIC VPN and online application process for receiving Internship applications at defined periodicities. Involved in designing registration forms, pamphlets, Certificates, and Flyers for various events conducted at the Institute. Provided database management and statistical role in the evaluation and Certification of Sub-national progress towards 'TB Free' status in India, using district-level survey-DLAS (2021-24).

EDP Role in Maintenance of IT Equipment

Maintenance of IT Equipment is done through Annual Maintenance Contract (AMC) and Warranty Service calls. The EDP registers IT equipment breakdown calls from the various department end users and based on the request EDP provides necessary services for the IT equipment.

Research activities

1. Development of a quantitative tool to assess barriers and facilitators in the completion of TB treatment.

Principal investigator	:	Mrs. Basilea Watson, Scientist D
Participating Institute	:	ICMR-National Insitute for Research in Tuberculosis (NIRT), National TB Elimination Programme centres
Source of funding	:	ICMR Intramural
Study period	:	2021-2023
Category	:	TB
Pillar	:	Treat

Background

The patient-centric ascertainment of barriers and facilitators is crucial in influencing completion of the TB diagnostic and treatment pathways. Barriers in TB diagnosis and treatment can be categorized as patient barriers, provider barriers. TB control programs must identify the barriers to plan appropriate interventions.

Objective

To develop a patient specific quantitative questionnaire to identify barriers and facilitators for patients with symptoms of TB to complete the diagnostic and treatment pathways in an urban Indian setting.

Methods

This is a sequential exploratory mixed method study which will utilize both qualitative and quantitative design following a sequential approach implemented in a phased manner to explore and identify patient centric barriers to completing TB diagnostic and treatment processes.

Study progress

Qualitative data collection is completed. We have completed a total of 32 In-depth interviews (IDI) and 10 Focus group discussions (FGD) altogether in Maduri, Kancheepuram, Tiruvallur and Chengalpattu districts. The transcription of the recorded interviews and discussions is currently ongoing.

2. Application of multiple imputation approaches to the prevalence estimation in large-scale tuberculosis prevalence surveys

Principal investigator	:	Mrs. Basilea Watson, Scientist D
Participating Institute	:	ICMR-National Insitute for Research in Tuberculosis (NIRT),
Source of funding	:	ICMR Intramural
Study period	:	2021-2023
Category	:	TB
Pillar	:	Build

Background

The analysis of the TB prevalence surveys using analytical methods adjusted for clustering and correcting for missing data will provide a robust estimate which uses the collected data to the maximum without any compromise on data wastage due to incomplete data records.

Objectives

1. To obtain overall point estimates of TB prevalence using robust standard error and random effects logistic regression methods with and without correction for missing data using multiple imputation.
2. To determine the method that yields the most unbiased estimate of TB prevalence among the methods mentioned in objective 1.

Methods

This is a secondary analysis of existing data. Multiple imputed data sets of the studies mentioned below are being used:

1. Surveys of PTB undertaken on representative population samples aged ⩾15 years before (1999 – 2001) and three repeat surveys (2001-2003, 2004-2006, 2006-2008) after the implementation of the DOTS strategy.
2. An independent survey conducted to estimate the prevalence of TB in 2008–2009 using a different set of villages and employing repeat survey methodology.

Study progress

The project has been initiated and the analysis is on-going.

INTERNATIONAL CENTRE FOR EXCELLENCE IN RESEARCH

ICER OVERVIEW AND MANDATES

The NIAID International Center for Excellence in Research (ICER) in India is a collaborative research partnership between NIAID and the Indian Ministry of Health and Family Welfare, specifically the Department of Health Research (DHR) and the Indian Council of Medical Research (ICMR).

ICER India is a team of NIAID/ Division of Intramural Research (DIR) and Indian researchers who use clinical research and field observations to drive laboratory and clinical investigations of endemic infectious diseases of particular importance in India.

The mission is to develop a sustained research program in areas of high infectious disease burden through partnerships with scientists and physicians working in similar areas of healthcare/ public health related research; to partner with Indian scientists to address specific endemic diseases and foster research in areas such as helminth infections, HIV, COVID-19 and tuberculosis; and to establish a robust clinical infrastructure that is pivotal in tackling important endemic infections and any future emerging/re-emerging infectious disease threats.

Studies in progress

1. A cross-sectional study to estimate the influence of malnutrition, diabetes mellitus and helminth infections on biosignatures in latent tuberculosis in a South Indian population

Principal Investigator	:	Dr. Subash Babu, Scientific Director
Participating Institutes	:	National Institute of Health(NIH)-National Institute of Allergy and Infectious Diseases (NIAID) and ICMR-National Insitute for Research in Tuberculosis(NIRT),
Source of funding	:	National Institute of Allergy and Infectious Diseases (NIAID) -Division of Intramural Research
Study period	:	2020-2025
Category	:	TB/Helminth/LTBI/ Malnutrition and Diabetes Mellitus
Pillar	:	Detect / Prevent

Background

Approximately 2 billion people worldwide are infected with *Mycobacterium tuberculosis* (TB), with 90% of individuals having a latent infection (LTBI). Among the various risk factors that are known to play a role in promoting active TB, HIV is the most well-studied and described. However, other risk factors might be more prominent in active TB pathogenesis in low-HIV-endemic countries like India. These include malnutrition, diabetes mellitus (DM), and helminth infections. LTBI individuals with these comorbidities or coinfections could be at a higher risk for developing active TB than their "healthy" LTBI counterparts without these comorbidities. Thus, studying the pathogenesis of TB infection and disease in these "at-risk" populations is imperative.

Objectives

- To estimate the prevalence of malnutrition, DM and helminth infections in LTBI individuals.
- To determine the effect of coinfections/ comorbidities on biosignatures of LTBI using RNA sequencing (RNA-seq), proteomics, metabolomics, and immunological assays.

Methods

This is a cross-sectional study to identify individuals with LTBI and coinfections/ comorbidities: malnutrition; DM; and helminth infections. Individuals will first be evaluated clinically for symptoms of active TB. Individuals with symptoms of active TB will be excluded from the study and referred for treatment. Individuals who are asymptomatic will be screened for LTBI by interferon-gamma (IFNγ) release assay (IGRA), screened for SARS-CoV2 antibodies and clinically assessed for malnutrition (by body mass index [BMI]), evaluated for DM status (by haemoglobin A1c [HbA1c] levels), and evaluated for helminth infection (by serology and stool quantitative polymerase chain reaction [qPCR]). The screening phase will enrol a total of 5000 participants.

