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NIRT
NATIONAL INSTITUTE FOR RESEARCH IN TUBERCULOSIS

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 2021 - 2022

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

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Preface

I am happy to give you the Annual Report of ICMR-NIRT for the year 2021-2022. As we march towards 2025 goal of TB elimination, ICMR-NIRT continues to contribute significantly to the National Programmes by conducting translational research and generating evidence for newer initiatives. Few such initiatives this year include: 4-month Moxifloxacin based treatment regimen for drug-sensitive TB; initiation of a socio-behavioural research network; launch of viral research & diagnostic laboratory, etc. This Annual Report briefs of such activities carried out by all departments of ICMR-NIRT to reach the common goal of TB elimination.

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ABBREVIATIONS

ABC	ATP Binding Cassette
ACE2	Angiotensin Converting Enzyme 2
ADAR	Adenosine Deaminase Acting on RNA
ADR	Adverse Drug Reactions
AI	Artificial Intelligence
AIC	Akaika Information Criterion
AIC	Airborne Infection Control
ARDS	Acute Respiratory Distress Syndrome
ArpE	Adult Retinal Pigment Epithelial
ARREST-TB	Accurate, Rapid, Robust & Economical Diagnostic Technologies For Tuberculosis
ART	Anti –Retroviral Treatment
ASP	Antisense Protein
ATT	Anti-TB Treatment
BCG	Bacille Calmette-Guérin
BDQ	Bedaquiline
BEAT	Building evidence against TB
BIC	Bayesian Information Criterion
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
CBNAAT	Cartridge Based Nucleic Acid Amplification Test
CC	Critical Concentration
CFU	Colony Forming Unit
CFZ	Clofazimine
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease – 19
CP	Common Protocol
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CRP	C-Reactive Protein
CRS	Clinical Research Sites
CSF	Cerebrospinal Fluid
CTAB	Hexadecyltrimethiammonium Bromide
C-TRIUMPH	Cohort For Tuberculosis Research By The Indo-US Medical Partnership
CVD	Cardiovascular Disease
CXCL	Chemokines
CXR	Chest X-Ray
DC	Dendritic Cells
DHR	Department of Health Research
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
ECG	Electrocardiogram
EFV	Efavirenz
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
FTIR	Fourier Transform Infrared
GCMS	Gas Chromatography Mass Spectrometry
GIS	Geographical Information System
GPS	Global Positioning System
GPU	Graphics Processing Unit
HEPS	HIV-1 Multiply-Exposed Seronegative Cohort Study
HHC	Healthy Household Contacts
HICON-R	High concentration of rifampicin
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
IRINS	Indian Research Information Network System
KII	Key Informant Interviews
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
MDR	Multidrug Resistant
MDR-TB	Multi-Drug Resistant TB
MDS	Molecular Dynamics Simulation
METRIF	Metformin rifampicin
MFS	Major Facilitator Superfamily
MGIT	Mycobacterium Growth Indicator Tube
MIC	Minimum Inhibitory Concentration
MIS-C	Multisystem Inflammatory Syndrome In Children
MMP	Matrix Metalloproteinases
MoHFW	Ministry of Health And Family Welfare
MOX	Moxifloxacin
MSM	Men Having Sex With Men
MTB	Mycobacterium Tuberculosis
MTBC	Mycobacterium Tuberculosis Complex
NABL	National Accreditation Board For Testing And Calibration Laboratories
NAbs	Neutralizing Antibodies
NACO	National Aids Control Organization
NC	Native Carnosine
NETS	Neutrophil Extracellular Traps
NFLG	Near Full Length Genome
NK	Natural Killer
NMR	Nuclear Magnetic Resonance
NRL	National Reference Laboratory
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NT	Non-Transmitted
NTEP	National TB Elimination Programme
NTM	Non Tuberculous Mycobacteria
NVP	Nevirapine
OFX	Ofloxacin
OSE	Onsite Evaluation
Pa	Pretomanid
PANTA	Polymyxin B, Amphotericin B, Nalidixic Acid, Trimethoprim, Azlocillin
PBMC	Peripheral Blood Mononuclear Cells
PCR-RFLP	Polymerase Chain Reaction - Restriction Fragment Length Polymorphism
PD	Positive Deviance
PDB	Protein Data Bank
PFT	Pulmonary Function Test
PK	Pharmacokinetic
PMDT	Programmatic Management Of Drug-Resistant Tb
POC	Point of Care
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
RATIONS	Reducing Activation Of Tuberculosis By Improvement Of Nutritional Status

RCT	Randomized Clinical Trials
RePORT	Regional Prospective Observational Research In TB
RF	Random Forest
RFT	Renal Function Tests
RI	Reduced Inoculum
RMP/RIF	Rifampicin
RNA	Ribo Nucleic Acid
RNTCP	Revised National TB Control Programme
RTPCR	Reverse Transcriptase Polymerase Chain Reaction
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
SHINE	Shorter treatment for minimal TB in children
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
TBL	Tuberculosis Lymphadenitis
TDM	Therapeutic Drug Monitoring
TEMA	Tetrazolium Microplate Based Assay
TF	Transmitted Founder
TIMP	Tissue Inhibitors of Matrix Metalloproteinases
TNF	Tumour Necrosis Factor
TNGS	Targeted Next Generation Sequencing
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
ZMA	Zobell Marine Agar

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 evaluate 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

CL – 1: 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).

Principal Investigator	:	Dr.C. Padmapriyadarsini, Scientist F
Participating Institutes	:	ICMR-NIRT, Govt. hospital of Thoracic Medicine And Gov Ottery TB Hospital, Chennai Rajan Babu Institute of Pulmonary Medicine and Tuberculosis (RBIPMT), New Delhi National Institute of Tuberculosis and Respiratory Disease (NITRD), New Delhi Group of Tuberculosis (GTB) Hospital (GTB Sewri TB hospital), Mumbai B.J. Medical College (BJMC) & Hospital - Ahmedabad
Source of funding	:	USAID
Study period	:	2019 – 2022
Category	:	TB
Pillar	:	Treat

Background

In India, under the Programmatic Management of Drug Resistant TB (PMDT) program, the current cure rates for MDR-TB is about 46%, while that for pre-extensive (pre-XDR) and extensively drug resistant (XDR) TB is around 29%. There is an opportunity now with the availability of new drugs for TB, to improve treatment outcomes. The scientific validity of comparing a 24-36 weeks (6-9 month) end point (Bdq + Dlm + Lzd + Cfz) with a 24-27 month endpoint (standard of care) would represent a significant challenge. Hence, we planned to conduct a prospective study in pre-XDR or XDR pulmonary TB patients attending the study sites.

Objective

1. To evaluate the efficacy of a new treatment regimen of 24 - 36 weeks (6-9 months) duration consisting of Bedaquiline (BDQ), Delamanid (DLM), Linezolid (LZD) and Clofazimine (CFZ) in adult patients with pre-XDR or XDR pulmonary TB.

Methodology

This is a multicentric, prospective cohort study. Screened and eligible participants were recruited to the study and treated with the study drugs for a period of 6-9 months depending on culture positivity at the end of 4 months of treatment. They are being followed up for 12 months after treatment completion.

Study progress

167 pulmonary Pre XDR and XDR TB patients were enrolled in New Delhi, Gujarat, and Mumbai and Chennai sites. The study is ongoing and all recruited patients are on follow-up.

Table: **Site wise enrolment data**

Site	Screened (n)	Enrolment (n)	Gender (n)	
			Male	Female
ICMR-NIRT, Chennai	35	22	13	9
NITRD, New Delhi	69	46	30	16
RBIPMT, New Delhi	75	34	16	18
BJMC, Gujarat	39	32	23	9
GTB, Mumbai	68	33	13	20
Total	286	167	95	72

CL – 2: 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 (MDR TI/NR) Pulmonary Tuberculosis in India.

Principal Investigator : Dr. C.Padmapriyadarsini, Scientist F

Participating Institutes : Sarvodaya Charitable Trust Hospital, Mumbai
Shatabdi Centenary Hospital, Mumbai
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 injectable and toxic drugs often lead to poor drug adherence and poor treatment outcomes. The ZeNIX study with consistent dosing of Bedaquiline (Bdq) and Pretomanid (Pa) reported more than 90% success rate with relatively higher proportion of adverse events. Modified BPaL (mBPaL) study is proposed with varying doses of Linezolid (Lzd) along with Bdq and Pa as planned reduction of Lzd for the treatment of Pre-XDR and MDR TI/NR pulmonary TB patients for 26-39 weeks. 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.

Objective

1. 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.

Methodology

This is a multicentric, randomized pragmatic clinical trial- 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 un favorable 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

About 230 Pre XDR and MDR (TI/NR) TB patients are enrolled in the study from the sites and all the enrolled patients are being followed regularly for completion of treatment and post treatment follow up.

Table: **Site wise enrolment data**

Study sites	Number Screened(n)	Number enrolled(n)	Gender (n)	
			Male	Female
SCH, Mumbai	136	56	25	31
SCTH, Mumbai	121	56	19	37
SNMC, Agra	71	38	23	15
NITRD, New Delhi	42	36	19	17
GRH, Madurai	7	4	3	1
KGMU, Lucknow	15	13	6	7
GMC, Surat	15	11	6	5
GMC, Bhavnagar	20	16	10	6
Total	427	230	111	119

CL - 3: 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-ITRC
Study period	:	2018 - 2023
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

1. 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.

Methodology

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 trial was initiated in October 2019 and the enrolment was completed in December 2020. A total of 2723 household contacts were screened and 2214 vaccinated. The follow-up of enrolled household contacts is ongoing.

CL– 4: 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
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 randomized 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

1. 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$_{7}$).

Methodology

In this multicenter, 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 every month during treatment and 2 years post-treatment (once in 3-Months during the first year and once every 6 months in the subsequent year). Sputum examination will be done during follow-up for response to treatment and for TB recurrence. In addition, drug adverse events will be documented.

Study progress

The study was initiated in March 2022 and the recruitment of study participants is ongoing.

CL -5: Randomized 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.

Principal Investigator	:	Dr. D. Baskaran, Scientist F
Participating Institutes	:	Govt. Medical College Hospitals in Chennai, Vellore and Madurai and NTEP centres Source of funding
	:	ICMR Intramural
Study period	:	2013 - 2022
Category	:	TB
Pillar	:	Treat

Background

Tuberculosis lymphadenitis (TBL) is the most common presentation of extra-pulmonary TB. Under the TB Program of India patients diagnosed with TBL are treated with a 6-month regimen. Shortening TB treatment is a global research priority and research involving quinolones group of drugs is of particular interest towards this goal.

Objective

1. To compare the efficacy in terms of response at the end of treatment and relapse up to 24 months post-treatment, in newly diagnosed superficial TBL patients treated with 4-month Ofloxacin containing test regimen (2RHZO daily/ 2RHO thrice-weekly), with the same outcome in those treated with a 6-month control regimen (2EHRZ thrice-weekly/2HR thrice- weekly).

Methodology

The open-label randomized clinical trial is being conducted in ICMR-NIRT sites in Chennai, Madurai and Vellore. Newly diagnosed, HIV sero-negative, non-diabetic adults aged $\geq$18 years with superficial lymph node biopsy/CBNAAT suggestive of TB were eligible for the trial. Participants are randomized to Rifampicin, Isoniazid, Pyrazinamide and Ofloxacin daily for 2 months followed by Rifampicin, Isoniazid, and Ofloxacin thrice weekly for 2 months (2 RHZO daily / 2RHO thrice-weekly) or to Rifampicin, Isoniazid, Ethambutol and Pyrazinamide thrice weekly for 2 months followed by Rifampicin and Isoniazid thrice weekly for 4 months (2 RHEZ thrice-weekly / 4 RH thrice-weekly). The participants are followed up every month up to 12 months, thereafter every 3 months till end of follow-up for a period of 2 years post-treatment.

Study progress

A total of 302 TBL patients have been enrolled (150 and 152 in the test and control regimen respectively). The follow-up of enrolled participants is ongoing.

CL -6: The evaluation of a Standard Treatment Regimen of Anti-tuberculosis drugs for patients with MDR-TB (STREAM – Stage 2).

Principal Investigator	:	Dr. G. Narendran, Scientist F
Participating Institutes	:	ICMR-NIRT, Chennai; BJMC, Ahmedabad, RBIPMT, New Delhi
Source of funding	:	USAID
Study period	:	2017-2023
Category	:	TB
Pillar	:	Treat

Background

Tuberculosis (TB) control worldwide is impeded by two major issues: (i) the emergence of multidrug resistance (MDR) and (ii) co-existent HIV infection. Stage 2 of STREAM was designed to investigate ways in which the 9 months regimen used in STREAM stage 1(Regimen B) could be improved either by removing the second-line injectable, which is associated with severe drug toxicity, or by shortening the regimen to 6 months, by the addition of Bedaquiline. The regimen B of STREAM was already taken up by WHO and became the recommended regimen with slight alteration for uncomplicated MDR-TB. The latest version of the protocol was to test the non-inferiority of Regimen C (fully all oral regimen and Regimen D containing Bedaquiline and aminoglycoside for 2 months) compared to Regimen B.

Objective

1. To assess whether the proportion of patients with a favorable efficacy outcome on Regimen C, the fully oral regimen, is non-inferior to that on Regimen B, the control regimen for Stage 2 at Week 76.

Methodology

The STREAM study is a multinational, multi-center, parallel-arm, open-label, randomized, controlled trial. Patients recruited to the study include those with multi-drug resistance tuberculosis (MDR-TB) and patients with rifampicin-resistant TB without quinolone or aminoglycoside resistance. Three regimens in the study include Reg B: 4KHPMEZC/5MEZC for 9 months; Reg C: 4-6 Beq, Lev, Clo, Emb, Z, H, Pro/ 5 Beq, Lev, Clo, Z, Emb;Reg D: 2-3 Beq, Lev, Clo, Z, H, K/ 4 Beq, Lev, Clo, Z

Study progress

127 patients were screened in ICMR-NIRT out of which 49 patients were randomized. Recruitment was stopped in January 2020 as the global sample size was achieved. As on 01 July 2022, all the participants in NIRT have completed their week 132 follow-up visit.

CL -7: Assessment of pulmonary impairment by spirometry in treated sputum positive pulmonary TB patients.

Principal Investigator	:	Dr.N.Poorana Ganga Devi, Scientist D
Participating Institutes	:	ICMR-NIRT Chennai and its subsites Madurai, Vellore, AIIMS Delhi
Source of funding	:	ICMR-ITRC and OSPF
Study period	:	2020-2022
Category	:	TB
Pillar	:	Treat

Background

Studies have shown that patients with pulmonary TB often have impaired lung spirometry parameters at the time of presentation; and while ventilator function improves with treatment, a significant residual deficit remains even after complete microbiological cure. This residual deficit leads to impaired quality of life and long-term morbidity and mortality in these successfully treated patients. In a retrospective study it was shown that treatment with metformin was associated with improvement in spirometry examinations in patients with both T2DM and COPD.

Objective

1. To assess the pulmonary impairment by spirometry in treated sputum smear

positive pulmonary TB patients after completion of treatment with 6-months of first-line anti-TB drugs of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol with or without metformin in the intensive phase of treatment.

Methodology

This cross-sectional study will include patients enrolled for the METRIF study and who have completed 6 months of treatment. Investigations include postero-anterior chest radiography, two sputum examination by smear and culture for tubercle bacilli, 12 lead Electrocardiogram (ECG) and Pulmonary function test (PFT) by Spirometry. The quality of life will be assessed using the St. Georges respiratory questionnaire (SGRQ). 10 ml of blood will be collected to assess the immunological impact of metformin on TB- specific immune responses.

Study progress

A total of 78 patients in metformin group and 85 in the control group were enrolled for the study. Mild disease pattern and less cytokine levels was higher in the metformin group compared to the control group.

CL – 8: Acceptability and feasibility of Mobile app in Adverse Drug Reactions (ADRs) reporting in National TB Elimination Programme (NTEP) centers.

Principal Investigator	:	Dr.S. Ramesh Kumar, Scientist E
Participating Institutes	:	Indian Pharmacopiea Commission,
and NTEP Source of funding	:	ICMR Intramural
Study period	:	2019 - 2023
Category	:	TB
Pillar	:	Treat

Background

Adverse drug reactions (ADR) can lead to a patient interrupting tuberculosis (TB) treatment before completion, and thus contribute to avoidable morbidity, treatment failure, reduced quality of life, or death. The overall burden of adversity directly attributable to anti-TB medicines is poorly quantified and it is not usually well profiled in individual TB control programmes. National TB Elimination Programme (NTEP) has emphasized on pharmacovigilance. Mobile app has been proved to be better than the classical reporting elsewhere. Govt of India has come out with new 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 centers for reporting ADRs

Objective

1. To assess the acceptability, feasibility of implementing ADRs reporting using 'PvPI ADR reporting App' of Govt of India in the NTEP Centers

Methodology

NTEP centers in Chennai and Madurai will be selected from both rural and urban areas with both high and low performing units and then 30 centers (15 from Madurai district and 15 from Chennai) will be randomly chosen and will be included for the study. The Medical Officers in the centers will be sensitized and trained in using the 'PvPI ADR reporting App' for reporting the ADRs during the TB treatment. ADR reporting will be assessed once in 3 months. We will observe the numbers and the process of ADR reporting, compiled for a period of one year. A Qualitative analysis of the data captured from the Medical Officers to

assess the feasibility and acceptability, will be done. Acceptability of the mobile App to report ADR by the Medical Officers will be assessed after a year by collecting data from the Medical Officers of the Study centers using a pre-designed questionnaire. Feasibility will be assessed by indicators namely recording of 'NIL ADRs' and deletion of the App from their mobile by the Medical Officers of the study centers.

Study progress

25 Medical Officers at Madurai site from 15 NTEP Centers, (random allocation) participated after prior consent. The data on previous ADRs reported by the Medical Officers have been collected. Sensitization and training of the Medical Officers on sending ADR through PVPI Mobile app has been completed. The ADRs reported by the Medical Officers, are being reported on monthly basis by Indian Pharmacopeia Commission as per the collaboration agreement. The study is ongoing.

CL- 9: Assessment of Knowledge and practice of TB management among the private practitioners in selected districts in Tamilnadu.

Principal Investigator	:	Dr.N.Poorana Ganga Devi, Scientist D
Participating Institutes	:	ICMR-NIRT
Source of funding	:	ICMR taskforce under Rational Use of Drugs
Study period	:	2020-2022
Category	:	TB
Pillar	:	Detect/Treat

Background

Many studies from India have documented that the private sector often deviates from the standard, internationally recommended, TB management practices. There is minimal information about the TB population managed in the private sector in South Tamilnadu and their quality of diagnosis and treatment, including treatment outcomes.

Objective

To assess the knowledge and the practices of Private Practitioners (PP) on the management of TB in the selected districts of Tamilnadu.

Methodology

This is a cross sectional survey of Private Practitioners in Theni, Dindigul, Virudhunagar and Sivagangai districts of Tamilnadu, India. All allopathic practitioners with private practice irrespective of their association with the government health services will be included in the study. They should have treated at least one TB case in the past 6 months. The study tool is a self-administered questionnaire, developed based on STCI (2014) and includes standards for diagnostic and treatment practices of pulmonary TB including drug-resistant TB among practitioners. Data on PPs' self-reported socio-demographic information, patient volume, TB disease knowledge, diagnostic and treatment practices will be collected. PPs will be asked to write about the drug regimen that they prescribe for their new patients with PTB using an open-ended format. We will assess PP-reported practices against the diagnostic and treatment standards.

Study progress

A total of one hundred and seventy one PP had consented for the study. The data is being analyzed.

CL-10: Predictors of Resistance Emergence Evaluation in Multidrug Resistant-Tuberculosis Patients on Treatment (PREEMPT Study).

Principal Investigator	:	Dr. C. Padmapriyadarsini, Scientist F
Participating Institutes	:	NIRT, Chennai; YRG Care, Chennai; JIPMER, Pondicherry; BJMC, Pune; Hinduja Hospital, Mumbai.
Source of funding	:	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-TB 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 anti mycobacterial 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

Methodology

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

The study has been initiated in January 2019 and the follow-up is ongoing. A total of 90 participants (Male-56, Female-34) have been enrolled so for. 31 participants have completed their entire follow-up visits as per study protocol. Screening for HIV co-infected MDR-TB participants is ongoing.

CL- 11: The Regional Prospective Observational Research for Tuberculosis (Report) India Phase II Common Protocol.

Principal Investigator	:	Dr Bhavani, P.K, Scientist D
Participating Institutes	;	ICMR – 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 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 and 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; Analysis of stored specimens and associated data

Objectives

1. To evaluate Novel diagnostics and Biomarkers of diverse States of *Mtb* Infection
2. To identify markers of treatment response
3. To identify markers of lung injury and impairment associated with Unfavorable 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

Methodology

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, Pediatric TB -100, EPTB-75
- Cohort A – 90 New adult (>18years) PTB participants

Additionally, follow-up of previously-consented Cohort B participants (n=223) to identify persons with sustained IGRA conversion, reversion and sustained infection-free status after TB exposure will be done.

Study progress

Study started recruiting patients from March 2022 and is on going

Table: Recruitment status till date

		March	April	May	June	Total (n)	Target (n)
Cohort – A	Screened	5	8	23	11	47	-
	Enrolled	2	6	10	3	21	90
	Biomarkers	1	2	2	3	8	75
	Nutrition PK	0	1	2	1	4	40
	Lung Health	1	5	6	2	14	75

		June	Total (n)	Target (n)
Diagnostic Cohort	Screened Patients (Adult)	8	8	
	Enrolled (Adult)	5	5	
	Adult	5	5	150
	Pediatric	-	-	100
	EPTB	-	-	75

CL - 12: Host RNA Expression for Diagnosis and Monitoring of Pediatric TB in Africa and India: RICC Pediatric Transcriptomic Study.

Principal Investigator	:	Dr. S. Syed Hisser, Scientist D
Participating Institutes	:	ICMR-NIRT; BJMC, Pune; JHU, USA; UCT, South Africa; and Imperial College, UK.
Source of funding	:	CRDF Global – RePORT International Supplemental Funding, NIH, USA
Study period	:	2020-2022
Category	:	TB
Pillar	:	Detect

Background

Improved methods to accurately diagnose childhood TB particularly in populations with high prevalence of HIV and malnutrition, and which can be evaluated on readily accessible samples are urgently needed. Changes in biomarker signature in response to treatment have not been studied and may be particularly helpful in better characterizing children in the 'unconfirmed' TB group. We hypothesize that treatment-associated changes in the

Transcriptomic profiles will differ between those children in the 'unconfirmed' TB group who had TB and those who had another respiratory illness. We propose to leverage the RePORT platform by including a cohort of Indian children together with African children in the large validation study, and doing an exploratory study on changes in gene expression profiles during treatment for TB.

Objectives

1. To derive and validate a global RNA expression signature for the diagnosis of pulmonary TB in children using bio-banked samples from the South Africa and Indian cohorts and clinical information from the TB RePORT Common Protocol (CP) and India parent protocol databases.
2. To derive and validate a global RNA expression signature for the diagnosis of extra- pulmonary TB in children using bio-banked samples from the South Africa and Indian cohorts and clinical information from the TB RePORT CP and India parent protocol databases.
3. To identify longitudinal changes in RNA expression with TB treatment in children who have microbiologically confirmed or clinically diagnosed TB, using bio banked samples at follow-up visits and clinical information from the TB RePORT CP database.

Methodology

RNA expression profiles collected from approximately 250 children from India (sequenced as part of this study) will be compared to 365 children from South Africa (sequenced as part of the Levin study); the total sample size will be 615 children [207 with confirmed TB, 258 with unconfirmed TB and 150 with unlikely TB]. RNA extraction done from whole blood collected in PAX gene Blood RNA tubes (Pre AnalytiX) and RNASeq will be done using the Illumina platform. The reduced 5-transcript RNA expression signature initially described by Anderson et al 2014 will be used to derive an individual patient TB risk assignment. Using this method transcripts from the TB signature are separated into up-regulated and down- regulated based on expression relative to the comparator group.

Study progress

The 58 samples have been processed and analysis of extracted RNA samples is ongoing and would be validated with the global RNA biomarker signature for the diagnosis of children with TB.

CL-13: Systems biology and immunology of the effect of tuberculosis chemoprophylaxis in HIV infection.

Principal Investigator	:	Dr. S. Syed Hissar, Scientist D
Participating Institutes	:	ICMR-NIRT; MMC & RGGGH, Chennai; GHTM, Tambaram; and KMC, Chennai.
Source of funding	:	ICMR AD-HOC
Study period	:	2021-2023
Category	:	TB/HIV
Pillar	:	Detect

Background

Tuberculosis (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

Methodology

HIV seropositive individuals will be screened for latent TB by Quantiferon TB gold plus (QFT) and recruited before administration of INH prophylaxis. At enrolment and after six months of isoniazid preventive therapy (IPT), peripheral blood mononuclear cells (PBMC) will be collected from the participants and preserved. 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 88 participants have been enrolled at baseline in this study. 30% of them (27/88) were diagnosed with latent TB using Quantiferon-TB gold plus and the study is ongoing.

CL-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 D
Participating Institutes	:	ICMR-NIRT; ICMR-NIE; CTD; WHO-India; and
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.

Methodology

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, utilization 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 2021, 10 states/UTs and 201 district claims from NTEP were submitted for verification. 8 States/UTs and 91 districts were recommended for awards in different categories of progress towards TB free status based on the decline in incidence of TB in 2021 compared to 2015. The study is ongoing.

COMPLETED STUDIES

Title of the project	Name of PI Designation	Source of funding	Category/Pillar
Evaluation of cause of death among adult TB patients registered for treatment under the Revised National TB Control Programme in Chennai District, Tamil Nadu using Verbal autopsy	Dr Bhavani P.K Scientist D	ICMR Extramural Funds	TB/Build

SOCIO - BEHAVIORAL STUDIES

DEPARTMENT OF SOCIAL AND BEHAVIORAL RESEARCH

DEPARTMENT OVERVIEW AND MANDATES

Department of Social and Behavioral Research (DSBR) remain 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 behavioral studies on 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 randomized 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. In addition to its research contribution, DSBR is known for its active community outreach toward the vulnerable sections of society that are affected by TB and HIV. DSBR also routinely organises Information, Education and Communications interventions to various sections of society to improve the knowledge, attitude and practices of the community with respect to TB prevention, diagnosis and treatment.

DSBR had developed a range of research tools, intervention 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 organizations with an aim to foster multi-centric studies relevant to addressing social aspects of TB.

Studies in progress

DSBR - 1: Study on Knowledge, Attitude, Practice towards Tuberculosis (TB) and Feasibility of TB Screening among Public and Private Drivers and Conductors in Tamil Nadu

Principal Investigator	:	Mr. P. Murugesan, Senior Technical Officer 2
Participating Institutes	:	ICMR-NIRT
Source of funding	:	ICMR-NIRT Intramural
Study period	:	2021 - 2022
Category	:	TB
Pillar	:	Build

Background

Drivers and conductors are at high risk for tuberculosis (TB) infection with millions of people using public transport, these transport services may be hotspots of increased TB transmission. However, until now there is a dearth of information about the knowledge of TB and the risk of transmission among drivers and conductors in the Indian context. Moreover due to the stigma which still prevails in TB, it is difficult to decide on what type of intervention is feasible and acceptable among drivers to advocate for TB screening. With this background, the present study is proposed.

Objectives

1. To assess the Knowledge, Attitude and health-seeking Practice towards TB among drivers and conductors.
2. To ascertain the feasibility and acceptability of TB screening among drivers and conductors.

Methodology

This is a mixed-methods study design that employs both qualitative and quantitative methods. The study population are Bus Drivers & Conductors, Auto Drivers and Taxi Drivers. The study is being carried out in Chennai and Madurai.

Qualitative phase: A total of 40 in-depth interviews will be conducted among the drivers, bus conductors, taxi and auto Drivers, 20 interviews will be conducted in each study site with equal representation of drivers & conductors (Bus, Taxi and Auto drivers). A total of 24 focus group discussions will be conducted with 12 from each study site with equal representation of drivers & conductors (Bus, Taxi and Auto drivers). Each group will have 6 to 8 participants, covering 144 to 192.

Quantitative phase: A total of 454 quantitative interviews will be done through a semi- structured interview schedule.

Study progress

The quantitative interview has been completed for 231 and 227 participants in Chennai and Madurai, respectively. The table lists the participants based on their type of work.

Table: List of participants in the study and details of occupation

Details of occupation	Chennai (N = 231)		Madurai (N = 227)	
	n	%	n	%
Auto driver	57	24.7	59	26
Taxi driver	59	25.5	55	24.2
Bus conductor	59	25.5	55	24.2
Bus driver public	50	21.6	12	5.3
Bus driver Omni	6	2.6	46	20.3

DSBR- 2: Measuring socio-economic risk-benefits and health related quality of life changes associated with tuberculosis disease disclosure

Principal Investigator	:	Dr. N Karikalan, Scientist C
Participating Institutes	:	ICMR-NIRT
Source of funding	:	IMPRESS Scheme of Indian Council of Social Science Research, New Delhi
Study period	:	2021 - 2022
Category	:	TB
Pillar	:	Treat

Background

TB patients often hide their disease from family, friends, neighbors, community, and at the workplace due to the fear of stigma and discrimination resulting from the disclosure of the disease. TB remains one of the highly stigmatized diseases in India till date, and patients suffer both perceived and enacted stigma throughout their disease period and even after completion of treatment. Disclosure has been extensively studied in the context of HIV disease which is a highly stigmatized disease. With regard to TB, only a few studies have assessed the disclosure status of TB patients and their experience after disclosing their disease.

Objective

To estimate the proportion of TB patients who disclose their disease status at different time points from diagnosis till the completion of treatment and to discern the disclosure patterns of TB patients.

Methodology

This is a prospective observational study involving quantitative methodology. The study is conducted in NTEP treatment units in Greater Chennai and adjoining urban areas. Study population includes newly diagnosed pulmonary and extra-pulmonary TB patients registered for treatment under NTEP. Patients who are lost to follow-up will also be included in the study. The study will be multi-centric with a time frame of 24 months. Each patient will be followed for a period of six months or till the treatment extension period. Questionnaire will be used for data collection.

Study progress

A total of 466 TB patients were followed-up and they had more than 4000 family, extra familial and social contacts. Maximum disclosures were made with family members (above 90) during the initial days of treatment. Almost half of non-familial contacts were disclosed at mid treatment. Incremental disclosures made during the end days of treatment was found highest among the neighborhood contacts. TB patients and contacts who were in the middle age who were illiterates were found to be more likely to disclose their TB status.

DSBR - 3: 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	:	ICMR-NIRT & Karnataka Health Promotion Trust.
Source of funding	:	USAID through KHPT
Study period	:	2020-2021
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 the enabling, facilitating, and other positive factors that aided their sick family member to achieve better treatment adherence and successful treatment completion

Methodology

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

The study was initiated in March 2021 and data collection is in progress. A total of 40 patients and 10 care-givers have been interviewed. Data analysis is in progress. Initial themes suggestive of self-attributes, self-deter mination and adaptive behaviors among DR TB patients have been identified

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 were performed. In addition WGS/TNGS have been harnessed for managing Drug Resistance Tuberculosis Patients. Lineage based studies have shown that lineage 1 is common in Southern part of India and lineage 3 increases as we go towards north. Effective diagnostic tool for pediatric TB is a challenge. Studies conducted have proven that non sputum based diagnostic methods like stool; 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 for deciphering the pharmacodynamics indices. Our department is planning to initiate a nation-wide DRS by Next generation sequencing technology for resistance prediction and transmission dynamic. All these studies have significant implications towards TB elimination.

ICMR - NIRT is one of the National Reference Laboratory under 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 during the present year 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) rugs in Treatment-Naïve Tuberculosis Patients from Tamilnadu: 2021-2023

Principal Investigator	:	Dr. S Siva Kumar, Scientist 'D'
Participating Institutes	:	IRL's In Tamil Nadu
Source of funding	:	ICMR
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 transmission of DR-TB. Microbiological monitoring of newer drugs is recommended prior to initiation of treatment, end-of-treatment and during follow-up.

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

Methodology

Whole-genome sequencing and MGIT DST will be performed in eligible MDR/RR-TB with FQ/SLI resistant, Treatment-naïve (not started on treatment with newer anti - TB drug containing regimen) patients to determine the resistance if any to the newer and repurposed drugs. 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 regimen. These sputum samples were cultured to isolate *M.tb*, same has been stored as an aliquot for further testing. A total of 47 samples DNA have been extracted by CTAB method from 47 samples. Phenotypic DST and whole genome sequencing have been performed for 10 samples and we have not observed any resistance pertaining to Bedaquiline and delamanid in the study. The study is ongoing

B-2: Deciphering the role of biofilms in conferring drug tolerance among clinical Mycobacterium tuberculosis isolates

Principal Investigator	:	Dr. S Siva Kumar, Scientist 'D'
Participating Institutes	:	ICMR NIRT
Source of funding	:	ICMR Intra-mural
Study period	:	2021-2022
Category	:	TB
Pillar	:	Treat

Background

The overall aim of the study is to understand the significance of biofilm formation on the pathogenesis and drug tolerance of clinical *M. tb* isolates. Drug tolerance and persistence are key adaptation features of *M. tb* that contribute to treatment failures and the development of drug- resistant strains. Mycobacterial biofilms have been shown to have a role in persistence with the involvement of crucial genes in stress tolerance, dormancy, and intracellular survival. The majority of *M. tb* strains across the world can be classified into 4 major lineages. Several studies have indicated the differences in drug resistance profile and associated genotypic changes within each lineage of *M. tb*. Thus, it becomes clinically vital to characterize different *M. tb* genotypes across four lineages for their ability to form biofilm, their drug tolerance profile, and the interaction of *M. tb* in these biofilms with the host immune cells (primarily macrophages). It is important to understand why and how the multicellular form of *M. tb* in biofilms influences the host-pathogen.

Objectives

1 Understand the role of resuscitation promotion factor in switching the growth characteristic of *M. tb* in biofilms

Methodology

The experimental design of this study comprises of selection of 20 clinical *M. tb* isolates from 4 different lineages based on their geographic, clinical and genotype data. Patients samples will not be used directly and only archived clinical *M. tb* isolates will be used. The clinical *M. tb* isolates will be grown in rich and minimal growth media under specific conditions to produce planktonic and biofilm formation. The protocols would be initially standardized in our laboratory conditions to get good biofilm model.

Further to this, *in vitro* drug tolerance will be assessed after treatment of both forms of *tb* with antibiotics and calculating the viability. For the drug tolerance assay, rifampicin and isoniazid will be added at 3x MIC concentration to the well containing biofilm and harvested after standard drug treatment period. As a pilot study, we will initially test the two first line antibiotics and later second line and repurposed drugs would be included once the assay has been standardized. For comparison, planktonic cultures will be treated with the same drug concentrations and viabilities determined by CFU. Uptake, intracellular survival assays and drug tolerance assays with adherent macrophages will be carried out. For this, the study would use human monocyte cell line, THP-1 after differentiation into macrophages in 24-well tissue culture plates. Experimental results will be analysed and statistical significance assessed.