Eligible individuals will be assigned to one of six study groups based on LTBI status and the presence of coinfections/ comorbidities. Participants will have an additional study visit within 6 months of screening for clinical assessment and provide blood (30 ml), urine, and stool samples for experimental studies and storage for future research. Key research evaluations will include gene expression analyses and immunophenotyping on blood samples. The study phase will enrol a total of 300 participants.

Study progress

We have screened 960 participants and 47 individuals are enrolled in the study. Out of the 960 screened, 151 have diabetes, 41 are malnourished and 330 have helminth infections. The common helminth infections are *Necator americanus* (31.5%) and *Strongyloides stercoralis* (6.4%). The screening and recruitment are ongoing.

2. Regional Prospective Observational Research in Tuberculosis (RePORT) – Phase II

Principal Investigator	:	Dr. Subash Babu, Scientific Director
Participating Institutes	:	Institutes in RePORT Consortium
Source of funding	:	Department of Biotechnology (DBT) and CRDF Global
Study period	:	2021-2026
Category	:	TB
Pillar	:	Detect / Treat / Prevent

Background

About 27% of India's 1.3 billion population is estimated to be latently infected with *Mycobacterium tuberculosis* (*M.tb*) and at risk of developing active TB disease. The World Health Organization (WHO) and the Indian government have an ambitious goal to eliminate TB within 20 years. To accomplish this, new TB research is needed, including the development of rapid, sensitive, low-cost diagnostics; identification of biomarkers to assess TB treatment response and risk of developing disease, and a deeper understanding of TB immunology and pathogenesis to inform vaccine development.

Objectives

To evaluate novel diagnostics and biomarkers of diverse states of *Mycobacterium tuberculosis* (*M.tb*) infection; To identify markers of treatment response; To identify markers of lung injury associated with unfavourable TB treatment outcomes; To examine mechanisms of protection against TB in exposed persons; To identify immunologic markers of persons at highest risk of the progress of latent TB infection to TB.

Methodology

Adult and child Participants will be enrolled into one of three prospective, observational cohorts:

- Diagnostic (Dx) Cohort: participants with suspected TB (all age groups), N=1500
- Cohort A: active PTB patients (≥ 15 years), N=490
- Cohort B: household contacts (HHCs) of active PTB patients (all age groups), N=767

The following specimens will be collected and stored in the RePORT India Central Biorepository:

Dx Cohort: *M.tb* isolates subculture, whole blood (PAXgene, plasma, genetic analyses), sputum and/or nasopharyngeal aspirate or gastric lavage, saliva, oral swabs, EPTB specimens, urine and stool.

Cohort A: *M.tb* isolates subculture, whole blood (PAXgene, plasma, peripheral blood mononuclear cells [PBMC], genetic analyses, pharmacokinetics), urine, sputum, stool, and saliva.

Cohort B: Whole blood PAXgene, whole blood plasma, whole blood PBMCs, whole blood genetic analyses, Interferon-Gamma Release Assay (IGRA) supernatant, sputum and *M.tb* isolate subculture.

Study progress

We have recruited 70 individuals in the diagnostic cohort and 30 individuals in cohort A.

3. A pilot study of the effects of helminth infection and SARS-CoV-2 seropositivity on immune response and the intestinal microbiota in India

Principal Investigator	:	Dr. Subash Babu, Scientific Director
Participating Institutes	:	National Institute of Health(NIH)-National Institute of Allergy and Infectious Diseases (NIAID) and ICMR-National Insitute for Research in Tuberculosis(NIRT),
Source of funding	:	National Institute of Allergy and Infectious Diseases (NIAID) - Division of Intramural Research
Study period	:	2020-2023
Category	:	COVID-19

Background

There is a poor understanding of why some individuals infected with SARS-CoV-2 are asymptomatic while others develop severe hyperinflammation, severe acute respiratory distress syndrome (ARDS), and multiorgan failure that can be fatal. Whether the cytokine storm is driven by the innate or adaptive immune response is still poorly understood. We hypothesize that immune regulation by helminth infection and the associated gut microbiota would alter the innate and adaptive immune response directed towards SARS-CoV-2 infection.

Objective

To characterize the immune response and the intestinal microbiota of participants exposed to SARS-CoV-2 in the presence of helminth co-infection.

Methods

This is a pilot, cross-sectional, community-based, sample collection study to characterize the immune response and intestinal microbiota in people with and without SARS-CoV-2 antibodies and helminth infection. Study team will enrol members of households in the Tiruvallur district for one-time blood and stool collection. Blood will be assessed for SARS-CoV-2 antibodies and experimental studies, including transcriptomics. The stool samples will be used for the diagnosis of parasitic infections and for microbiome 16S sequencing and transcriptomics.

Study progress

We have screened 859 participants and 855 individuals are enrolled in the study. Seropositive SARS-CoV2 prevalence is 69.8% and helminth prevalence is 16.8%. The screening and recruitment are ongoing.

4. A cross-sectional study of the systems immunology and viral diversity of SARS-CoV2 infection, COVID-19 disease and Multisystem Inflammatory Syndrome in children

Principal Investigator	:	Dr. Subash Babu, Scientific Director
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis(NIRT),
Source of funding	:	National Institute of Allergy and Infectious Diseases (NIAID) - Division of Intramural Research
Study period	:	2020-2023
Category	:	COVID-19

Background

The medical community has been concerned since the beginning of the outbreak about the potential impact of COVID-19 in children, especially in those with underlying chronic diseases. Unfortunately, a new multisystem inflammatory syndrome apparently related to infection with SARS-CoV-2 has been reported in older children (known as MIS-C), manifested by severe abdominal pain, cardiac dysfunction and shock. However, the SARS-CoV2 infection and the underlying immunology of COVID-19, its correlation with disease severity and MIS-C in children is not fully explored.

Objective

To perform systems immunology and strain diversity among SARS-CoV2 and MIS-C infected children.

Methods

In this Cross-sectional study four groups of children will be studied: Group 1: Prior SARS-CoV2 infection as defined by being positive for IgG; Group 2: COVID-19 disease as defined as children positive by RT-PCR; Group 3: Children with MIS-C according to the WHO or CDC criteria; Group 4: Control children who are negative for both RT-PCR and antibody. A total of 180 children will be recruited for this study. Children will be seen at baseline for enrolment, initial data collection (including a detailed medical history), blood sampling (3-5 ml) for immunology assays and antibody estimation and nasopharyngeal swab for RT-PCR and identifying the strain diversity only in the group 2 and group 3.