Study progress

To achieve the differential phenotype, the cultures were taken in triplicates and maintained in both Middlebrooks 7H9-ADS liquid media supplemented with 0.05% Tween-80 as well as in in Sauton's

minimal medium supplemented with 0.05% Tween-80. The cultures in Sautons liquid media in 24-well plates has been left undisturbed for the formation of biofilm. Towards the assessment of drug tolerance, the cultures in Middlebrook 7H9-ADS liquid media supplemented with 0.05% Tween-80 as well as in Sauton's liquid media in glass containers were treated with rifampicin and isoniazid at 3xMIC concentration. The viabilities are currently assessed for the planktonic cultures at different time points and plated in Middlebrook 7H10-OADC solid media supplemented with 0.05% Tween-80 for calculation of CFUs/ml. The drug tolerance would be hereby established for the cultures.

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

Investigator and other details

Principal Investigator	:	Dr. S Siva Kumar, Scientist 'D'
Participating Institutes	:	ICMR NIRT
Source of funding	:	ICMR Extra-mural
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 to understand the dynamics of 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 strain from each state, using macrophage phagocytic index and intracellular growth assays and co-relate the findings with disease transmission in the community.

Methodology

A total of 1183 *M.tb* isolates, 211 from Chennai, 130 from Bengaluru, 167 from New Delhi, 129 from Jabalpur, 241 from Kerala, 181 from Ahmadabad and 122 from Wardha were available to be included in the project. Sample collection is in progress in Punjab and Bihar. A total of 1200 samples were retrieved and DNA extraction, quantification was carried out. A total of 1181 samples were suitable for spoligotyping.

Study progress

Spoligotyping: The figure 1 shows the spoligotyping pattern of 1181 *M.tb* isolates 211 from Chennai, 130 from Bengaluru, 167 from New Delhi, 129 from Jabalpur, 241 from Kerala, 181 from Ahmadabad and 122 from Wardha that were matched with SpolDB4 data base. Study is ongoing

Figure: The figure provides the 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 north and EAI spoligotype predominant (Blue) in South India.

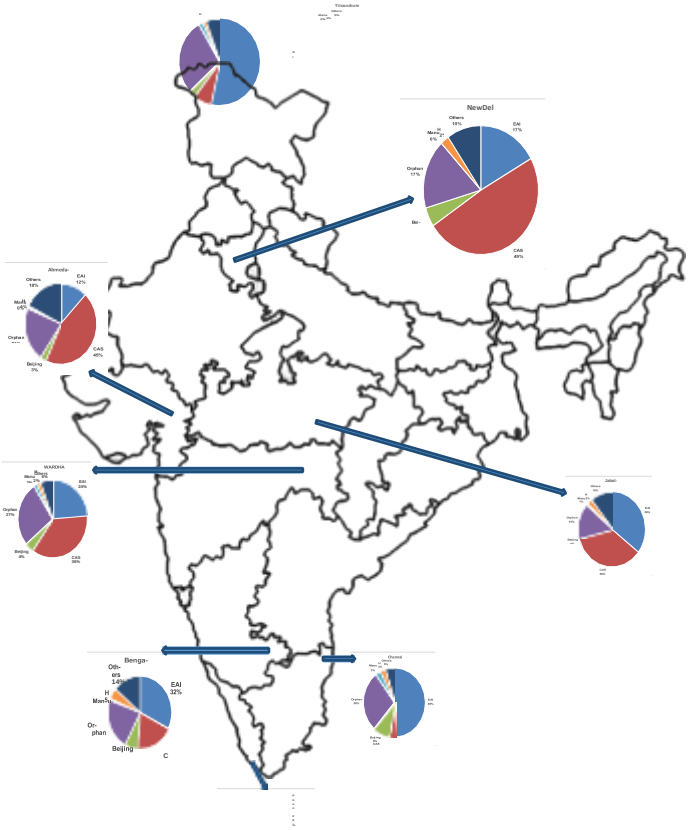
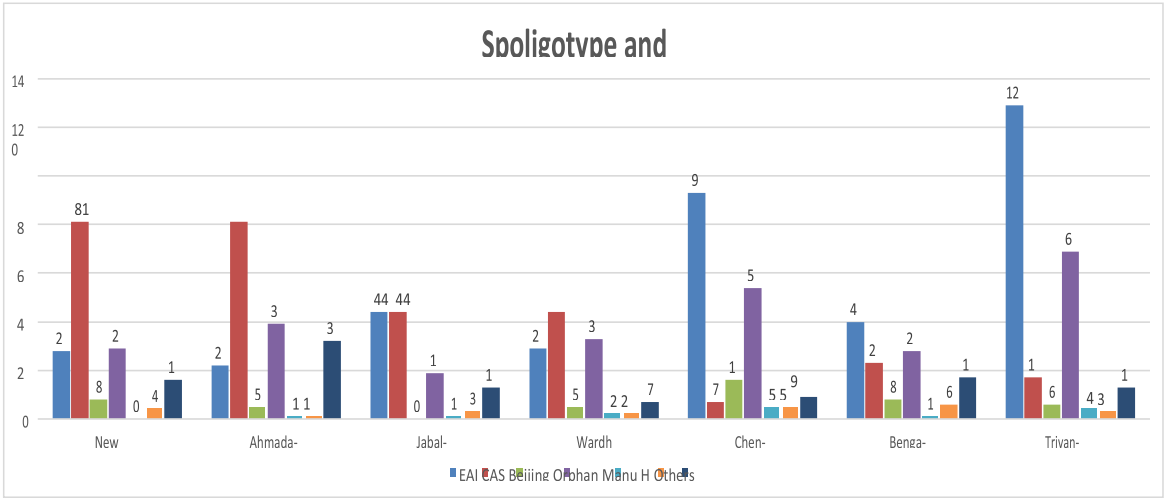


Figure 2: Spoligotype and city: The figure provides the information on the different spoligotype distribution among the Indian cities, representing most of the sates in north and south India. There is a clear demarcation of CAS spoligotype predominant in north and EAI spoligotype predominant in south India.



B – 4: MIC distributions of newer and repurposed anti-TB drugs for the phenotype based wild-type *M. tuberculosis* isolates and their critical concentration levels

Principal Investigator	:	Dr. V. N. Azger Dusthackeer, Scientist D
Participating Institutes	:	ICMR-NIRT
Source of funding	:	ICMR Intra-mural
Study period	:	2021-2022
Category	:	TB
Pillar	:	Treat

Background

WHO recommended critical concentrations are universally followed to determine the susceptibility pattern in Drug susceptibility testing (DST). Bedaquiline, Delamanid, Pretomanid, Linezolid, Clofazimine, Moxifloxacin and Levofloxacin are important anti-TB drugs to treat drug resistant forms of TB. Even though these drugs are most effective, the occurrence of resistance is unavoidable. Hence, DST is very essential and is performed by different methods employing the use of critical concentration to define the drug resistance for each of the anti-TB drugs. But there has been variability in determining the critical concentration cutoff, from place to place for some of the drugs The study reports the critical concentrations of Bedaquiline, Delamanid, PA824 Moxifloxacin, Linezolid, Clofazimine and Levofloxacin for the wildtype isolates of *M. tuberculosis* using in-house broth micro dilution method.

Objectives

1. To determine the MIC distribution of Bedaquiline, Delamanid, Pretomanid, Linezolid, Clofazimine, Moxifloxacin and Levofloxacin for validating the existing critical concentrations for determining drug susceptibility among the South Indian isolates of *M. tuberculosis.*

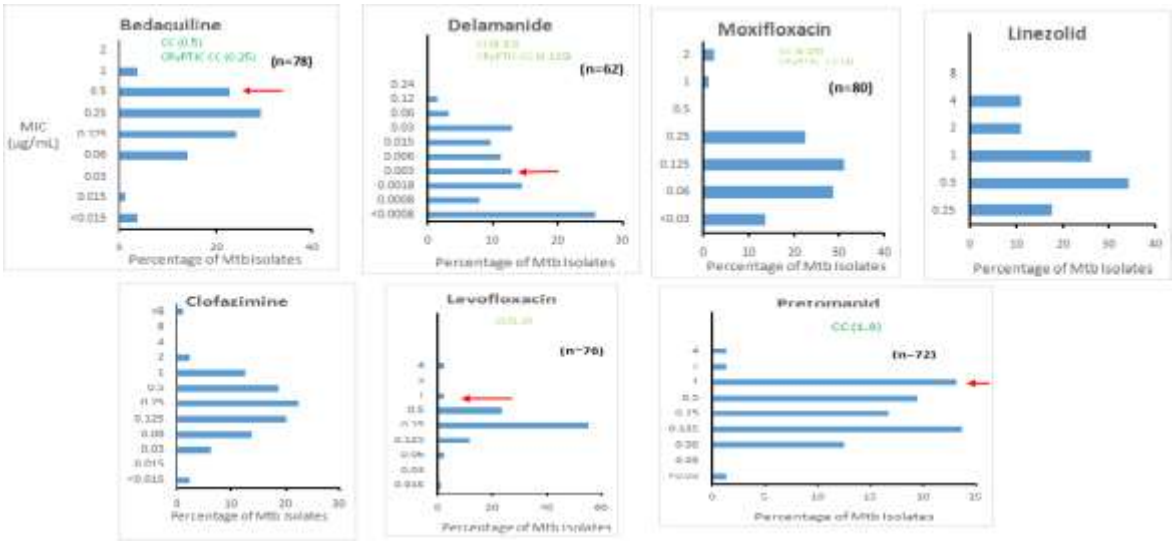
Methodology

Critical concentration (CC) of the newer and repurposed anti-TB drugs was determined using wild-type isolates among TB patients from Chennai, who had no history of TB treatment in the past. MICs were determined for Bedaquiline (n=78), Delamanid (n=62), PA824(n=72), Moxifloxacin(n=80), Linezolid(n=73), Clofazimine (n=80) and Levofloxacin (n=76) by broth micro dilution method using 1 McFarland inoculum size diluted 20 times using Middlebrook 7H9 with OADC in glycerol (BD) (yielded 1 to 0.5 x 10^5CFU/ml) and exposed with drugs in duplicates in 96 well plates. They were read under inverted microscope by two readers after incubation at 37°C for 10 to 14 days kept in a sealable plastic bags with distilled water in the outer peripheral wells. It was ensured to have sufficient growth in the drug free inoculum control (100%) in addition to its' 100 times diluted ones (1%).

Study progress

CCs were determined and were found to be dissimilar for all the drugs tested except Levofloxacin when compared with the ECOFF proposed by the CRyPTIC Consortium using 0.5 Mcfarland inoculum diluted 111 times. For instance Janssen et al used 1 McFarland inoculum diluted 98 times and arrived at a CC of 0.125 mg/L for bedaquiline as against 0.25 mg/L with more diluted inoculum of CRyPTIC, whereas it was 0.5 mg/L for BDQ in our study. But incubation period used by the CRyPTIC consortium and that of Janssen was 21 days with lesser incoculum, but the turnaround time ranged between 9 - 12 days by our method. CC for Pa824 was not available from any of the agency and our study reports it to be 1 mg/L. WHO proposed the same level of the inoculums size reported by the CRyPTIC consortium with CO_2 but our study with higher inoculums size resulted in the same range of CFU without CO_2 in lesser incubation period.

Figure:Wild-type MIC distribution of Bedaquiline, Delamanid, Moxifloxacin, Clofazimine, Levofloxacin, Kinezolid and pretomaniid along with the deduced CC from thos study and the CRyPTIC proposed CC levels in mg/L



B- 5: Title: Role of membrane proteins responsible for drug efflux mechanisms in Mycobacterium tuberculosis

Principal Investigator	:	Dr. V. N. Azger Dusthackeer, Scientist D
	:	Dr. E. Padmasini, Research Associate
Participating Institutes	:	ICMR-NIRT
Source of funding	:	ICMR Extramural
Study period	:	2021-2023
Category	:	TB
Pillar	:	Treat

Background

Efflux pump activity contributes to drug resistance in *Mycobacterium tuberculosis* (*M.tb*) by allowing the bacteria to survive for a longer period of time in the presence of sub inhibitory concentrations of antibiotics, until chancesfor acquiring chromosomal mutations for resistance emerge and are established in the bacterial population. Mutations in several genes, including katG, ahp C, inhA, kasA, and ndh, have all been associated with INH resistance. It has been demonstrated that efflux systems could be induced by prolonged exposure of *M.tb*to INH, resulting in an increased resistance phenotype. *M.tb*showed that various major facilitator superfamily (MFS) efflux pump genes (efpA [Rv2846c], Rv1258c, jefA [Rv2459], and P55 [Rv1410c]) and ATP-binding cassette (ABC) superfamily transporters (Rv1819c and pstB [Rv0933]) were overexpressed in the presence of INH. Rv0194 and Rv0933 were efflux pump genes which are not much explored and Rv0933 is also known as phosphate-transport ATP-binding protein ABC transporter pstB whereas, Rv0194 is a Multidrug efflux ATP-binding/permease protein whose overexpression in *M. smegmatis* increases resistance to erythromycin, ampicillin, novobiocin and vancomycin.

Objectives

1. In silico structure analysis and validation of membrane proteins Rv0933 and Rv0194.+

2. Validation and significance of membrane efflux proteins Rv0933 and Rv0194 – In vitro conditions
3. Identification and design of small molecular inhibitors to inhibit the efflux mechanism exhibited by Rv0933 and Rv0194

Methodology

1. In silico structure analysis and validation of drug efflux proteins Rv0933 and Rv0194
   i) Homology modelling and active site prediction of efflux pump genes Rv0933 and Rv0194 using I-Tasser.
   ii) E-pharmacophore modelling for inhibitors of Multidrug Efflux pump. The predicted structures for the proteins will be individually docked against verapamil, thioridazine and chlorpromazine.
2. In vitro validation of the significant role of efflux proteins Rv0933 and Rv0194 will be carried out by preparing plasmid constructs in recombination substrate (*E. coli* DH5 α). Growth kinetics and antibiotic susceptibility testing for the wildtype H37Rv strain and the knock-out construct.
3. Identification and validation of small molecular inhibitors to inhibit the efflux mechanism. The validated pharmacophore models will be used as 3D query to search against Natural compound databases.
4. In silico validation for the shortlisted lead compounds against the membrane protein(s) will be carried out by ADMET property prediction which includes human intestinal absorption, hepatotoxicity, blood brain barrier penetration and Lipinski's rule of 5.
5. Validation of small molecule inhibitors against efflux pump proteins: The MICs will be determined by tetrazolium micro plate- based assay (TEMA) for the shortlisted compounds and antibiotics.
6. Determination of Fractional inhibitory concentrations and time-kill assay will be performed.

Study progress

Five resistant *M.tb* isolates were selected and their genomic DNA was isolated by CTAB method. The respective genes were checked by PCR by selecting appropriate primers from PDB database. The genes were amplified by gradient PCR and the PCR amplicons were gel electrophoresed to check for the presence of respective genes Rv0933 and Rv0194. The PCR products and pMV261 plasmid with kanamycin backbone were restriction digested (double digestion) with enzymes XbaI and HindIII and ligated with T_4 DNA ligase enzyme. The ligated DNA into shuttle vector were then transformed into DH5α *E. coli* cells and screened on LB agar with kanamycin (35µg/ml) (Figure 1). The colonies were picked and grown in LB broth. Plasmid isolation was carried out and checked for presence of respective genes from transformed colonies and electroporated in *M. smegmatis* for efflux protein expression. Simultaneously, Insilico analysis of small molecule inhibitors were analysed by Zinc Data Base and 10 lead molecules each were selected based on best glide score for further validation.

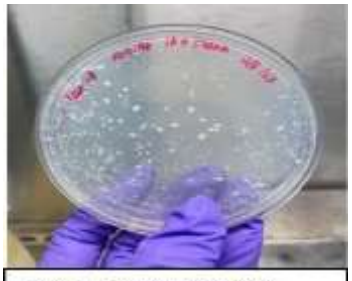


Fig1: Clones of Rv0194 electroporated in *M. smegmatis* in 7H11 agar with Kanamycin 25µg/ml conc.

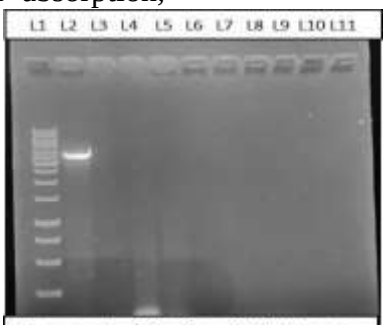


Figure 2: PCR for RV0194 gene (3585bp): L1-1Kb DNA ladder; L2: RV0194 gene positive; L3: Negative; L4: Negative control

Figure 3: PCR for RV0933 gene (833bp): L1: col 1; L2: col 2; L3: col 3; L4: col 4; L5: col5; L6: 1Kb DNA ladder; L7: col 7; L8: col 8; L9: Negative control

B. - 6: **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-NIRT
Source of funding	:	Indian council of Medical Research
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 damage among the pulmonary TB patients.

Objectives

1. To identify and determine the concentration of *M. tb* induced MMP expression directly from the smear Positive sputum samples.
2. To identify small molecule inhibitors for *M. tb*-induced MMPs using *In silico* virtual screening.
3. To analyse the MMP inhibitory activity of lead molecules by *ex-vivo* methods using peripheral blood mononuclear cells.

Methodology

1. Smear-positive sputum samples from TB patients will be used for screening the presence of MMPs..
2. The decontaminated samples were divided into two parts so that one is taken for smear microscopy, *M. tb* culturing, and drug susceptibility testing by Gold standard method. Another vial is processed for MMP isolation. Only the smear positive (3+) samples were taken for MMP isolation.
3. Based on the method validated by Elkington *et al.,* (2006) the samples were centrifuged at 430 g and the cell debris were removed. The isolated MMPs were stored in -20ºC until further analysis.
4. The concentration of the MMPs in the sputum samples were analysed using substrate specific zymography as described by Heussen *et al.,*
5. Auto dock was used to screen and shortlist small molecules inhibitors against MMPs.