Study progress

MIS-C is characterized by elevated levels of type 1 (interferon-γ, interleukin [IL] 2), type 2 (IL-4, IL-13), type 17 (IL-17), and other proinflammatory cytokines (IL-1α, IL-6, IL-12p70, IL-18, granulocyte-macrophage colony-stimulating factor), CCL2, CCL3, and CXCL10 chemokines in comparison to COVID-19 and other infectious diseases following stimulation with SARS-CoV-2–specific antigens. Children with MIS-C had elevated levels of MMPs ($P < 0.005$ statistically significant) in comparison to acute COVID-19, other tropical diseases (Dengue fever, typhoid fever, and scrub typhus fever) and convalescent COVID-19 children. MMP levels exhibited a significant correlation with laboratory parameters, including lymphocyte counts, CRP, D-dimer, Ferritin and Sodium levels. Immunological experiments and analysis are ongoing.

Completed studies

S.no	Title of the project	Name of PI Designation	Source of funding	Category: / Pillar
1	Role of neutralizing antibodies and inflammatory biomarkers in children with Pediatric Inflammatory Multisystem Syndrome - Temporally Associated with SARS-CoV-2 (PIMS-TS).	Dr. Subash Babu, Scientific Director, (ICER India) Dr. Aishwarya Venkataraman, Scientist E (ICMR-NIRT)	NIAID-DIR	COVID-19
2	An observational study of clinical and immunological features of children with SARS-COV-2 (COVID-19) infection over a period of 12 to 16 weeks	Dr. Subash Babu, Scientific Director, (ICER India) Dr Padmasani Venkat Ramanan, Professor and HOD, Sri Ramachandra Institute of Higher Education and Research, Chennai Dr. Aishwarya Venkataraman, Scientist E (ICMR-NIRT)	NIAID-DIR	COVID-19
3	Humoral and cellular immune response among recovered COVID-19 patients: A cross-sectional study, Tiruvallur district and Chennai, Tamil Nadu, India	Dr. Subash Babu, Scientific Director (ICER-India) Dr Jeromie Wesley Vivian Thangaraj Scientist (ICMR-NIE)	NIAID-DIR	COVID-19
4	Study to Evaluate the Effectiveness of the BCG vaccine in Reducing Morbidity and Mortality in Elderly individuals in COVID-19 Hotspots in India	Dr. Subash Babu, Scientific Director, (ICER India) Dr. C. Padmapriyadarsini, Director and Scientist G (ICMR-NIRT)	ICMR and NIAID-DIR	COVID-19

LIBRARY AND INFORMATION CENTRE

NIRT LIBRARY

The Library and Information System of NIRT is laid down to gather wide range of resources on health information and make it accessible to its patrons, promoting research, intellectual growth and constantly evolving to meet the changing needs of the users. Besides holding an excellent print and online collection of books, journals, and databases on health sciences it also holds CD-ROMs, gratis materials, photographs, reprints, slides, theses, video cassettes, and WHO Publications. The NIRT Library, being the heart of the Institute, supports its mission by providing quality resources on time through its digital platform. Our electronic collection of journals, books, and archives is unique in respiratory health areas. These information resources' value to scientists makes them advance their research. Now it is a hybrid library, moving towards an integrated electronic platform.

- **V**alue-**A**dded **S**ervices (**VAS**)
  The NIRT Library provides a wide range of Valued Services with excellence and commitment to quality information services to our researchers and scholars.

- **Access to Digital Resources:** The Digital Library serves as an essential gateway for accessing our electronic resources:
  - **Digital Library** *(established in 2001)* Portal has been updated with
    - Annual Reports *(NIRT)*
    - Catalogue *(OPAC)*
    - E-Books
    - E-Journals (*including Archives*)
    - Library Forms
    - E-Office interlink for File Management System *(Firefox)*
    - ICMR e-Consortium
    - *(Journals)* Impact Factor(*by Clarivate Analytics- a Web of Science Group)*
    - **Institutional Scholarship Repository** *(it keeps getting updated/uploaded with full-text publications with copyright policy)*
    - IRINS *(Indian Research Information Network System),*
    - iThenticate *(plagiarism software)*
    - NIH Library *(Resource Sharing)*
    - Open Access Resources
    - Predatory Journals
    - Science Citation Index
    - Specialised Databases
    - STHIRA *(a tool for NIRT staff)*
    - Tamizh Books
    - *(Pointing)* International Tuberculosis organizations
- **Archives**: Our institutional scholarship archive *(scholarly database)* offers access to all research publications since 1958, ensuring a comprehensive collection of our research contributions over the years;
- **Circulation**: Electronic Check-in and Check-out services since 2002;
- **C**urrent **A**wareness **S**ervice (**CAS**) – Daily Service**:**
  This service helps researchers and scholars stay up-to-date about the latest information and development without having to actively search for new content themselves. It saves them time and effort by delivering relevant content directly to them, allowing them to focus on their work without missing any important updates. Our libray offering the following CAS services:

- **Digital Information Alert Services** on
    - Press Clippings in particular on Tuberculosis and HIV *(COVID during Covid)*; and health in general
    - New Article(s) Alert on Tuberculosis and HIV
        - Online First Article
        - Accepted Manuscript(s) online
        - Ahead of Print
        - In Press
        - High Impact Articles
    - Table of Contents
    - Weekly Updates
    - Monthly Updates
    - Information about Awards, Conferences, Seminars, Workshops, Webinars etc;

- **Historical Slides:** A collection of 'slide(s)' presentations predating the era of PowerPoint, crafted by our esteemed scientists, remains archived in the library to serve as a valuable resource for historical research;
- **Open Access Support:** Our Library support open access publishing and repository, which enhance the visibility to the research output at the global level and increase the citation;
- **Photographic References:** We maintain an accessible repository of photographs, providing a visual reference for research purposes and preserving moments that have shaped our institution's historical journey;
- **Website:** For over two decades, the Library was holding the responsibilities for the Designing, Hosting, and Maintenance (2003-2020) of the NIRT website;
- **Reference Manager:** The library uses and assists the scientist in organizing and styling of citations using the tool viz., EndNote;
- **Remote Access:** The Laibrary offers off-campus researchers and scholars the ability to remotely access NIRT research publications spanning from 1958.
- **S**elective **D**issemination of **I**nformation (**SDI**) Service**:** SDI services enhance the overall experience for library patrons and contribute to the community's research needs; particularly useful for researchers who need to stay current in their field(s). It will help patrons stay informed about the latest developments, research findings, publications, and other relevant content without having to activey search for it themselves. The Library extends the following SDI services:
    - Information Resources/Journal Articles Published [*on Tuberculosis, COVID-19 (during COVID) and HIV*]
    - Digital Document Delivery Service*(DDDS)*
    - Literature search
    - Reference Assistance (*Face-to-face, Telephone, E-Mail*)
    - Resource Sharing (*NIRT-ICMR Institutes and Medical Institutions*)

These services collectively enhance the research experience for scholars and researchers by providing the necessary tools, resources and expertise for their impactful research.

E-PUBLICATIONS

To effectively fulfill the SDI and CAS Services, the library employs a combination of these resources called publications. This will leverage modern technology and tools to process collecting and disseminating relevant information to users who have expressed interest in specific topics or fields of research. The NIRT Library publishes the following three publications to fulfil the patrons needs:

- **TB Alert** *(Fortnightly)*
- **HIV Monitor** *(Fortnightly)*
- **News Bulletin** *(Weekly)*

CONTRIBUTION TO NATIONAL PROGRAMME

NTEP activities in National Reference laboratory, ICMR-NIRT, Chennai

(Contact person: Dr S. Sivakumar, Scientist D)

National Institute for Research in Tuberculosis (NIRT), Chennai is one of the National Reference Laboratory (NRL) that closely monitors five states (Andhra Pradesh, Gujarat, Kerala, Tamil Nadu, Telangana) and five Union territories (Andaman & Nicobar, Puducherry, Lakshadweep, Daman & Diu and Dadra & Nagar Haveli) for NTEP activities in India. NRL Microbiologists visit each state at least once a year for 3 to 5 days for onsite evaluation (OSE) and monitoring EQA activities of smear microscopy, NAAT, culture, and DST by both phenotypic and genotypic methods as per the NTEP protocol. During OSE visits, NRL microbiologists provide technical support for establishing quality assured smear microscopy, NAAT, and C&DST services, including facility design for the introduction of newer diagnostic tools (liquid culture and molecular tests) for the rapid diagnosis of DR-TB (MDR/XDR).

NRL also undertakes yearly proficiency testing of IRL and Culture and Drug susceptibility Test labs as part of the certification process under NTEP. Seven IRLs, 12 C & DST labs have been certified and certification of 8 C& DST labs is in progress for the diagnosis of DR-TB patients from the aforementioned states. During 2022-2023, the Institute conducted thirteenth round of proficiency testing for 25 labs including five NRLs in India, with panel of 20 cultures with different resistant pattern for susceptibility testing for both first and second line anti-TB drugs by genotypic and phenotypic methods including newer anti-TB drugs (Bedaquiline and delamanid).

Retesting process has been completed for three C&DST laboratory, KAPV Medical college, Trichy, TN, CMCH, Coimbatore, TN and SMC Medical College, Vijayawada, AP for certification by Liquid /LPA. As part of PMDT activities, the Institute is supporting for diagnosis of DR-TB patients by both first & second line DST in NTEP settings. A total of 12782 samples were received for DR-TB diagnosis and 2400 samples were received for follow up cultures from 10 districts of Tamil Nadu. As part of NRL EQA activities, On Site Evaluation (OSE) of sputum microscopy and C&DST has been conducted by NRL Microbiologists for five states (Gujarat, Tamil Nadu, Kerala, Andhra Pradesh, and Telangana) and 2 UTs (Andaman & Nicobar Island and Dadar & Nager Haveli). During on site evaluation 550 panel slides were used to assess the Panel testing for 110 laboratory personnel including LT, STLS and SLTs and Microbiologist for smear microscopy. C&DST training has been provided for 95 laboratory personnel for NTEP from different states in India.

Regional Reference Lab for the National AIDS Control Organization
(Contact person: Dr Luke Elizabeth Hanna, Scientist F)

The Department of Virology and Biotechnology functions as a Regional Reference Lab for NACO and continues to provide support for HIV-1 viral load testing and molecular diagnosis of HIV infection. For the EID program, the lab received and tested a total of 2516 DBS samples from the states of Tamil Nadu, Kerala, Pondicherry, Andhra Pradesh, Orissa and Telangana during the period of report. For the National ART program, the lab has received and tested a total of 14534 samples for HIV-1 viral load from various districts of Tamil Nadu as well as from Andamans during the period of report.

Table: Testing Details of HIV-1 Viral load and HIV-1 TNA PCR

HIV testing details		EID Testing details	
Total samples received, tested	14534	Total DBS received	3572
<1000 copies/ml	1163	Tested	2516
>1000 copies/ml	823	Confirmed positives	45
Not Detected	12735	Not Detected	2456
No. of Proficiency panels participated	1 (Oct 2022)	No. of Proficiency panels participated	2 (May/Oct 2022)
Proficiency test score	100%	Proficiency scoring	100%

BUILDING COHORTS, BIOREPOSITORY AND LABORATORY CAPACITY

Studies in progress

1. Regional Prospective Observational Research for TB (RePORT) India Phase II Common Protocol

Principal Investigator	:	Dr. Bhavani PK, Scientist E
Participating institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT),
Source of funding	:	Department of Biotechnology (DBT)
Study period	:	2022-2025
Category	:	TB
Pillar	:	Build

Background

RePORT India Phase II was launched in 2022 with a view to leverage on existing infrastructure, processes and scientific partnerships established during RePORT India Phase I. RePORT Phase II has 5 in-built scientific aims that will be addressed during the period of the study in addition to a small amount of sample collection from a new cohort of presumptive TB cases (diagnostic cohort) as well as TB cohort.

Objectives

i. To evaluate novel diagnostics and biomarkers for diverse states of *Mycobacterium tuberculosis* infection.
ii. To identify markers of treatment response.
iii. To identify markers of lung injury associated with unfavourable TB treatment outcomes.
iv. To examine mechanisms of protection against TB in exposed persons.
v. To identify immunologic markers of progression of latent TB infection to active TB disease.

Methods

The Cellular Immunology Division of the Department of Virology undertakes processing and storage of whole blood, serum, plasma and PBMC for the study. Inventory of the stored samples is maintained in the form of logs sheets as well as in digital format in the cloud-based specimen inventory management system (Freezer PRO). The samples are periodically shipped to the Central Biorepository for long term storage as per the protocol.

Study progress

The study is ongoing. The number of specimens received, processed and stored for this study during the reporting period is shown in Table.