Study progress

Identification of the MMPs present in the sputum sample is being carried out using Zymography. Till date, 32 specimens were collected and 28 samples were analyzed to identify the MMPs present in it. MMP1 and 2 were identified in the same sputum sample (54 and 45 kDA) and MMP 1 in another sputum sample (54 kDA). A faint band was seen with 94 kDA which denotes the presence of MMP-9. Using *In-silico* based approaches 44 lead molecules from zinc- natural database against MMP were short- listed. These compounds will be further subjected to molecular dynamics study, *in vitro* and *ex-vivo* validation studies.

B -7: Identification, purification and structure elucidation of potent anti-mycobacterial molecules from True Mangroves from coastal lagoon

Principal Investigator	:	Dr. V. N. Azger Dusthackeer Scientist D,
	:	Mrs. B. Angayarkanni,
		Senior Technical Officer 1
Participating Institutes	:	ICMR-NIRT
Source of funding	:	Intramural
Study period	:	2020-2023
Category	:	TB
Pillar	:	Treat

Background

Management of TB/MDR-TB patient requires intense treatment for at least six months to two years. The emergence of drug resistance to the medicines now in use warrants search for new anti-TB agents worldwide. Flora of mangrove forests is unique from others in that their habitat extends along the border where the fresh and sea water merge. Therefore, unlike common terrestrial plants, they can withstand high salt concentration, can remain submerged in water, and maintain an efficient nutrient retention mechanism. Plants often produce secondary metabolites under stressful conditions, as the mangrove plants, facing various ecological and environmental stresses, biosynthesize a wide range secondary metabolite of potential medicinal importance. In this regard, the present study has been aimed to elucidate potent leads from medicinally important mangrove plant against M. tuberculosis.

Objectives

1. Collection of cured extract from true mangrove from coastal lagoon of Tamilnadu and in vitro screening for its anti *M. tb* and cytotoxicity activity.
2. Identification, evaluation and elucidation of pure lead molecules from mangrove
3. *In vitro* and *in vivo efficacy* of the drug alone and in combination with the current SOC studies on lead compounds from mangrove and its

Methodology

Leaves, stem, and flower from mangrove species were collected from Muthupet lagoon of Thiruvarur district and Islands of Gulf of Mannar at Ramnad District. Crude were extracted from pulverised mangrove parts by using Soxhlet apparatus with different polar and non-polar solvents. The dried crude was subjected to anti mycobacterial activity using broth micro dilution method and cytotoxicity was determined by rezasurin reduction assay. Fractions were eluted by chromatography method from crude which showed inhibitory activity against MTB and molecular structure will be identified by NMR. The In-vitro and In-vivo efficacy of the potent lead from mangrove will be deciphered as per standard procedure

Study progress

Sample collection -1: (May 2021 and June 2021)**.** Two species of mangrove were collected from Pullivasal and Kurusadai Island of Gulf of Mannar, Ramnad district under supervision of Mandapam forest ranger and six species of mangrove were collected form Muthupet Lagoon *(Avicennia marina, Acentus ilicifolius, Rhizopora apiculata, Rhizopora mucaranta, Excoecaria agalocha, Ageceras carniculata*) at Thiruvarur District under supervision of Forest ranger officer. stability, potential for aggregation and shelf- life studies

Sample Collection-2: (May 2022)- *Ceriops tagal* was collected from Kurusadai island of

Gulf of Mannar, Ramnad district under supervision of Mandapam forest ranger.Crude were extracted with different solvents by Soxhlet apparatus. Among 9 species of mangrove, one species' crude resulted in the inhibition of *Mycobacterium tuberculosis* $H_{37}RV$ strain using Broth micro dilution method at 1mg/m. The extracts were not toxic to Vero, THP-1 and PBMC cells up to 2 mg/ml. Twelve fractions were eluted from hexane extract leaf of the plant, 9^{th} fraction showed inhibition at the MIC of 0.5mg/ml against $H_{37}RV$. Eight compounds were identified by GC-MS from 9^{th} fraction.

Table. List of Collected of Mangrove from Muthupet Lagoon, Gulf of Mannar

Mangrove Name	Plant's Parts	Collection Date	Collection area
Pemphis acidula	Leaf , Flower	May 2021	Pullivaasal island
Avicennia marina	Leaf	June 2021	Muthupet lagoon
Acentus ilicifolius	Leaf	June 2021	Muthupet lagoon
Rhizopora apiculata	Leaf	June 2021	Muthupet lagoon
Rhizopora mucaranta	Leaf	June 2021	Muthupet lagoon
Excoecaria agalocha	Leaf, flower	June 2021	Muthupet lagoon
Ageceras carniculata	Leaf	June 2021	Muthupet lagoon
Pemphis acidula	Leaf	May 2022	Kurusadai
Bruguiera cylindrica	Leaf	May 2021	Pullivasal
Ceriops tagal	Leaf	May 2022	Kurusadai

B – 8 : 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

Principal Investigator	:	Dr. R. Priya, Scientist C
Participating Institutes	:	ICMR - NIRT, Empe Diagnostics Pvt Ltd
Source of funding	:	Empe Diagnostics Pvt Ltd
Study period	:	2021 -2022
Category	:	TB
Pillar	:	Detect

Background

Drug-resistant forms of TB is increasing at an alarming rate due to fault in diagnosis and widespread prescription of incorrect antibiotics. Current commercial diagnostics for MDR-TB often deliver incomplete diagnoses and require long lag times, costly equipment, and highly trained personnel. Simple, low cost and customizable diagnostic tools are needed to enable point-of-care testing in low- and mid-income countries. By strictly following WHO recommendations and guidelines, EMPE Diagnostics has developed two products *mfloDx®MDR-TB and mfloDx®MDR-TB plus*. This platform can be implemented in decentralized clinics, ensuring availability of high-quality TB diagnostics and its drug resistance detection in remote and rural areas also. In this study we aim to evaluate its performance characteristics and determine its utility in TB diagnosis.

Objectives

1. To determine the performance characteristics of *mfloDx®MDR- TB* test in terms of Specimen stability, Limit of Detection (LOD), Analytical specificity (Interference and cross

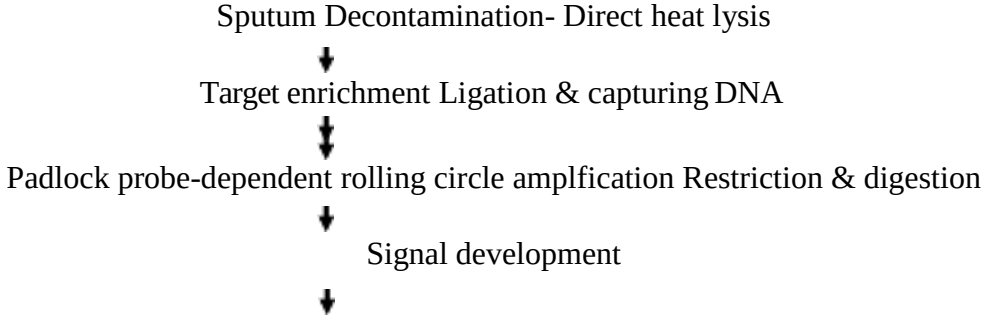
reactivity), Analytical reactivity (inclusivity), reproducibility and repeatability.

2. To determine the performance characteristics of *mfloDx®MDR-TBplus* test in terms of Specimen stability, Limit of Detection (LOD), Analytical specificity (Interference and cross reactivity), Analytical reactivity (inclusivity), reproducibility and repeatability

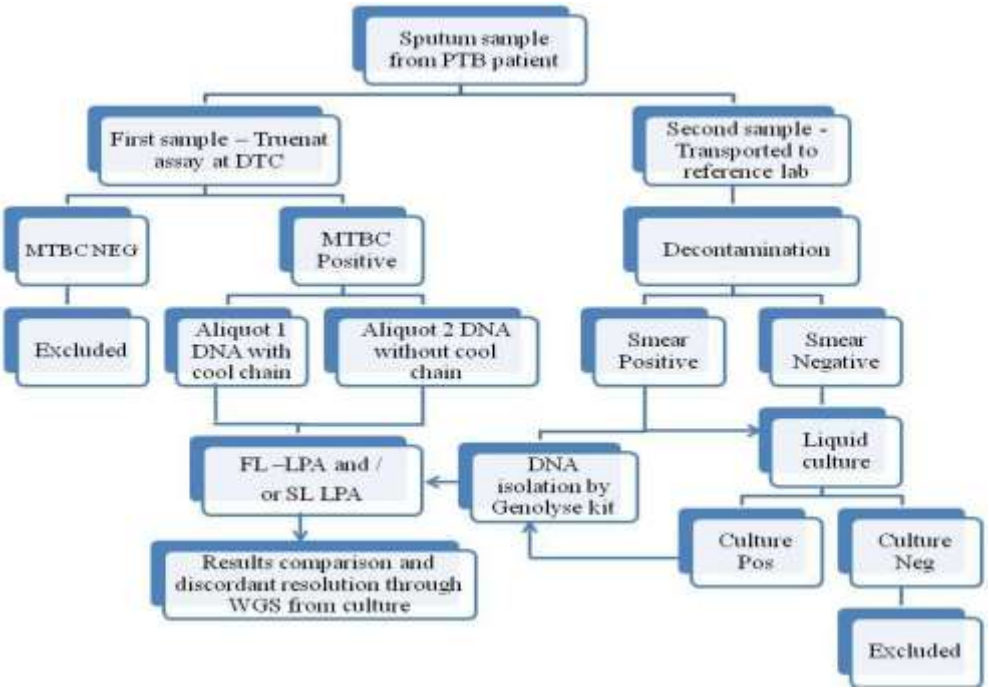
Methodology

A total of 225 sputum samples (smear positive and negative samples) from presumptive TB patients were included in this retrospective study. The samples were decontaminated by NaLC-NAOH, heat-lysed and directly tested with *mfloDx*™ MDR-TB test kits. The Genotype MTBDR plusv2 (LPA) test was used as the comparator for drug Resistance testing. The *mfloDx*™ MDR-TB test kit has 2 components: *mfloDx*™ MDR-TB AMP a molecular amplification kit for *M. tuberculosis* and its genotypes coding resistance for rifampicin and isoniazid and *mfloDx*™ MDR-TB VIS kit a lateral flow-based rapid test kit for the visualization of the amplicons produced by the above MDR-TB AMP kit.

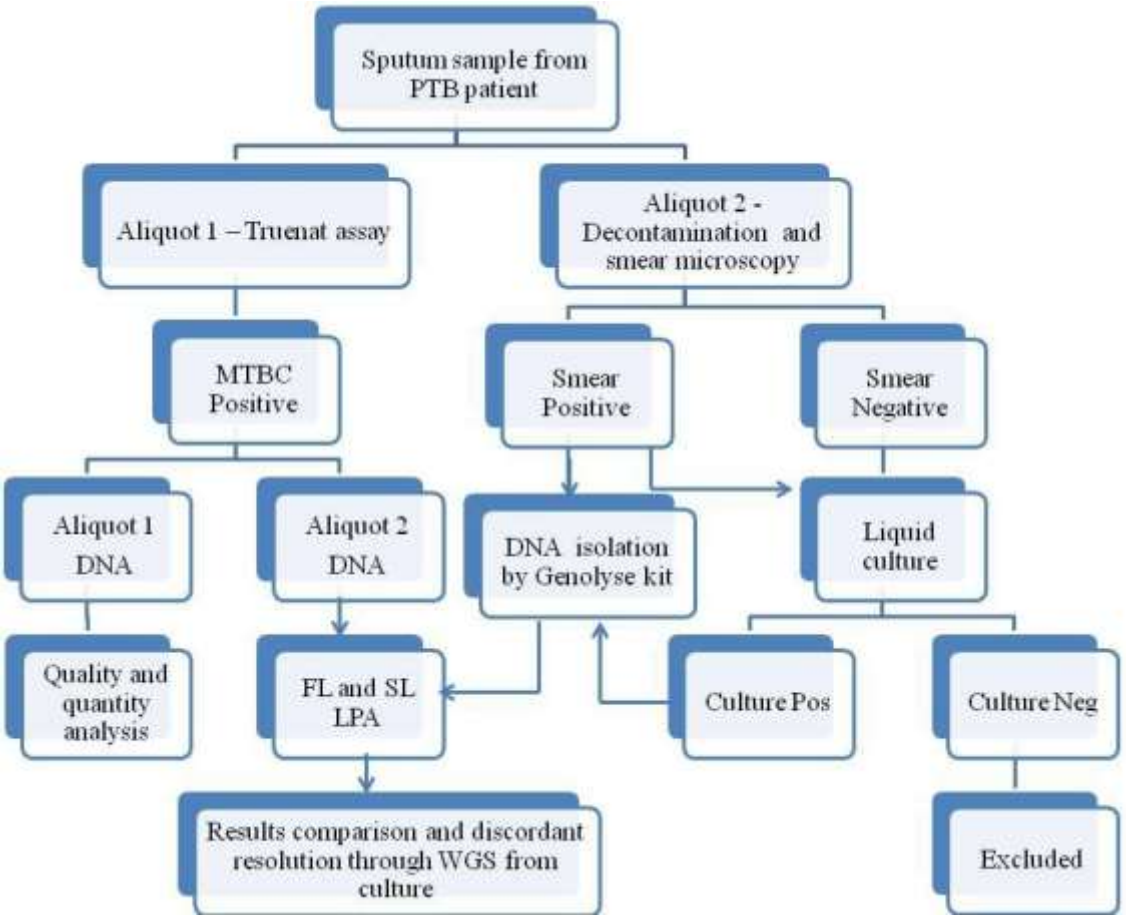
Testing protocol



Work flow for Phase I



Work flow for Phase II



Study progress

Among 225 sputum samples, 154 samples (104 smear positive presumptive TB and 50 TB negative) were tested and compared with LPA. Clinical sensitivity and specificity of the *mfloDx*™ MDR-TB for TB detection was 100% with an invalid rate of <1% (103/104) from smear positive samples. All the 50 TB negative sputum samples were negative indicating its 100% specificity. Among the TB positive samples, 49 were sensitive to both RIF and INH, 7 were MDR-TB, 4 were mono resistant to RIF and 37 were mono resistant to INH. The *mfloDx*™ MDR- TB test has shown 100% sensitivity for RIF and INH resistance samples, while 100% specificity for RIF and 98.5% for INH resistance. The indeterminate rate was 1.9% and 5.8% for RIF and INH genotyping, respectively. Testing of smear negative samples is ongoing. Validation of MDRTB plus test is yet to be initiated

COMPLETED STUDIES

Title of the project	Name of PI/ Co-PI/ Co- Investigator Designation	Source of funding	Category/ Pillar
Prediction of treatment failure among diabetes-TB patients by peripheral blood transcriptional signature	Dr S. Siva Kumar Scientist D	DBT	TB/Detect
A Study on the Strain specific Modulation of Tuberculosis gr anulomatous reaction using *in -vitro* 3D granuloma model	Dr. Azger Dusthackeer Scientist D	ICMR-PDF	TB/ Treat
Molecular manipulation and hybrid strategy in design and discovery of Cytochromebc1 inhibitors as potent leads for drug resistant tuberculosis	Co-PI: Dr Azger Dusthackeer Scientist D	SERB	TB/ Treat
MIC distributions of Bedaquiline, Delamanid, Pretomanid, Linezolid, Clofazimine, moxifloxacin and levofloxacin namongwild- type, MDR and XDR isolates of *M.tuberculosis*among South Indian population	Dr Azger Dusthackeer Scientist D	ICMR-Intramural	TB/Detect
A study to evaluate the endometrial samples for asymptomatic *Mycobacterium tuberculosis* infection in unexplained infertility	Co-Investigator Dr Azger Dusthackeer Scientist D	ICMR-Intramural	TB/Detect
Prevalence of non-resolving pneumonia in children suspected with TB	Dr. R. Priya Scientist C	ICMR-Intramural	TB/Detect
Evaluation of stool concentration methods for detection of *M.tuberculosis* in children	Dr. R. Priya Scientist C	ICMR-Intramural	TB/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 that includes immunology, molecular biology and epidemiology to study 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. Antigen purification and immuno diagnosis are other major areas. More recently, the department has added facility for Next generation sequencing of mycobacterial clinical isolates and performing research activities in understanding the drug resistance, transmission dynamics and identification of novel mutation. Apart from these, the department also focusing on understanding the zoonotic and reverse zoonotic transmission of tuberculosis between humans and cattle.

Studies in progress

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

Principal Investigator	:	Dr. K. R. Uma Devi, Scientist E
Participating Institutes	:	ICMR-NIRT, GHTM, Greater Chennai Corporation
Source of funding	:	DBT
Study period	:	2020-2022
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.

Methodology

(a) Develop molecular probes and portable optical devices for improved 'triage'

We will develop point of care low cost handheld systems, which will enable in field (including rural sites), detection of suspected TB in sputum samples. This will be enabled by optical technology being developed by the University of Edinburgh The target product profile of the technology will involve the simple processing of sputum and in situ labelling of Mycobacteria coupled with a simple portable detection, which does not require microscopy. The technology will build upon fluorescent labels of Mycobacteria coupled with sensitive photon detection. The key technical developments will be the synthesis of a suite of chemical labels which will be stable, manufactured at low cost and coupled with a simple and frugal recording device with interconnectivity with portable smartphones.

(b) 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.

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, we will develop a method that will allow rapid interpretation of results and automatically collate and report information to a central location. To achieve this, an "app" will be developed that will provide readout of the multiplexed assay to allow detection/diagnosis of Mycobacterium tuberculosis complex infection and/or multidrug resistant TB.

(c) Develop assays for detection of TB-specific microRNAs:

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) Develop molecular probes and portable optical devices for improved 'triage': Collection of 1000 sputum and evaluation of stain in 100 sputum samples has been completed with the parent probes provided by the collaborator.