Table: Number of specimens received, processed and stored for RePORT phase II

Cohort A					
Visit type	**Plasma**	**Whole blood (for DNA)**	**Whole blood for NAT Assay**	**Paxgene**	**PBMC**
BL	495	165	110	55	58
M1	297	0	0	33	33
M2	243	0	0	22	31
EOT	198	66	44	22	27
Total	1233	231	154	132	149
Diagnostic Cohort					
BL	369			82	
M2	198			44	
Total	567			126	

2. Central Biorepository for TB Specimens - Phase II

Principal Investigator	:	Dr.Luke Elizabeth Hanna, Scientist F
Participating institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT),
Source of funding	:	Department of Biotechnology (DBT)
Study period	:	2022-2026
Category	:	TB
Pillar	:	Build

Background

The RePORT India Central Biorepository in ICMR-NIRT was established in 2016, as an initiative of RePORT India Common Protocol with financial support from the Department of Biotechnology, Govt. of India, and became fully operational in April 2017. The Central Biorepository has since then been receiving, storing and disbursing high quality biospecimens with well characterized clinical data to support future research in TB.

Objectives

i. To undertake long term storage of biological specimens with linked clinical data collected from study participants enrolled and followed up at all the RePORT India Clinical Research Units.
ii. To disburse archived samples to TB researchers with protocols approved by the Executive Committee (including the sponsors and Executive Committee of the RePORT India Consortium).

Methods

The Central Biorepository has continued to receive various kinds of biospecimens including *Mycobacterium tuberculosis* isolates, whole blood for DNA, whole blood for RNA (PAXgene), sputum, saliva, urine, peripheral blood mononuclear cells (PBMC), serum, plasma and IGRA supernatants from 9 participating sites located in Chandigarh, Chennai, Hyderabad, Mumbai, Puducherry, Pune, Shillong and Vellore. The samples are appropriately stored in ultra-low deep freezers and liquid nitrogen tanks. The chain of custody and inventory of sample in the Central Biorepository is managed through the FreezerPro specimen inventory management system. Operations of the Biorepository and QC processes are followed as per standardized SOPs.

Study progress

The project is ongoing. The Table provides a list of the samples received stored in the Central Biorepository for different cohorts during the reporting period.

Table: Total samples stored in the Central Biorepository during April 2022-March 2023

Phase II_RePORT India Dx Cohort (N=477)	18438
Phase II_RePORT India Cohort A (N=233)	15988
Phase II_RePORT India Cohort B (N=223)	4225
Total specimens stored	**38651**

3. NIRT PBMC (Peripheral Blood Mononuclear Cells) Cryopreservation Proficiency Testing Program

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT),
Source of funding	:	National Institute for Research in Tuberculosis (NIH)-CRDF
Study period	:	2017-2022
Category	:	TB
Pillar	:	Build

Background

The RePORT India Consortium supported the establishment of the first and only proficiency testing program for isolation and cryopreservation of PBMCs which is a crucial specimen for undertaking future immunological studies, at ICMR-NIRT. The NIRT-PBMC PT program was designed to mirror the IQA Program of Duke University and started implementing quarterly surveys since 2017. The PBMC PT team at ICMR-NIRT scores PBMCs prepared by the participating sites for viability and recovery and sends out score cards for continual assessment and improvement where required.

Objectives

i. To evaluate a lab's ability to prepare good quality PBMC for use in protocols
ii. To respond quickly to poor performance
iii. To give laboratories sufficient opportunities to improve performance
iv. To provide data to networks for choosing labs and/or specimens for studies

Method

Six RePORT Indian Clinical Research Units are enrolled and participate in the NIRT PBMC-PT Program. These include CMC, MVDRC, JIPMER, BJMC, BMMRC and NIRT. The program rolls out four quarterly surveys in a year. For each quarter, the participating labs are required to prepare and submit two aliquots of PBMCs (~3 to 5.0x10^6 cells/ml) from each of two donors. At NIRT the samples are thawed as per the thawing protocol and scored for viability and recovery using a performance scoring method established by the cryopreservation proficiency testing advisory group. The scores are shared with the respective sites for continual of approved status. In case of suboptimal performance the labs are required to submit an investigation report stating the reason for their low performance. The PBMC EQA team works with the sites to improve their performance through calls and refresher trainings.

Study progress

All four surveys were successfully implemented during the reporting period.

4. Cohorts for HIV Resistance and Progression in Indian Children and Adults (CoHRPICA)

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT), ICMR-National Institute for Epidemiology (NIE), ICMR-'National AIDS Research Institute (NARI), YR Gaitonde Centre for AIDS Research and Education (YRGCARE), Indira Gandhi Institute of Child Health.
Source of funding	:	Indian council of Medical Research (ICMR)/Department of Biotechnology (DBT)/ International AIDS Vaccine Initiative (IAVI)
Study period	:	2018 - 2023
Category	:	HIV

Background
Longitudinal cohort studies carried out across the globe such as the acute HIV infection cohort study (CAPRISA 002), HIV-1 multiply-exposed seronegative cohort study (HEPS), early infection cohort study etc. have been instrumental in spurring research on the genetic, immunologic and viral factors that alter susceptibility/ resistance to HIV infection in a sub-group of HIV-infected/exposed persons. This is an ambitious project targeting the development of well characterized cohorts of HIV infected and HIV uninfected high-risk individuals, as well as a biorepository of well characterized longitudinal specimens collected from the participants, for future research that would help devise strategies for HIV prevention and/or control.

Aim
The aim of the study is to build well-characterized cohorts of high risk HIV-exposed seronegative individuals, as well as HIV-infected adults and children, and to collect longitudinal clinical and socio-demographic data as well as biological specimens from enrolled participants for undertaking studies aimed at answering pertinent questions with regard to HIV transmission, genetic susceptibility/ resistance and pathogenesis.

Methods
The target of the study is to enroll 1050 HIV-exposed uninfected individuals from key high risk populations (350 each of MSM/TG, PWID and FSW), 250 HIV-infected adult participants (including 100 individuals without co-morbidities and 150 with/at-risk of co-morbidities like TB, cardiovascular disease and diabetes mellitus), and 100 HIV-infected children (including 50 mother-child transmission pairs) across the sites. Collection of data and biological specimens from enrolled participants were done using well-standardized templates and procedures harmonized across the participating sites.

Study progress
During the reporting period, 93 participants were screened and 53 enrolled in the un-infected cohort and 14 participants were screened and 2 were enrolled in the HIV-infected cohort. The study is ongoing and all recruited participants are being followed-up.