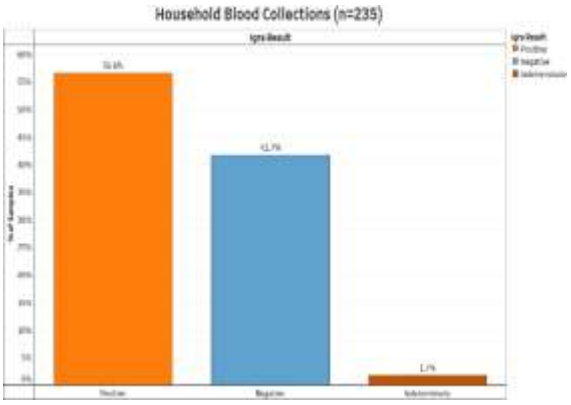
(B) Develop and validate novel molecular diagnostics for the detection of Mycobacterium tuberculosis complex and multidrug-resistant TB, with seamless Data interpretation, collation and 'real- time' reporting:

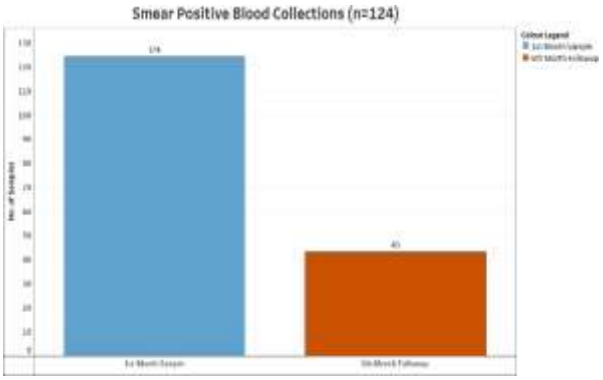
Evaluation of spin tubes for detection of Pulmonary TB: First version of spin tube developed and tested. 1000 samples for presumptive TB has been completed and Comparator tests have been done, of which 285 samples were positive by GeneXpert and by MGIT 301 samples were positive.

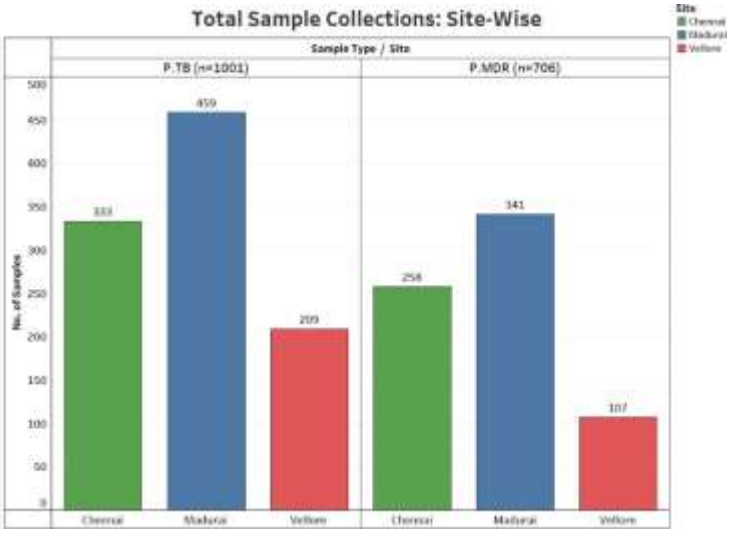
For presumptive MDR-TB, 773 samples have been collected till date. Comparator tests have been completed for the above samples. Telemetry app concept developed and is awaiting relearning.

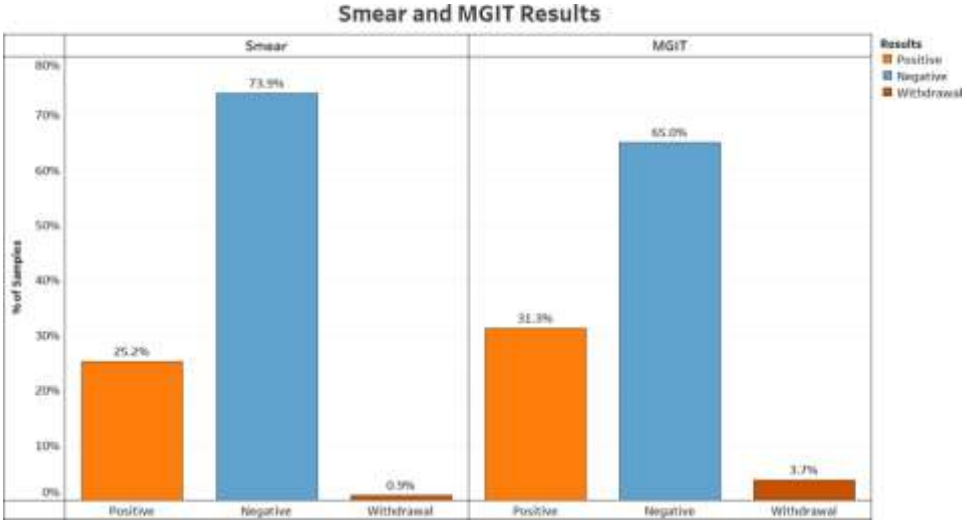
(C) Develop assays for detection of TB-specific microRNAs: Collection of blood samples for AFB positive patients and household contacts has been completed. IGRA testing has been done for the received samples.

Sample Collection and Sample processing done at NIRT from Jan 2021 to Jul 2022









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

Principal Investigator	:	Dr. K. R. Uma Devi, Scientist E Ms. J S V Soundarya (SRF-ICMR)
Participating Institutes	:	ICMR-NIRT
Source of funding	:	ICMR Intramural
Study period	:	2017-2022
Category	:	TB
Pillar	:	Prevent

Background

The currently available BCG vaccine has shown to have varying efficacy in adult population 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 Th1 type cellular responses in BALB/c mice. Studies have shown that rBCG::Ag85B-ESAT6-Rv2608 is a potential candidate against M. TB in C57BL/6 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 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 rABCG (Recombinant attenuated BCG) by deletions in either of two genes, Rv3409c(*ChoD)* or Rv3088 *(Tgs4*) 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 rABCG for their immunogenicity and to compare their efficacy with that of BCG.

Methodology

1. Cloning of the fusion protein insert into Mycobacterial shuttle vectors and confirmation of the same through restriction digestion.
2. Electroporation of the confirmed plasmids into *M.smegmatis* and *M.bovis* BCG.
3. Selection of clones and growth.
4. Protein extraction, SDS and confirmation of the protein expression in western blot.
5. 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

1. Designing and construction of recombinant plasmids with inserts have been achieved.
2. The recombinant plasmids transformed in *E.coli* were screened.
3. Recombinant *M.smegmatis* and BCG strains have been constructed after electroporation.
4. Western blot confirmation of the expression of the fusion protein in *M.smegmatis* has been achieved
5. Recombinant *M.smegmatis* harboring eGFP along with fusion protein has been constructed.
6. PCR confirmation and western blot confirmation of recombinant BCG strains have been achieved.

Table: List of recombinant *M.smegmatis* cultures constructed along with their designated numbers

Strain	Designated Number
mc2 155(pBRL34)	NIRT S1
mc2 155 (pNIRT1)	NIRT S2
mc2 155 (pMV306kan)	NIRT S3
mc2 155 (pNIRT2)	NIRT S4
mc2 155 (pMV206kan)	NIRT S5
mc2 155 (pNIRT3)	NIRT S6
mc2 155 (pMV206Hyg)	NIRT S7
mc2 155 (pNIRT4)	NIRT S8

Table: List of recombinant BCG cultures constructed along with their designated numbers

Strain	Designated Number
BCG (pBRL34)	NIRT B001
BCG (pNIRT1)	NIRT B002
BCG (pMV306kan)	NIRT B003
BCG (pNIRT2)	NIRT B004
BCG (pMV206kan)	NIRT B005
BCG (pNIRT3)	NIRT B006

Figure :Western blot analysis of fusion protein expressed in recombinant mc^2155

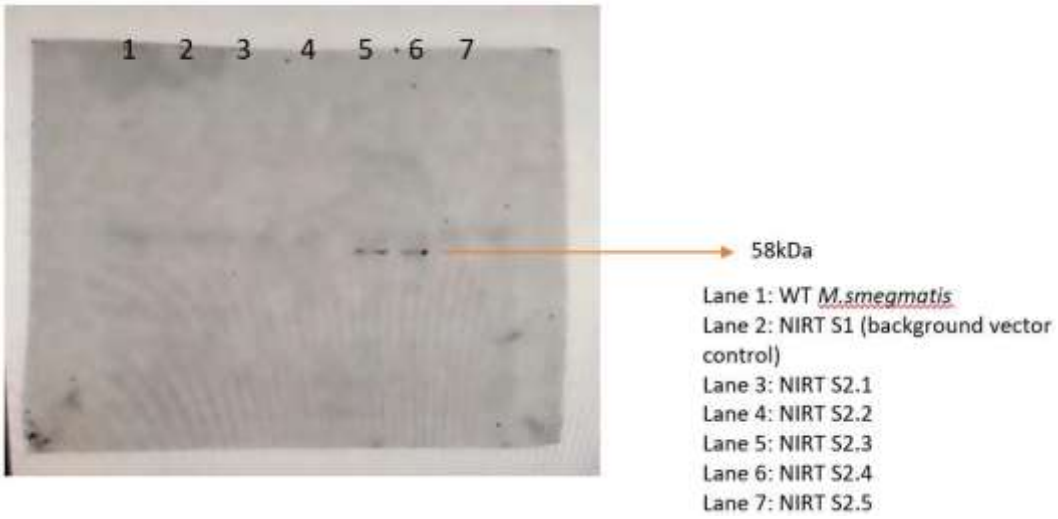
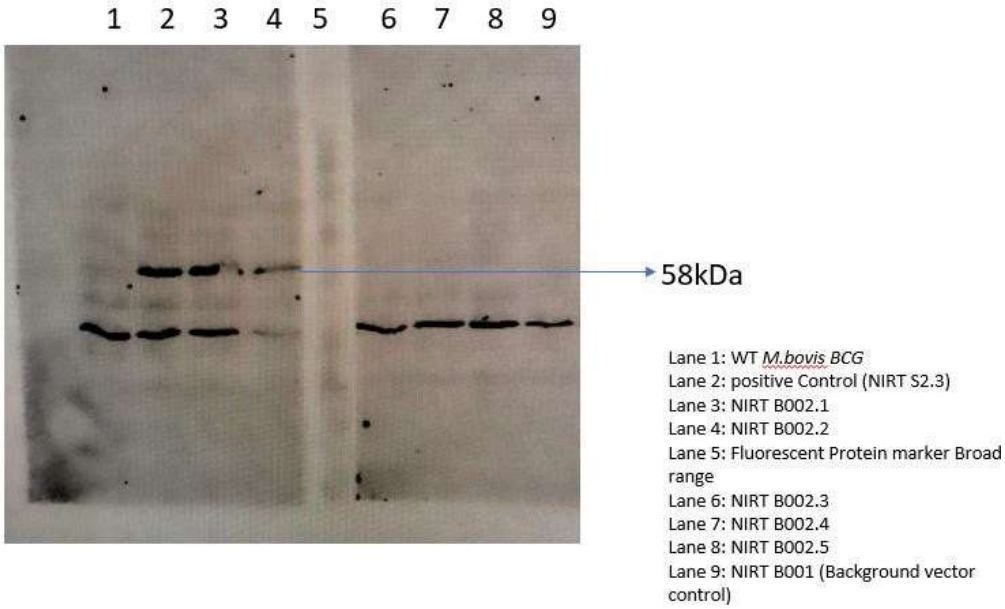


Figure: Western blot analysis of fusion protein expressed in recombinant BCG



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

Principal Investigator	:	Dr. K. R. Uma Devi, Scientist E,
	:	Mr. P. Venkatesan (SRF–Lady Tata Memorial Trust Fellowship)
Participating Institutes	:	ICMR-NIRT, 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 (M.tb)* 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 *M.tb.*
2. To evaluate the performance of developed CRISPR Cas13a detection tool in clinical isolates of *M.tb.*
3. To evaluate the performance of developed CRISPR Cas13a detection tool in biological specimens of *M.tb.*

Methodology

Step 1: Expression and Purification of Cas13a: The Cas13a bacterial expression system was purchased from Addgene. Then, 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: RNA isolation: The RNA isolation from the respective samples was carried out as per optimised protocol and the sample subjected to Cas13a assay.

Step 4: Collateral detection assay: Detection assay was performed for both detection and identification drug resistance 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.

Study progress

We have carried out Ion-exchange and size exclusion chromatography purification of Cas13a protein for achieving the improved performance of the CRISPR-M.tb assay. With the purified protein, we have evaluated the performance of the CRISPR-M.tb assay for detection and drug resistance pattern. The *M.tb* detection probe has detected *M.tb* from clinical isolates and laboratory strains. It was also differentiated from NTM and other pathogens. The validation of the drug resistance probe is in progress.

Figure: FPLC purification of Cas13a protein

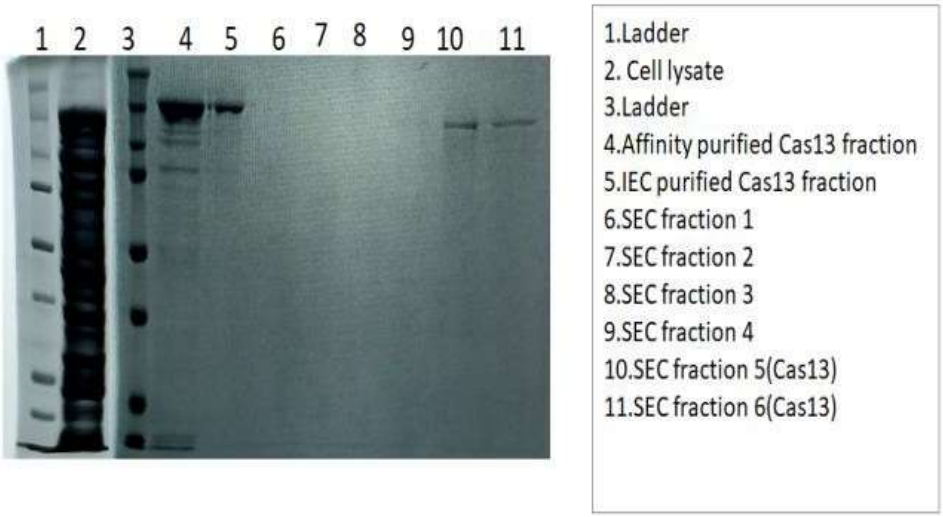
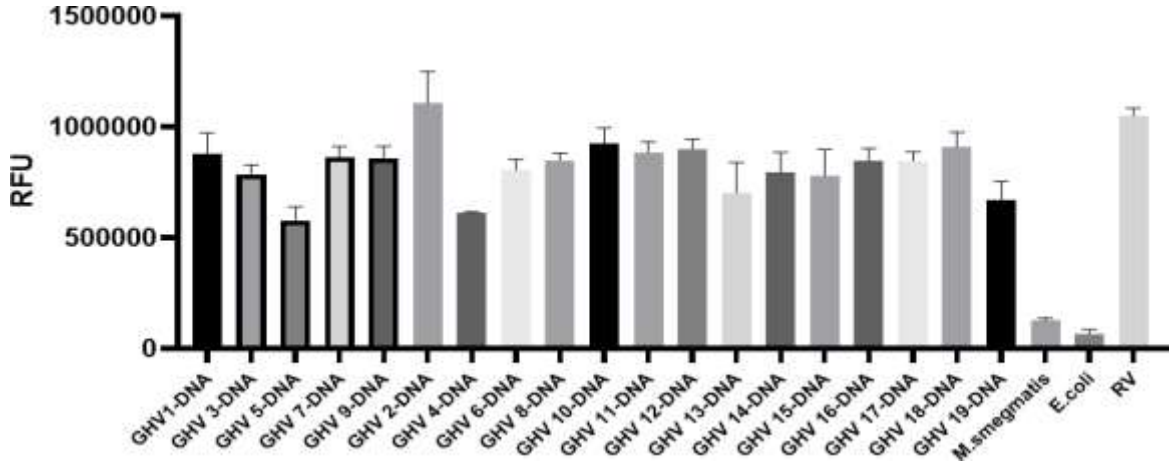


Figure:*M.tb* detection and differentiation



I-4: Identification of the latent tuberculosis specific marker by the immunoproteomic analysis of the cell wall and membrane proteins of *M. tuberculosis*.

Principal Investigator	:	Dr. K. R. Uma Devi, Scientist E
Participating Institutes	:	ICMR-NIRT, Greater Chennai Corporation (GCC), CBST and VIT, Vellore
Source of funding	:	DST-SERB
Study period	:	2019-2022
Category	:	TB
Pillar	:	Detect

Background

The proteins of the cell wall and cell membrane of mycobacterium are unique and many of them play a crucial role in the pathogenesis of tuberculosis (TB). Therefore, immunological characterisations of these mycobacterium surface associated proteins will help in understanding the pathogenesis of TB. However, the hydrophobic nature of mycobacterial cell wall and membrane proteins makes it technically challenging in terms of solubilisation and separation of these proteins. In this study, we plan to perform a novel two dimensional separation approaches for separation of these hydrophobic proteins. The separated protein fractions will be subjected to immunological characterisation *in vitro* using biological samples. We anticipate that this new approach will facilitate the identification of novel biomarkers for diagnosis of latent TB infection.

Objective

To identify latent TB specific markers by comparing immune responses against cell wall and membrane proteins of *M. tuberculosis* between latent and active TB participants.

Methodology

From Mycobacterial cell culture, *M. tuberculosis* cells (S7 strain) will be isolated by centrifugation. Isolated cell pellet will be lysed by sonication. From the whole cell lysate, cell wall and cell membrane proteins

Will be isolated by ultra-centrifugation method. Cell wall and cell membrane proteins of *M. tuberculosis* to be initially separated based on their iso electric point by preparative IEF using Rotofor

instrument. The Rotofor separated fractions will be subjected to a second dimensional separation based on molecular weight by preparative SDS-PAGE. Separated proteins will be eluted using whole gel elutor. This two dimensional approach separates cell wall and cell membrane proteins as individual antigens and the less complex mixtures. These separated fractions will be subjected to immunological characterization by cellular assays using whole blood assay and their antibody response will also be assessed.

Study progress

300 mg of cell wall proteins were separated into 210 fractions by two dimension preparative electrophoresis approach (Preparative IEF using rotofor followed by preparative SDS-PAGE followed by whole gel elution). 100 mg of the cell membrane proteins were separated into 270 fractions by two dimension preparative electrophoresis approach. Since the number of fractions screened is larger, we had grouped the isolated fractions as 3 major groups as described below.

1. High molecular weight protein fractions (Molecular weight more than 50 Kda),
2. Medium molecular weight protein fractions (Molecular weight in the range of 49-20 Kda),
3. Low molecular weight protein fractions (Molecular weight less than 20 kda),

In each group 10 fractions were pooled. By this approach we had obtained 11 pooled cell wall proteins fractions and 13 pooled cell

Membrane fractions. Immunological characterisation of these pooled fractions has been carried out in 10 QFT positive (LTBI) participants, 10 healthy controls (QFT negative) and 10 smear positive pulmonary TB patients (PTB). IFN-γ and TNF-α cytokine response was studied by cytokine ELISA method. Six pooled fractions induced significantly higher IFN-γ response in LTBI compared with PTB. Mass spectrometry based proteomic analysis is now ongoing to identify the proteins in those fractions.

I-5 : Molecular Analysis of Monocyte Subsets from Humans Infected with Mycobacterium tuberculosis

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

Background

Cytokines and chemokines are the two essential mediators of inflammation and the activation of immune responses during TB infection. Emerging research findings revealed that the source of the cytokines does not restrict to T cells alone, but also innate cells like monocytes and macrophages. These soluble factors and their levels in circulation are identified as potential biomarker targets for TB disease severity, bacterial burden and treatment outcomes.

Objective

To estimate the circulating levels of cytokines and chemokines across the TB disease spectrum from latency to drug-sensitive and drug-resistant conditions in comparison with healthy individuals

through multiplex assay towards better understanding of the role of monocytes and macrophages in influencing the effector immune response.

Methodology

Plasma samples from all participants of 4 study groups (Healthy Control (HC) N=40, Latent TB (LTB) N=40, Drug-sensitive TB (DS-TB) N=40 and Drug-resistant (DR-TB) N=40 have been separated and stored at-80^{o}C. Circulating plasma levels of cytokines and chemokines were measured by Luminex Magpix Multiplex Assay (14 plex for cytokines and 10 plex for chemokines) using the Luminex Human Magnetic Assay kit. Statistically significant differences between DR-TB, DS-TB, LTB and HC were analyzed using the Kruskal-Wallis test with Dunn's multiple comparisons. $p<0.05$ was considered statistically significant. Analyses were performed using Graph-Pad PRISM Version 9.0.

Study Progress

1. Differential expression of cytokines and chemokines from latency to drug sensitive and to drug resistance could be observed
2. As per the heat map, the expression of TNF-a, IL-6 and IL- 10 are abundantly increased in DR-TB whereas, IL-1a expression is higher in DS-TB compared to other groups. On the contrary, IL- 5 expression is moderate in the LTB and HC group and low in DS-TB and DR- TB groups. Thus, these analyses help to reveal the Power of cytokines to demarcate the spectrum of TB disease/infection (DR-TB, DS-TB and LTB) from HC.
3. Cytokines (IL-17 & IL-10) and chemokines (CXCL10 & CXCL9) showed better discriminating ability of DS-TB/DR-TB from HC/LTB

Further validation of these cytokine combination in larger cohort at multiple sites may unravel their biomarker potency in distinguishing different forms of TB. Figure: Heat maps representing the measured levels of cytokines (1a) and chemokines (1b) across the TB disease spectrum after normalization with the HC group mean.

Figure 1

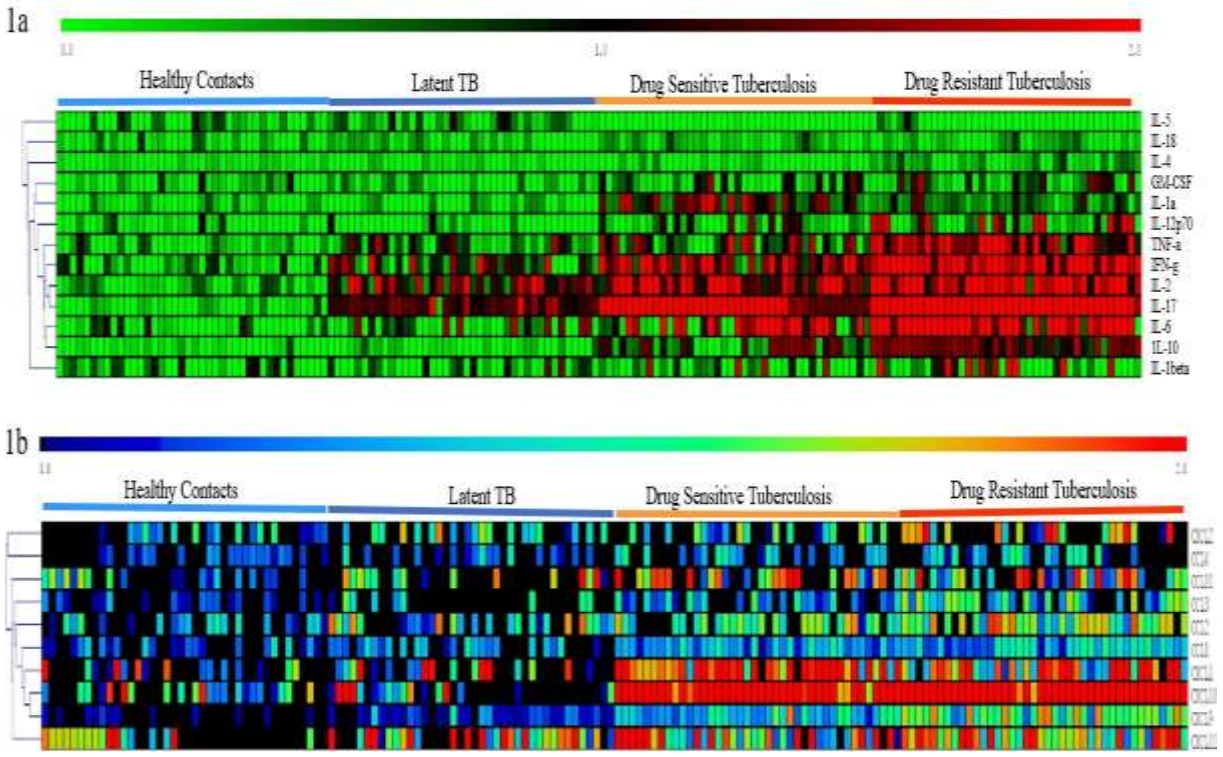
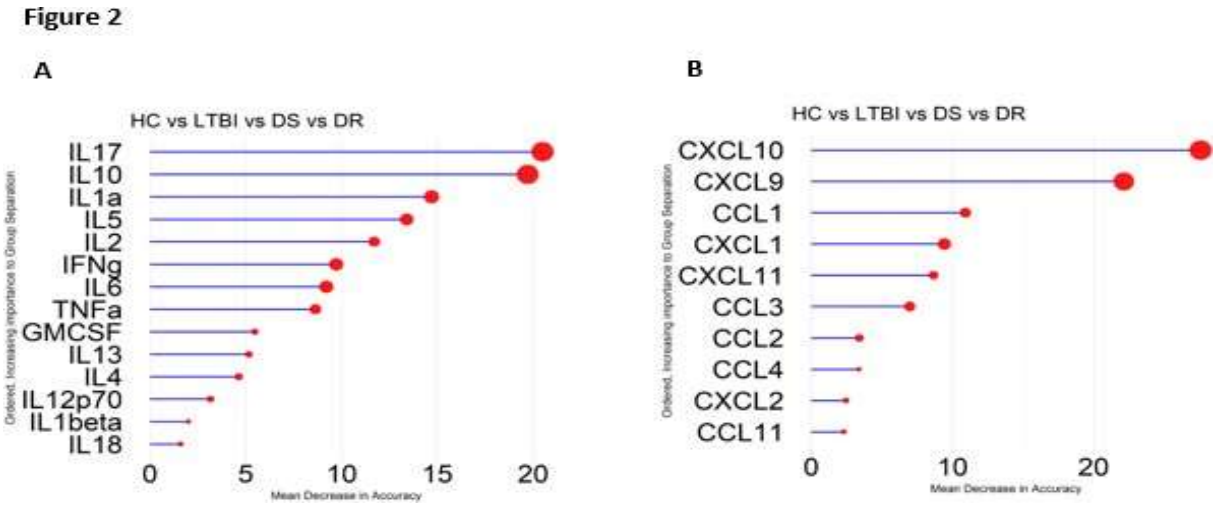


Figure: Random Forest (RF) plots of cytokines (2A) and chemokines (2B) ordered according to their contribution towards group discrimination of HC, LTB, DS-TB and DR-TB.



I-6. : CYP27b1 gene promoter polymorphisms in pulmonary tuberculosis

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

Background

Cyp27b1 gene encodes 1α-hydroxylase enzyme which synthesize active form of vitamin D3. Promoter region often associated with gene regulation and polymorphisms in this region may alter 1α-hydroxylase expression which may lead to vitamin D deficiency and TB outcome.

Objective

To find out the association of *Cyp27b1* gene promoter -1077(C/G) and -1260 (A/C) polymorphisms with susceptibility/protection to pulmonary tuberculosis in healthy controls (HCs) and pulmonary tuberculosis (PTB) patients and its influence on 25(OH)D levels.

Methodology

Totally 100 HCs and PTB patients will be genotyped by polymerase chain reaction followed by restriction fragment length polymorphism (PCR-RFLP) method. 25(OH)D levels will be estimated by ELISA method. Genotypic associations, p-values with OR adjusted for gender and age will be calculated by logistic regression under codominant, dominant, recessive and overdominant models using the online SNP stats program . The best fitting model of association will be determined using the Akaike information criterion (AIC) and Bayesian information criterion (BIC) provided by the software. Genotypes will be correlated with vitamin D levels. p-value≤0.05 will be considered statistically significant.

Table: Number of study participants and genotype details using PCR-RFLP method

Cyp27b1 Promoter SNPs	Study participants		PCR size in bp	Restriction enzyme	Genotypes	Restricted fragment length in base pair (bp)
	HCs	PTB				
-1077(C/G)	60	50	666	TaqI	CC-single band CT-3 bands GG-2 bands	436bp 436+182+48bp 182+48bp
-1260 (A/C)	60	50	666	TfiI	AA-single band AG-3 bands CC-2 bands	423bp 423+177+66bp 177+66bp

I-7 : 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-NIRT, TANUVAS
Source of funding	:	ICMR Extramural
Study period	:	2019-2022
Category	:	TB
Pillar	:	Detect

Background

Bovine tuberculosis (bTB) is one of the important areas of concern because of the serious impact it causes on economic losses and public health. *Mycobacterium tuberculosis* and *Mycobacterium bovis* are the predominant cause of tuberculosis in humans and cattle, respectively. Diagnosis of bTB is generally done by a wide range of tests on live animals as well as at post-mortem. However, post-mortem inspection often fails to detect early cases where lesions have not yet developed, cases where lesions are present in organs or parts of the carcass, which are not routinely examined, or in cases where the lesions are confused with those due to other infectious agents. Slaughterhouse examination of bTB is generally carried out in animals only when visible lesions are seen at the inspection sites. It has been reported that the bacilli survive inside the lymph node of the cattle even though it does not show any clinical symptoms nor any visible lesions during post-mortem depicting the status of latent infection in human.

Objective

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

Methodology

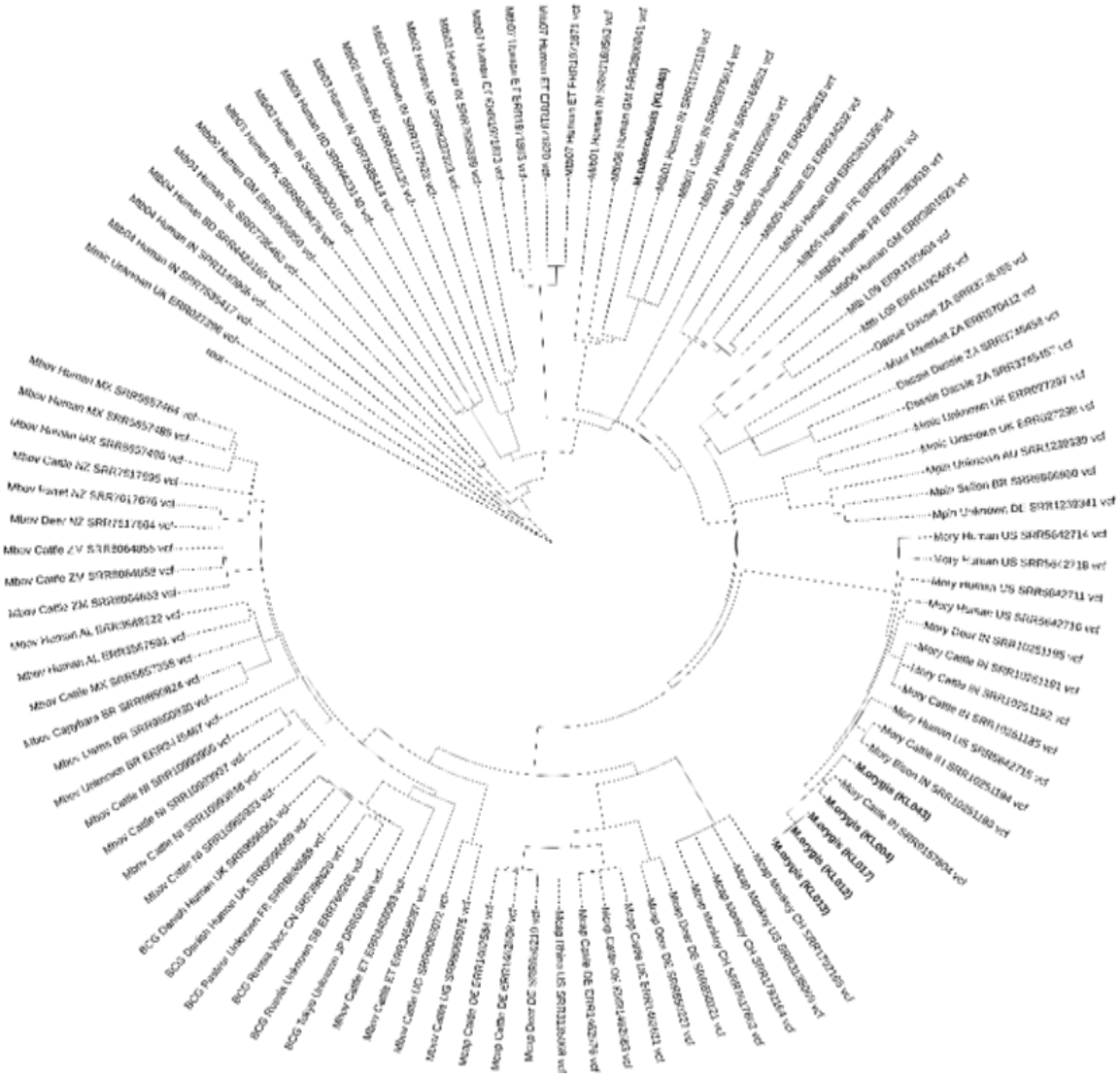
This cross-sectional study will be conducted in the Corporation Slaughter house, Perambur, Chennai. The sample size calculated is 500 based on the published report of prevalence of bTB in this region. The lymph node samples will be collected from the slaughtered cattle with or without visible lesions of TB. The samples will be decontaminated and inoculated into liquid and solid medium for MTBC isolation. The MTBC will be tested for drug susceptibility (DST). Whole genome sequencing (WGS) will be performed to identify the genetic relatedness of the MTBC. Global Positioning System (GPS) data of slaughter house, animal market from where it was traded and its farm location will be collected to locate the endemic pockets of bovine TB.

Study progress

1. A total of 380 samples have been collected from Perambur slaughterhouse in two batches, from September 2020 until now.
2. Six samples out of the 380 samples have been identified to belong to MTBC by phenotypic methods (colony morphology, microscopy) and using immunochromatographic ICT test.
3. PCR using the IS6110 primers was performed, which confirmed that all these isolates belonged to MTBC organisms.
4. Spoligotyping pattern exhibited the spoligotype 587 (ST587) as compared against the SpolDB4 database corresponding to *M. orygis* for 5 of the MTBC isolates.
5. Whole genome sequencing (WGS) revealed that five of these isolates are *M. orygis* and one isolate is *M. tuberculosis*.
6. Apart from this, 72 non-tuberculous mycobacteria (NTM) have been identified in this study and DNA isolation was carried out using CTAB-NaCl method for 35 NTM cultures. PCR performed using MPT64 primers (specific for MTBC) revealed that 12 of these samples were mixed cultures with MTBC. Spoligotyping and WGS for these samples will be performed.