5. Virus Research and Diagnostic Laboratory (VRDL)

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Participating Institutes	:	ICMR-National Insitute for Research in Tuberculosis (NIRT),
Source of funding	:	Department of Health Research (DHR)
Study period	:	2021-2026
Category	:	Emerging and reemerging viruses

Background
Given the longstanding expertise of the study team as well as the institute in viral research, we were sanctioned a medical college level VRDL which is being set up at the NIRT Thiruvallur site.

Objectives
i. To create infrastructure for timely identification of viruses and other agents causing epidemics or morbidity significant at the public health level.
ii. To develop capacity for identification of novel and unknown viruses and other organisms, and develop diagnostic kits.
iii. To provide training to health professionals.
iv. To undertake research for identification of emerging and newer genetically active/modified agents.

Status update
The Department was approved by ICMR as a COVID-19 testing laboratory in April 2020 and had supported the State Government of Tamil Nadu with COVID-19 testing during the last 3 waves of the pandemic. Since the approval of the VRDL project, project staff were recruited and provided essential trainings. NIRT VRDL was registered with ICMR-NIV for Proficiency panel testing. We participated in testing of 4 PT panels and scored 100%. The renovation of the infrastructure and procurement of equipment for the project is ongoing.

TRANSLATIONAL VALUE OF RESEARCH PROJECTS

TRANSLATIONAL VALUE OF RESEARCH PROJECTS – 2022-23

Research in ICMR-NIRT is aligned with the target for TB elimination in India. The research activities in TB diagnosis, treatment and prevention have immense translation value for clinical use.

TB diagnosis

- ICMR-NIRT established the country's first NRL-based drug-resistant TB sequencing platform, inclusive of customized bioinformatics pipelines, developed India's first national DR-TB sequencing database which was then used to build and publish a national catalogue of bacteria mutations associated with DR-TB the first India-specific reference of its kind, modelled after the WHO Catalogue.
- Development and deployment of Artificial Intelligence (AI) aided tool for screening of chest x-ray for enhanced detection of Pulmonary TB is being done by the Centre. The objective is to develop and validate a quality AI tool, integrated with online electronic systems like e-Hospital made available for use for auto-reading of chest x-ray to detect abnormalities and create appropriate testing, referral and management of TB.
- The in-house protocol for processing of stool specimens was standardised for molecular detection of MTB from presumptive TB in paediatric population. A large-scale study is further planned for confirming the validity of our findings and to incorporate the protocol in the TB programme.
- Accurate, Rapid, Robust & Economical Diagnostic Technologies for Tuberculosis (ARREST-TB) aims to develop and validate novel molecular diagnostics for the detection of Mycobacterium tuberculosis complex and multidrug-resistant TB, with seamless data interpretation, collation and 'real-time' reporting.
- Performance evaluation of mfloDx® MDR-TB and mfloDx® MDR-TB plus test will provide evidence for the detection of *M. tuberculosis* and its drug resistance from sputum samples.
- The results from the ongoing study on the identification of biomarkers for predicting progression from Latent Tuberculosis Infection to Active Tuberculosis disease has implications for the development of a simple, point-of-care test for early identification of individuals with the highest immediate risk of progression to active TB.

TB treatment

- The ongoing dose finding pharmacokinetic of Vitamin C to be used as an adjunct in TB treatment for better treatment outcomes will provide valuable evidence on the appropriate dosage of Vitamin C.
- Pulmonary rehabilitation study will provide evidence on the exercise tolerance in sputum positive pulmonary TB patients which addresses the important issue of post-TB sequelae.

- Development and characterization of a novel Nanopeptide system for therapeutic application in residual lung injury caused by pulmonary TB had implications in the treatment of TB.
- The results from the following ongoing studies will have implications in the treatment of drug resistant TB patients
    - ✓ Prospective Cohort Study (BEAT Study) which evaluates a Combination regimen of Bedaquiline, Delamanid, Linezolid and Clofazimine in Adults with pre-extensive and Extensively Drug-resistant Pulmonary Tuberculosis.
    - ✓ A multicentric study on various doses and duration of Linezolid in combination with Bedaquiline and Pretomanid (mBPaL study) after 26 weeks of treatment in adults with either Pre-Extensively Drug-Resistant OR Treatment Intolerant / Non-responsive multidrug-resistant Pulmonary Tuberculosis
- The ongoing study will provide information on the effectiveness of shorter 4 -month moxifloxacin containing regimen in drug sensitive pulmonary TB.
- The STREAM stage 2 clinical trial where ICMR-NIRT was the Nodal site in India contributed to the adoption of fully oral regimen of 9 Months in the National TB treatment guidelines. The ultra-short regimen of 6 months with two months injectable gave an efficacy above 80% even among rifampicin resistant study participants with pulmonary TB.
- Completed and published a study on understanding TB disclosure patterns and have developed a new tool to measure TB disclosure.
- Validated a measurement tool for patient-perceived quality of care for TB (PPQCTB) which measured the patient's satisfaction with reference to healthcare providers and health care services. This tool could support quality of care evaluation frameworks for TB health services in India.
- Economic evaluation of STREAM stage 2 study observed that at current costs, the oral bedaquiline-containing regimen for rifampicin-resistant TB is unlikely to be cost-effective in many low-income and middle-income countries. The 6-month regimen represents a cost-effective alternative if injectable use for 2 months is acceptable.
- Cost-effectiveness analysis documented that shorter 4-month moxifloxacin-based regimen for treating drug sensitive TB in India is cost-effective than the 6-month regimen for both patients and National TB programme.

TB prevention

- The results from the ongoing placebo-controlled TB vaccine trial which evaluates the Efficacy and Safety of two vaccines VPM1002 and Immuvac (M*w*) in preventing TB in Healthy Household Contacts of Newly Diagnosed Sputum Positive Pulmonary TB patients will provide evidence for TB vaccine
- Retrospective data analysis of Chingleput BCG vaccination trial, revealed that BCG revaccination in a community offered modest protection (36%) against the development of TB disease at the end of 15 years. This requires further evaluation in future studies.
- The ongoing demonstration project short course TB preventive regimen containing Isoniazid and Rifapentine given once-weekly for three months (3HP) among household

contacts of sputum positive drug sensitive pulmonary TB patients across India will provide information on the implementation of 3HP in TB program settings and the challenges involved.