Figure: Global contextual phylogenetic tree combining the 6 study isolates with different members of the MTB

Tree Scale : 0.1 _____



I-8: 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-NIRT
Source of funding	:	ICMR Extramural
Study period	:	2019-2022
Category	:	TB
Pillar	:	Detect

Background

Mycobacterium tuberculosis tends to show various types of resistance mechanism for various drugs. Among these drugs Pyrazinamide (PZA) is an indispensable first line drug that potentially targets dormant bacilli. Pyrazinamide (PZA) is an important first line drug in TB therapy. Because of its indispensable sterilizing activity, all new TB drug candidates in clinical trials are used together with PZA. Although PZA has been continuously used to treat TB, the WHO does not include PZA in the group of antimycobacterial drugs to be routinely tested for resistance because PZA drug susceptibility testing (DST) is notoriously difficult and often inaccurate. Strains showing resistance to PZA increases in number substantially in recent years. Resistance to PZA will severely affect the treatment outcome in TB cases.

Objective

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

Methodology

All clinical strains isolated from presumptive drug resistant stored cultures from three districts of Greater Chennai were be included in the study. Approximately 400 strains collected during 2017-2018 were used for this study. All isolates were processed immediately and subjected to phenotypic DST, PZase activity, and targeted gene sequencing. Resistance for first line TB drugs which includes Rifampicin (RIF), Isoniazid (INH) and Pyrazinamide (PZA) among clinical strains were determined using phenotypic MGIT 960 method. Detection of PZA resistance was followed by using reduced inoculum (RI) method (Piersimoni 2013). Targeted sequencing was done by using the Big Dye Terminator v3.1 Cycle Sequencing kit (Qiagen).

Study progress

Screening of first line drug resistance along with PZA resistance*:* Among 400 isolates, 79 isolates were INH resistant, 17 isolates were INH+RIF Resistant, 13 were INH+PZA resistant, 13 isolates were INH+RIF+PZA resistant, one isolate showed RIF+PZA resistant and 23 isolates were found to be PZA alone resistant and 254 isolates were INH+RIF+PZA sensitive (Table 1).

Phenotypic by Wayne's method: MGIT positive strains were screened for PZA susceptibility testing by alternative method of pyrazinamidase (PZase) assay. Total number of 100 clinical isolates were tested and correlated with MGIT DST results. The resistant control strains (*M. bovis* BCG) used with each batch of test did not produce PZase and were found to be resistant by MGIT 960 method.

Targeted gene sequencing: A total 142 isolates were subjected for *pncA*

sequencing, among which 37 isolates were resistant and 105 were susceptible by PZA MGIT DST. Of the 37 resistant isolates, 11 had mutation in the *pncA* gene and 22 isolates did not show *pncA* gene mutation. This discrepant result due to the involvement of other genes associated with PZA resistance. Whole genome sequencing was performed for the PZA resistant isolates to check for the presence of the PZA resistance associated genes. Among 105 susceptible isolates, 9 showed synonymous mutation and remaining were correlated well.

Whole Genome Sequence analysis (WGS): 17 PZA resistant isolates was performed for 17. Among these, one isolate had mutation in the *pncA* gene alone; five had *pncA* mutation along with *clp C1*and *mas* gene, 2 had mutation in *pncA* and *mas* gene. Two isolates had mutation *panD* along with *clpC1* and *mas*, one had in *panD* and *clpC1*. Five isolates had mutation in *clpC1* along with *mas* gene and one had mutation in *mas* gene.

Table 1: Comparison and performance parameter of PZA susceptibility testing results for MGIT 960, Wayne's method of PZase activity

Test	PZA DST by MGIT 960	Pzase activity by Wayne's method	No of isolates
Results for indicated test (total no. of isolates 400)	Sensitive	Sensitive	349
	Sensitive	Resistant	01
	Resistant	Sensitive	37
	Resistant	Resistant	13

I- 9 : Dereplication-guided bio-prospecting of cyclic lipopeptides from marine Bacillus sp. for inhibition of *Mycobacterium tuberculosis*

Principal Investigator	:	Dr. P. Kannan, Scientist E
	:	Dr. Sagarika Devi (Woman Scientist- DST),
Participating Institutes	:	ICMR-NIRT
Source of funding	:	Department of Science &Technology (DST), New Delhi
Study period	:	2019-2022
Category	:	TB
Pillar	:	Detect

Background

The limitations in existing treatment regimens and emergence of multi drug resistant strains of *M. tuberculosis* emphasize urgency to unearth novel molecular scaffolds for benign and effective antimicrobials from nature. Lipopeptides, have reserved enormous curiosity for their manifold biological roles. *M. tuberculosis* is unique among bacteria and shares many common features with pathogenic fungi. It is thus pertinent to anticipate and important to pursue the unorthodox potential of lipopeptides against *M. tuberculosis.* With fewer published reports onevaluation and validation of the potential of marine *Bacillus* sp. against mycobacterial strains, this proposed investigation aims at bio-guided isolation, fractionation, chromatographic separation and identification of potent *Bacillus* cyclic

lipopeptides with antimycobacterial activity.

Objectives

1. To perform bio-guided fractionation in combination with dereplication using Mass spectrometry (LC-DAD- MS) based analysis and identify a potent marine *Bacillus* species with antimycobacterial activity.
2. To isolate desired extrolites of the selected *Bacillus* species, purify and structurally characterize potential lipopeptides of interest from the active *Bacillus* species.
3. To evaluate and determine the preliminary mode of action of the chosen lipopeptides candidate against *Mycobacterium* strains using time kill assay, fluorescent spectrometry and whole metabolite profiling (using NMR and GC-MS) followed by determination of key pathways regulation using *in silico* BIOCYC MTB metabolome database.

Methodology

Non-calcareous marine sponges (Class Demospongiae) were collected from Mithapur and Poshitra in Gulf of Kachchh, Gujarat by snorkelling following the Okha tide table. The sponge samples were processed for taxonomic study and microbiological analysis. Pure cultures of sponge associated bacteria were cultured and maintained on Zobell Marine Agar (ZMA) at 25 ± 2º C for 3-5 days. The individual slant cultures were studied for Gram

staining and bacterial plugs were harvested for metabolite isolation. The metabolite extracts were tested for anti-tubercular activity against *M. smegmatis* and *M.tuberculosis* H37Rv. The potent extracts have been accessed for cell toxicity. The potent bacillus strains have been identified by molecular sequencing methods. The active metabolite extracts have been isolated by chromatographic separation for identification and structural elucidation using LC/MS/MS, FTIR, ESI (MS) and NMR.

Study progress

1. Non - calcareous marine sponges (n=12) belonging to Demo spongiae were identified.
2. Metabolite extracts of 21 sponge associated gram positive bacteria screened for anti-tubercular activity.
3. Potent metabolite extracts (n = 2) were demonstrate anti-tubercular activity with Minimum Inhibitory Concentration ranging below 2000µg/ml.
4. The isolated bioactive extracts are water soluble and demonstrate 100% cell viability in the cytotoxicity studies with VERO and THP1 cell lines.
5. Potent marine cyclic lipopeptides producing *Bacillus* sp (n=2) identified by molecular sequencing methods.

Work is in progress to perform solid phase extraction-based fractionation, semi-preparative HPLC using diode-array-detection and bioassay guided chromatographic separation. The structures of isolated pure compounds will be elucidated primarily based on interpretation of 1- and 2-D NMR and LC-MS/MS fragmentation analysis data. The study outcome is being discussed for translational research.

I-10 : Identification of tuberculosis specific biomarkers in children by the proteomic analysis of urine

Principal Investigator	:	Dr. D. Anbarasu, Technical Officer B
Participating Institutes	:	ICMR-NIRT, Madras Medical College and Govt. Stanley Medical College, Chennai
Source of funding	:	DHR-ICMR
Study period	:	2019-2022
Category	:	TB
Pillar	:	Detect

Background

Newer diagnostic methods are urgently needed for the diagnosis of the childhood tuberculosis (TB). Identification of childhood TB-specific biomarkers will be useful in the development of newer diagnostic tool in diagnosing childhood TB. MS-based biomarker identification in the urine specimen of children with TB is so far not carried out. Hence, in the present study we are studying the use of MS-based proteomic approach in urine specimen to identify the biomarker specific for childhood TB.

Objectives

1. To identify the childhood TB specific biomarkers by urine proteomic analysis.
2. To identify disease-specific biomarker for childhood TB in urine.
3. To understand the disease-specific modification of the identified biomarker proteins in urine by using high-resolution mass spectrometry analysis

Methodology

Study Groups:

Group A: Children with confirmed TB: (N=62)

Group B: Children having respiratory infection other than TB: (N=62)

Group C: Healthy children: (N=62)

Urine Proteomic Analysis: Urine obtained from the above group of children will be centrifuged. Supernatant of urine will be subjected to TCA cold acetone precipitation protocol for the extraction of urine proteins. Extracted urine proteins will be dissolved using Rapigest detergent. Dissolved proteins will be subjected to trypsin digestion. Digested peptides will be subjected to high- resolution mass spectrometry analysis.

Study progress

The study is ongoing. We have recruited 28 children with Confirmed TB (Group A), 62 children with respiratory infection other than TB (Group B) and 62 healthy children (Total of 152 children).

I-11: 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 E Participating
Institutes	:	ICMR-NIRT, CTD
Source of funding	:	US Centers for Disease Control and
Prevention, Atlanta Study period	:	2015-2022
Category	:	TB
Pillar	:	Build, Detect and Prevent

Background

The prevalence of tuberculosis (TB) in India is the highest in the globe. Even though various developments have made TB easily detectable and treatable, the illness is still progressing due to the advent and ongoing spread of drug-resistant TB, 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

1. 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
2. Perform Whole genome sequencing
3. Perform 12 drug DST via MGIT (Gold standard)
4. Assess sensitivity and specificity for detection of known markers of genotypic drug resistance using NGS versus DST via MGIT (MGIT is gold standard).
5. Assess strain diversity and clustering using existing pipelines
6. Assess for unknown markers of resistance by comparing to international databases
7. 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

1. DR-TB isolates from Chennai retrieved from NIRT repository.
2. 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.
3. The major four lineages identified among the Indian TB patients based on their genetic relatedness using WGS was identified.
4. Current prevalence and mutational diversity of PZA- resistant (PZAR) and multidrug- resistant TB (MDR-TB) in India was studied.
5. Identified *rpoB* mutations outside of RRDR region for rifampicin resistance in few of the isolates originally classified as pan- susceptible and mono-isoniazid resistance by the currently available molecular methods. The extent of rifabutin sensitive rifampicin resistant MDR/XDR isolates in the Indian population was studied.

I-12 : 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-NIRT
Source of funding	:	DBT/ICER
Study period	:	2020-2023
Category	:	TB
Pillar	:	Detect

Background

Tuberculosis (TB), a life-threatening immune challenging disease to the global human community has to be diagnosed earlier and eradicated in the upcoming era. Vitamin D, a fat-soluble micronutrient, mainly from epidermal cells of the skin and few from the dietary sources is associated with the immune system in various disease management. Therefore, a better understanding of vitamin D metabolism and immune function in TB should be studied for the consideration of biomarkers.

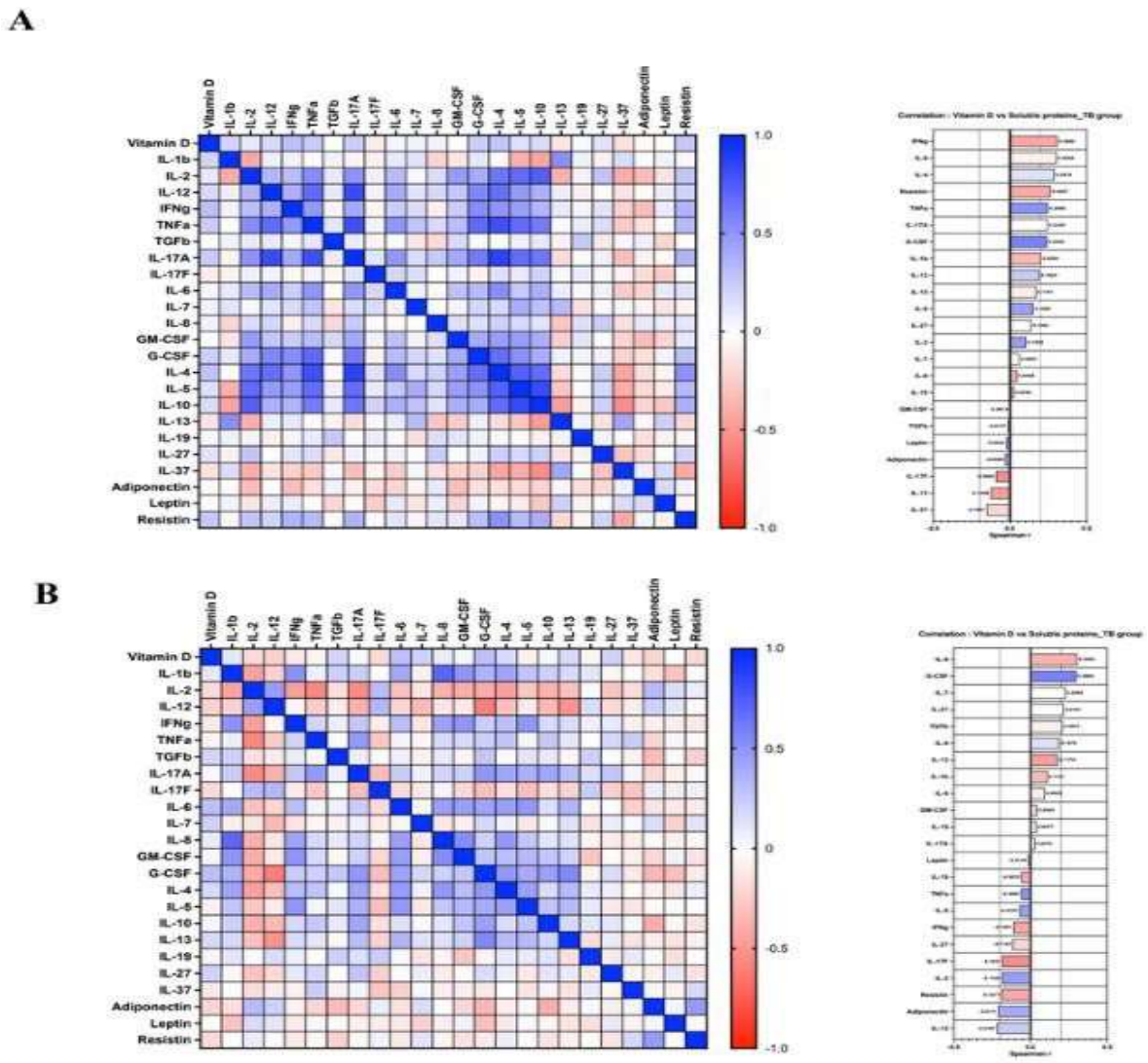
Methodology

The study population comprised of Pulmonary TB (PTB) patients (n=32) evaluated at two time points at Baseline (PTB BL) and after 6 months of anti-TB treatment (ATT) (PTB PT), those with latent *Mtb* infection (IFNγ+) group (n=32) and a non-LTB healthy control (IFNγ-) group (n=32). Vitamin D levels were measured using High performance liquid chromatography (HPLC). The cytokine data from the same participants assayed by ELISA from our earlier investigations were used to correlate it with serum Vitamin D levels.

Study progress

The assayed serum Vitamin D levels between the groups showed significantly lower levels in PTB BL when compared with LTB and HC groups. The Vitamin D levels in the PTB group after ATT is significantly lower than the baseline levels. The Vitamin D data were compared with pro and anti- inflammatory cytokines and adipokines levels by performing a principal component regression analysis. Based on the PC scores, the study group showed distinct clusters for the TB group and control group (Fig.1 A and B). The correlation analysis between the study group and immunological indices showed significant correlations. To profile a TB biomarker, AUROC was performed showing Vitamin D significantly correlated with IFNγ, TNFα, IL17A, IL-4 and Resistin in the TB group, whereas in the control group, IL-6 and G-CSF were found to corelate significant together with Vitamin D.

Figure. Correlation of Immunological indices with Serum Vitamin D levels. (A) Spearman Coreelation matrix analysis performed among TB group. The bar graph showing the correlation between Vitamin D and immunological indices in TB group. (B) Spearman correlation matrix analysis was performed among control group. The bar graph represents the correlation between vitamin D and immunological indices in control group.



I-13 : 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-NIRT
Sourceoffunding	:	ICMR Extra-mural
Studyperiod	:	2021-2024
Category	:	TB
Pillar	:	Detect

Background

The key role of mobile genetic elements or insertion sequences (IS6110) are exclusively found in MTBC and this feature makes *IS6110* a valuable diagnostic tool making it a most reliable TB epidemiological marker. Our previous study identified variable IS6110 copy numbers among the isolates from humans and cattle. The 15 IS*6110* identified in the 6 isolates from humans were all intergenic and located in a conserved region of the genome whereas the 23 IS*6110* identified in 4 isolates from cattle were more widely distributed across the genome and 7 (30%) were intragenic. 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.

Objectives

1. To study the genetic characteristics (*IS6110*, SNPs and InDels) of the animal-adapted *Mycobacterium tuberculosis* complex (MTBC) isolates by whole genome sequencing
2. To determine the differential level of gene expression interrupted by these genetic characteristics and to perform a pathway enrichment analysis of these genes leading to host adaptation.
3. To dissect the molecular mechanism of *IS6110* transposition and its dynamic distribution between the different lineages of the MTBC during laboratory growth and macrophage infection.