Epidemiology

- District level Annual Survey in India uses an innovative mixed method study with a triangulation design to assess the incidence of TB at the district levels in India. Verification of sub-national claims for progress towards 'TB Free' status in India, 2022 was completed.
- District wise prevalence of microbiologically confirmed pulmonary tuberculosis in Tamil Nadu among persons aged ≥15 years in Tamil Nadu was completed. The findings would help the state of Tamil Nadu to plan and strategize interventions based on the prevalence estimates in different districts and would serve as a base line for assessing the progress towards ending TB in Tamil Nadu.

Zoonotic TB

Study focusing on Zoonotic TB documented that bovine TB is endemic in this region and unlike found in most other places worldwide, results primarily from infection with *M. orygis* and *M. tuberculosis,* but not *M. bovis*. There is a need for robust epidemiological investigations to understand better the public health risks associated with zoonotic TB in India.

APPENDICES

LIST OF PUBLICATIONS FOR THE YEAR 2022 – 2023

1. Adhikari T, Aggarwal S, Nair S, Joshi A, Diwan V, Stephen A, Devi KR, Kumar Mishra B, Yadav GK, Bangar SD, Sahu D, Yadav J, Ovung S, Gulati BK, Sharma S, Singh C, Duggal C, Sharma M, Ujagare D, Padmakar Chinchore S, Rebecca PB, Rani S, Selvaraj P, Xavier GG, Peter V, Watson B, Kannan T, Asmathulla KSM, Bhattacharya D, Turuk J, Palo SK, Kanungo S, Kumar Behera A, Pandey AK, Zaman K, Misra BR, Kumar N, Behera SP, Singh R, Narain K, Kant R, Sahay S, Tiwari RR, Thomas BE, Rao MVV. Factors associated with COVID-19 stigma during the onset of the global pandemic in India: A cross-sectional study. Front Public Health. 2022 Oct 14;10:992046. doi: 10.3389/fpubh.2022.992046. PMID: 36311615; PMCID: PMC9615248.

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Pulmonary Tuberculosis, Antibiotics 2023, 12(4), 714; https://doi.org/10.3390/antibiotics12040714. Impact factor – 5.22

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Workshop(s)/Symposium/OtherEvents

Details available at NIRT Webpage: http://www.nirt.res.in/html/events.htm

Staff List

Details available at NIRT Webpage: http://www.nirt.res.in/html/scientistPro.htm

APPENDIX 2: LIST OF PHD, POST DOC /RA AT NATIONAL INSTITUTE FOR RESEARCH IN TUBERCULOSIS

Sl. No	Name of the Candidate	Name of the Guide Department	University Affiliation	PhD/Post - Doc/RA	Part time/ Full time	Title of Thesis	Source of funding	Ongoing/ Completed
1.	V Sudha	Hemanth Kumar AK Clinical Pharmacology	Meenakshi Academy of Higher Education and Research (MAHER) Deemed University	Ph.D.	Part-time	Bioavailability of fixed dose combination of first line anti- TB drugs in patients with pulmonary tuberculosis	Intramural	Ongoing
2.	N Usharani	Saravanan N Biochemistry	NA	RA	Full-time	Development and Characterization of a Novel Nanopeptide System for Therapeutic Application in Residual Lung Injury caused by Pulmonary Tuberculosis	Intramural	Ongoing
3.	A Vijayakumar	Hemanth Kumar AK Clinical Pharmacology	Meenakshi Academy of Higher Education and Research (MAHER), Deemed University)	Ph.D.	Part-time	Pharmacokinetics of Linezolid when administered with other second line anti- TB drugs in MDR-TB/Pre-XDR-TB Patients	Intramural	Ongoing
4.	Bindu. D	Dr. Subash Babu ICER	NA	Research Associate-I	Full-time	Impact of COVID-19 on clinical manifestations, diagnosis, treatment outcome and immune response for pulmonary tuberculosis - “Associative BRICS Research in COVID-19 and Tuberculosis	DBT	Ongoing

Sl. No	Name of the Candidate	Name of the Guide Department	University Affiliation	PhD/Post - Doc/RA	Part time/ Full time	Title of Thesis	Source of funding	Ongoing/ Completed
5.	Saravanan. M	Dr. Subash Babu ICER	NA	Research Associate-III	Full-time	A cross-sectional study to estimate the influence of malnutrition, diabetes mellitus and helminth infections on biosignatures in latent tuberculosis in a South Indian population	ICER	Ongoing
6.	Dr. A. Divyadarshini	Dr. Hanna LE Virology & Biotechnology		Research Associate	Full time	Role of Interferon-induced Interferon Stimulated Genes (ISGs) in the establishment/ maintenance of latency in HIV and HIV-TB infections	ICMR	Ongoing
7.	Mr. B. Aanand Sonawane	Dr. LE Hanna Virology & Biotechnology	University of Madras	PhD	Full time	Molecular mechanisms of HIV pathogenesis in target cells	CSIR	Ongoing
8.	Mr. Deepak Selvam	Dr. LE Hanna Virology & Biotechnology	University of Madras	PhD	Full time	Generation of stable lactic acid bacteria strains for enhanced DNA stability and protein expression	ICMR	Ongoing
9.	Ms. Evangeline Ann Daniel	Dr. LE Hanna Virology & Biotechnology	University of Madras	PhD	Full time	Identification of biomarkers that can predict progression from latent tuberculosis infection to active disease	DST INSPIRE	Ongoing

Sl. No	Name of the Candidate	Name of the Guide Department	University Affiliation	PhD/Post - Doc/RA	Part time/ Full time	Title of Thesis	Source of funding	Ongoing/ Completed
10.	Mr. S. Balakumaran	Dr. LE Hanna Virology & Biotechnology	University of Madras	PhD	Full time	Pre-mRNA editing of HIV-1 using adenosine deaminase acting on RNA (ADAR)	ICMR	Ongoing
11.	Ms. Sandhya V	Dr. LE Hanna Virology & Biotechnology	University of Madras	PhD	Full time	Isolation and characterisation of broadly neutralising antibodies from HIV infected elite neutralizers	DBT	Ongoing
12.	Mrs K.Lucia Precilla	Dr. LE Hanna Virology & Biotechnology	University of Madras	PhD	Part-time	Characterizing the molecular mechanism of Protease Inhibitor resistance in HIV-1 Infected individuals.	Intramural	Ongoing
13.	Mr.P.Sathyamurthi	Dr. LE Hanna Virology & Biotechnology	University of Madras	PhD	Part-time	Mechanisticinsights into the role of immunosenescenese and increased mortality in cured TB Patients	Intramural	Ongoing
14.	Mr. Michel Premkumar	Dr Sivakumar Bacteriology	University of Madras	PhD	Part-time	Rapid Diagnosis and drug susceptibility testing of Mycobacterium tuberculosis	Intramural	Ongoing
15.	Mrs. K.Silambuchelvi	Dr Sivakumar Bacteriology	University of Madras	PhD	Part-time	Diagnostic Utility and Implications of Molecular methods for the Drug Resistance Tuberculosis.	Intramural	Ongoing

Sl. No	Name of the Candidate	Name of the Guide Department	University Affiliation	PhD/Post - Doc/RA	Part time/ Full time	Title of Thesis	Source of funding	Ongoing/ Completed
16.	Mr.C.Manjunath	Dr Sivakumar Bacteriology	University of Madras	PhD	Full time	Manipulation of Autophage for host directed therapy in *Mycobacterium tuberculosis*	ICMR – JRF	Ongoing
17.	Mrs.B.Angayarkanni	Dr.V.N Azger Dusthackeer Bacteriology	University of Madras	PhD	Part-time	Novel Anti Mycobacterial agents from Indian Traditional System of Medicine	Intramural	Ongoing
18.	Mrs.B.Magizhaveni	Dr.V.N Azger Dusthackeer Bacteriology	University of Madras	PhD	Part-time	Isolation, stabilization and Encapsulation of Myco-bacterophages for phage therapy	Intramural	Ongoing
19.	Mr.A.Radhakrishnan	Dr.V.N Azger Dusthackeer Bacteriology	University of Madras	PhD	Part-time	Evaluation of essential oils, volatile chemicals and repurposing of drug for anti TB activity	Intramural	Ongoing
20.	Dr. E. Padmasini	Dr. V. N. Azger Dusthackeer	Bacteriology	ICMR-RA	Full time	Role of membrane proteins responsible for drug efflux mechanisms in *Mycobacterium tuberculosis*	ICMR	Ongoing
21.	Shaik Fayaz Ahamed	Dr. C. Ponnuraja Statistics	University of Madras	Ph.D	Full Time	Flexible machine learning methods for survival analysis of high dimensional clinical trial health care data	Abricot	Ongoing

Sl. No	Name of the Candidate	Name of the Guide Department	University Affiliation	PhD/Post - Doc/RA	Part time/ Full time	Title of Thesis	Source of funding	Ongoing/ Completed
22.	JSV Soundarya	Dr.K.R. Uma Devi Immunology	University of Madras	Ph.D	Part time	Attenuated Mycobacterial based vaccine against tuberculosis with a novel strategy for T cell priming	-	Ongoing
23.	Venkatesan P	Dr.K.R. Uma Devi Immunology	University of Madras	Ph.D	Full Time	CRISPR Mediated Platform for Diagnosis and Rapid Detection Of Drug Resistance Pattern In Mycobacterium Tuberculosis.	LTF	Ongoing
24.	Kadar Mohideen	Dr. Ramalingam B Immunology	University of Madras	Ph.D	Full Time	Biomarkers and immune responses in pulmonary tuberculosis severity and its treatment monitoring.	ICER	Ongoing
25.	Pavithra Sampath	Dr. Ramalingam B Immunology	University of Madras	Ph.D	Full Time	Molecular analysis of monocyte subsets in humans infected with Mycobacterium tuberculosis	DST INSPIRE	Ongoing
26.	Arul Nancy	Dr. Ramalingam B Immunology	University of Madras	Ph.D	Full Time	Characterization of host immune response to unfavourable treatment outcomes in tuberculosis	DBT	Ongoing
27.	Harinisri G	Dr. Ramalingam B Immunology	University of Madras	Ph.D	Full Time	Evaluation of Inflammatory and Immunological markers among latent TB infection.	CSIR	Ongoing

Sl. No	Name of the Candidate	Name of the Guide Department	University Affiliation	PhD/Post - Doc/RA	Part time/ Full time	Title of Thesis	Source of funding	Ongoing/ Completed
28.	Dr Sagarika Devi	Dr .P. Kannan Immunology	NA	Post Doc	Full Time	Dereplication-guided bio-prospecting of cyclic lipopeptides from marine Bacillus sp. for inhibition of Mycobacterium tuberculosis	ICMR	Ongoing
29.	Dr Ahmed Kabir Refaya	Dr P. Kannan Immunology	NA	RA	Full time	Insights into the genomic adaptations of Mycobacterium tuberculosis (MTBC) species in cattle	ICMR	Ongoing
30.	Mr.S.Arunkumar	Dr.K.R.Uma Devi Immunology	University of Madras	PhD	Full-time	Functional study of Drug resistant Mutation in Mycobacterium tuberculosis	DBT-JRF	Ongoing
31.	Mrs. Ananthi	Dr. P. Kannan Immunology	University of Madras	PhD	Full time	Study on Mutations Associated with Pyrazinamide Resistance in Mycobacterium tuberculosis	ICMR	Ongoing
32.	Ms. R. Harini	Dr. P. Kannan Immunology	University of Madras	PhD	Full time	Comparative genomics of Mycobacterium tuberculosis complex isolates from animals	ICMR	Ongoing
33.	Dr.Sriram Selvaraju	Dr.Gopalan Epidemiology and Public Health	Central University of Tamil Nadu	PhD	Part time	Sub Clinical Tuberculosis	Nil	Ongoing

OBITUARY

S.No	NAME AND DESGINATION OF THE STAFF	DEPARTMENT	DATE OF DEATH
1	Smt. Savithiri Sukumar Ex - Senior Research Officer	Clinical Research	25.04.2022
2	Shri. J. Natarajan Ex - Senior Technical Officer	Transport	23.05.2022
3	Smt. Ambujam Ganesh Ex - Nursing Officer	Clinical Research	03.11.2022
4	Shri. Santhana Krishnan Ex - Technical Assistant	Bacteriology	11.09.2022
5	Shri. A. Ganapathy Ex - Sr Driver Spl Grade	Transport	27.06.2022
6	Shri. N. Shanmugam Ex - Lab Assistant	Field	02.10.2022
7	Smt. Vasanthira Patturaj Ex - Senior Technical Assitant (Nursing)	Clinical Research	24.10.2022
8	Shri. R. Ravichandran Ex - Senior Technician-2	Field	17.06.2022
9	R.Krishnamurthy Ex - Senior Technical Officer	Statistics	24.12.2022

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