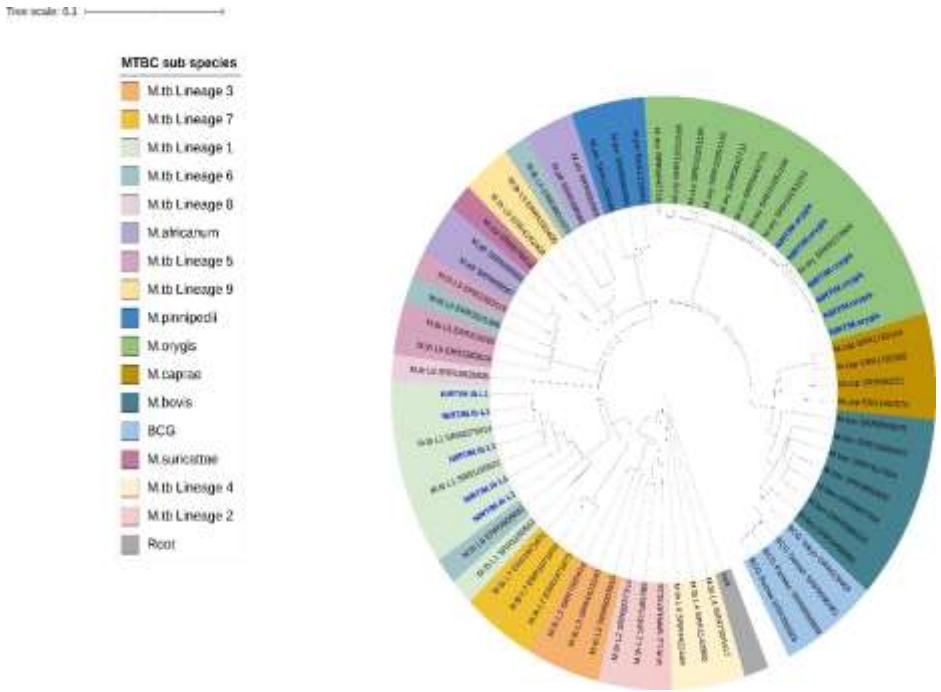
Methodology

20 MTBC isolates from animals including 4 *M. tuberculosis* and 1 *M. orygis* isolate from our previous study was selected. 6 *M. tuberculosis* isolates from human and a standard laboratory strain, *M. tuberculosis* H37Rv was also included for comparison and control respectively. Tissue samples taken from animals during post-mortem examination were processed, stained and inoculated LJ slants (with or without glycerol and sodium pyruvate) and MGIT tubes supplemented with 800 µl of PANTA antibiotic mixtures. DNAs were extracted from these MTBC isolates by hexade cyltrime thiammonium bromide (CTAB) method. DNA libraries were constructed using Nextra XT DNA library preparation kit (Illumina) as per the manufacturer's instructions.

Study progress

1. We currently have 14/20 isolates from cattle, the remaining 6 samples are being revived from the repository. 2 isolates (AH143, AH15) out of 14 were found to be MDR. In WGS, we observed that only 11 isolates out of 14 perfectly mapped with MTBC and 3 isolates were found to be contaminated.
2. WGS analysis identified 5/11 isolates as *M. tuberculosis* and 6/11 isolates as *M. orygis*. The IS*6110* copy number ranged from 3 to 5 (median 4) for *M. tuberculosis* isolates, and 13 to 22 (median 17) for *M.orygis* isolates.

Figure : Contextual phylogenetic tree combining the 11 study isolates with various other MTBC isolates around the globe. Constructed using whole genome SNPs identified after alignment to the H37Rv reference genome and generated using RAxML with 1000 bootstraps. Study isolates are shown in red



I-14 : 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. N. Pavan Kumar, Scientist C
Participating Institutes	:	Institute of Child Health and Hospital for Children, Rainbow Children's Hospital, Dr. Mehta's children hospital
Source of funding	:	NIRT-ICER
Study period	:	2020-2022
Category	:	Covid 19

Background:

Severe Acute Respiratory Syndrome – Coronavirus – 2 (SARS-CoV2) and its related Coronavirus Disease – 19 (COVID- has become a health emergency worldwide. 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. Fortunately, COVID-19 has been reported to be less severe in children than in adults. However, a new multisystem inflammatory syndrome apparently related to infection with SARS-CoV-2 has recently 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.

Objectives

1. To perform systems immunology of SARS-CoV2 infection, COVID-19 disease and MIS-C in children
2. To identify the SARS-CoV2 viral diversity in the pediatric population and correlate with immune responses and disease severity.

Methodology

Study Population: 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

Since there is no previous evidence related to these study objectives, arbitrarily we plan to include n=50 children each group except n=30 in group 3 for this pilot study, which will give us sufficient samples size to perform systems immunology. In addition to this n=55 retrospectively stored COVID-19 by RT-PCR positive pediatric RNA samples in the NIRT central biorespository will be used for characterising the SARS-CoV-2 strain diversity.

SARS-CoV-2 IgG antibody titer assay kit will be employed for estimating the titers of nCov-2019 specific IgG antibody, ex vivo phenotyping of whole blood for immune subsets such as T cells, B cells, monocytes, and dendritic cells the PBMCs will be isolated from study groups to elucidate the mechanism of this SARS-CoV-2/COVID-19 antigen specific immune responses. PBMC cells from study participants will be assessed by multi-parameter flow cytometry for cytokine responses in innate and adaptive immune cells after stimulation with peptide pools of PepTivator SARS-CoV-2 Prot_S1 and PepTivator SARS-CoV-2 Prot_S.

Study progress

Our findings suggest that MMPs might play a pivotal role in the pathogenesis of MIS-C and COVID-19 in children and in addition help distinguish MIS-C from other syndromes with overlapping clinical presentation.

1. Our data suggests that MIS-C is characterized by SARS-CoV-2 antigen specific enhanced production of cytokines and chemokines that may be associated with disease pathogenesis. PCA analysis revealed clearly distinguish of cytokines and chemokines of MIS-C children from COVID-19 and other infections.
2. In our study cohort we were able to identify a larger panel of SARS- CoV-2 antigen specific cellular immune biosignatures that differentiates MIS-C from acute COVID-19 and other infections and these responses were restored after MIS-C treatment completion.

I-15 : Characterization and Durability of COVID-19 vaccine induced immune responses in healthcare/frontline workers

Principal Investigator	:	Dr. N. Pavan Kumar, Scientist C
Participating Institutes	:	ICMR-NIRT, ICMR- NIE
Source of funding	:	ICMR
Study period	:	2021-2023
Category	:	Covid 19

Background

Early in the covid-19 pandemic, it was unclear whether and how individuals and populations would develop protective and enduring immunity against SARS-CoV-2, either after infection or vaccination. It is still not clear what role might immune cellular responses play in the development of immunity to SARS-CoV-2 infection and the implications for vaccines. As T cells recognise and respond to viral antigens they produce many protective reactions and effector molecules. One such molecule is the cytokine interferon γ, secreted by CD4+ and CD8+ T cells and their memory cells. This can be measured means of documenting specific T cell responses to viral antigens. We propose to describe and characterize the humoral, innate and long-term adaptive immune responses and the neutralization potential generated by COVID-19 vaccination (Covaxin, Covishield) among healthcare and frontline workers

Objectives

1. To estimate the SARS-CoV-2 specific IgG, IgM, IgA and neutralizing antibodies titre
2. against SARS CoV-2 by vaccine type (Covaxin or Covishield) in healthcare/frontline workers.
3. To identify and characterize the immune biomarkers for long term innate and adaptive immune response by vaccine type.

Methodology

The study population includes Healthcare/frontline workers working in the ICMR-NIRT and ICMR-NIE aged 18 to 60 years. Participants should receive one dose of COVID- 19 vaccine (Covaxin or Covishield) at baseline and one second dose after 28 days (Window period of +3 days) intra muscularly. This study aims to recruit ~150 n=75 participants who have

Study progress

1. Our preliminary data suggested that a single dose of BBV152-induced humoral immunity in previously infected individuals was equivalent to two doses of the vaccine in infection-naïve individuals. However, these findings need to be confirmed with large sized cohort studies
2. Our results demonstrate that Covaxin induces enhanced plasma levels of Type 1 cytokines (IFNg, IL-2, TNFa), Type 2/regulatory cytokines received first dose of either Covaxin or Covishield vaccine. 10 ml of whole blood will be collected at baseline (on the same day of receiving COVID-19 Vaccine) and on day 28 during second dose vaccination, and at months 2, 3, 6, 12, 18 and 24 post first dose of vaccine. In addition to above time points blood will also be collected at the time when/if the participant develops COVID-19 disease (IL-4, IL-5, IL-10 and IL-13), Type 17 cytokine (IL-17A), other proinflammatory cytokines (IL-6, IL- 12, IL-1a, IL-1b)
3. Covaxin also induced enhanced plasma levels of CC chemokine (CCL4) and CXC
   chemokines (CXCL1, CXCL2 and CX3CL1) but diminished levels of CXCL10. Covaxin vaccination induces enhanced cytokine and chemokine responses as early as month 1, following prime-boost vaccination, indicating robust activation of innate and adaptive immune responses in vaccine recipients.

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

P-1: Pharmacokinetics of second-line anti-TB drugs in children and adolescents with MDR TB

Principal Investigator	:	Dr.S.M. Jeyakumar, Scientist 'E'
Participating Institutes	:	ICH, BJ WADIA, JJ Hospital and NITRD
Source of funding	:	ICMR-ITRC
Study period	:	2019-2022
Category	:	TB
Pillar	:	Treat

Background

Drug-resistant TB (DR TB) is a continuing threat and is an issue in children. It was estimated that more than 30,000 children become sick every year with strains of multidrug-resistant TB (MDR TB). A survey by the National Tuberculosis Elimination Programme (NTEP) in India found that 9% of children with TB were already resistant to rifampicin, which is an important first-line anti-TB drug, before they started treatment. This indicates that they were infected with DR TB. As per WHO consolidated DRTB Guidelines 2020 being implemented by the pediatric NTEP presently include shorter and longer regimens. However, there is paucity of pharmacokinetic data of second-line anti-TB drugs in children with MDR TB. Therefore, here we undertook a study on the pharmacokinetic profile of some of the second-line anti-TB drugs among children and adolescents, who are undergoing treatment for MDR-TB.

Objective

To study the pharmacokinetics of second-line anti-TB drugs (cycloserine, ethionamide, levofloxacin, pyrazinamide, moxifloxacin, kanamycin, amikacin) in children with MDR TB.

Methodology

This is a prospective cross-sectional study with the estimated sample size of 200 MDR TB children and adolescents aged between 1 to 18 yrs. Those diagnosed with H mono/poly, RR/MDRTB with or without additional resistance and receiving ATT regimen for at least 15 days will be included. Upon two weeks completion of anti-TB treatment, PK study will be conducted.

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, which will be followed by administration of anti-TB medications. The time of drug administration will be noted. Blood samples (2.5 ml equivalent to half teaspoon) will be collected at 2, and 4 hours after drug administration.

Plasma concentrations of levofloxacin, ethionamide, cycloserine, moxifloxacin, isoniazid, rifampicin and pyrazinamide will be estimated by HPLC according to methods developed and validated at NIRT. The maximum drug concentration at 2 and 4 hours will be taken as peak concentration (Cmax) and taken for analysis.

Study progress

A total of 65 patients were recruited; female (77%); median age 11 yrs and body weight 30kg. The mean haemoglobin was 11.3 ± gm/dl (Mean ± SD). Further, from the total cases, pulmonary TB constituted 45%. Analysis of anti-TB drug concentration in plasma is in progress.

P–2 : Bioavailability of fixed dose combination of first line anti-TB drugs in patients with pulmonary tuberculosis

Principal Investigator	:	Dr.S.M. Jeyakumar, Scientist 'E'
Participating Institutes	:	GHTM & ICH
Source of funding	:	Intramural
Study period	:	2020-2022
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). 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 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

Methodology

This study bioavailability study includes 12 patients each receiving treatment under 5 different weight bands in adults and 6 different weight bands in pediatric population. Newly diagnosed pulmonary TB patients as per the NTEP guidelines (both adult and children), willing for blood draws and parent/guardian of pediatric patients willing to give written informed consent will be included in the study.

On the day of 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 and subsequently anti-TB drugs will be administered. The time of drug administration will be noted. 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

Patient recruitment is in progress to obtain the required sample size in each weight bands of adult and pediatric population on anti-TB treatment.

DEPARTMENT OF BIOCHEMISTRY

DEPARTMENT OVERVIEW AND MANDATES

The Clinical Biochemistry Laboratory (CBL) plays an important role in providing high-quality diagnostic and research support to various research projects conducted at NIRT. Currently, the analytical services of the CBL are extended to about 18 clinical trials and a few research studies and it is ensured that the reports generated are externally quality assured. In the year 2021-22, around 4000 clinical samples from various trials were analysed in CBL. The focus of research in the department is to establish the newer point of care (POC) TB diagnostic tools, develop nano delivery systems for the delivery of nutrients and therapeutics and to explore adjuvant therapeutic leads from functional foods and natural compounds.

To address various basic research aspects and to biomarker discovery, we have initiated a process to establish a lipidomics facility (LC/MSMS) in the Department of Biochemistry. The Laboratory Information Management System (LIMS) that is in practice is been instrumental in decreasing the turnaround time (TAT) and improving the clinical care management of study participants in time. Presently the laboratory is in the process of getting accreditation with the National Accreditation Board for Testing and Calibration Laboratories (*NABL*).

Studies in progress

BC-1: Point of care estimation of Vitamin D and C - reactive protein for tuberculosis screening in household contacts of active pulmonary tuberculosis patients in Tamil Nadu, India

Principal Investigator	:	Dr.N Saravanan, Scientist D
Participating Institutes	:	ICMR-NIRT, Chetpet, And Chennai
Source of funding	:	ICMR-ADHOC (Technically approved)
Study period	:	2022-2025
Category	:	TB
Pillar	:	Detect

Background:

TB continues to be a major public health problem globally. The problems associated with missed or delayed diagnosis of active TB in the general public and high- risk population's lead to increased TB transmission, disease and death. National Tuberculosis Elimination Program (NTEP) has stressed employing efficient screening tools for active case finding in high-risk population such as household contacts (HHC). Symptom-based screening procedure of WHO is sensitive but less specific. Evidence supports the role of vitamin D (vit-D) deficiency and elevated C-reactive protine (CRP) in predicting active PTB. Therefore, the utility of point of case (POC) estimation of Vit-D and CRP in HHC of active PTB patients was explored as a screening tool elimination of TB, WHO stressed the importance of 'systematic screening' of high-risk populations such as household contacts (HHC) of index cases to detect TB early.

Objectives

1. C-reactive protein and Vitamin D to compare the diagnostic accuracy (sensitivity and specificity) and the predictive value of point-of-care (POC) estimation of C-reactive protein and Vitamin D with WHO symptom-based screening for active TB in household contacts of PTB patients.
2. To compare the diagnostic accuracy and the predictive value of point-of-care (POC) estimation of C-reactive protein & Vitamin D, and Chest X-Ray (CXR) with WHO symptom- based screening for active TB in household contacts of PTB patients.

To compare the diagnostic accuracy and the predictive value of point-of- care (POC) estimation of C-reactive protein & Vitamin D with the bioanalyses-based estimation of C- reactive protein & Vitamin D in household contacts of PTB patients.

Methodology

This prospective cross-sectional study will be conducted among HHC of active TB patients recruited for various clinical trials at ICMR- NIRT. The POC test for CRP will be conducted using a hand-held immune analyser from 2-3 µL capillary blood and the POC test for vitamin D will be done in the serum (50 µL) and simultaneously both the analyte will be analysed in a bioanalyzer. The diagnostic accuracy and the predictive value of POC estimations of CRP & vitamin D with or without CXR will be compared with symptom-based screening for active TB in HHC of PTB patients with reference to culture results and Xpert MTB/RIF data independently.

Study progress

We have conducted a pilot study to understand the usefulness of POC CRP & vitamin D tests as a predictive marker in the stored plasma samples of symptoms and X- Ray abnormal HHC. Plasma samples of 200 HHC and related information were collected from the Cohort for Tuberculosis Research by the Indo-US Medical Partnership (C-TRIUMPH) repository and C-TRIUMPH database respectively and used for the analysis.a 10 µL of plasma was used for the POC estimation of CRP and 50 µL of plasma was used for the POC estimation of Vitamin D separately. Due to the very small proportion of active cases (1 out of 192; eight samples were excluded due to loss to follow- up) neither the POC tests nor the WHO symptom-based screening procedures could predict the active TB in household contacts (Table). The proposed main study with 1600 HHC will appropriately address the issue.

Table-1. Demographic and clinical profile of study participants

Total		No TB	TB		*LTFU
			Prevalent	Incident	
Gender					
Male	96	92	1	--	3
Female	104	96	2	1	5
Age					
<18	59	55	3	1	1
18-29	58	58	--	--	2
30-39	27	27	--	--	2
>/=40	56	56	--	--	3
Vitamin D (ng/mL)					
<9.99	9	8	--	--	1
10-19.99	75	69	2	--	4
≥20	116	111	1	1	3
CRP (mg/L)					
<5	182	172	3	1	6
5.1-9.9	9	8	--	--	1
≥10.0	9	8	--	--	1
WHO symptom					
Cough	192	25	1	--	3
Fever	192	12	--	--	--
Weight loss	192	6	--	--	1

*loss to follow up

BC-2: 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 D,
	:	Dr. N Usha Rani, ICMR-RA
Participating Institutes	:	ICMR-NIRT, Chennai and CSIR-CLRI, Chennai
Source of funding	:	ICMR
Study period	:	2021-2024
Category	:	TB
Pillar	:	Treat

Background

The survival of *M.tb* within the host depends on the immuno-modulations induced by *M.tb* within the host. The hyper inflammation occurred due to chronic TB infection and biochemical changes caused by anti-tubercular therapy (ATT) drugs, leading to severe residual lung injury which is a common risk factor for TB reinfection after cure. Carnosine (β-alanyl-L-histidine) is a dipeptide, which is shown to have anti- inflammatory, antioxidant, and wound healing properties. This dipeptide can be self- assembled into nanostructures in response to variations in pH, ionic strength, and the presence of a crosslinker. The self-assembled nanostructure can be used as a nanocarrier in the therapeutic application of select ATT drugs.

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 TB.
3. To investigate the therapeutic potential in, *in vivo* experimental infection system of pulmonary TB.

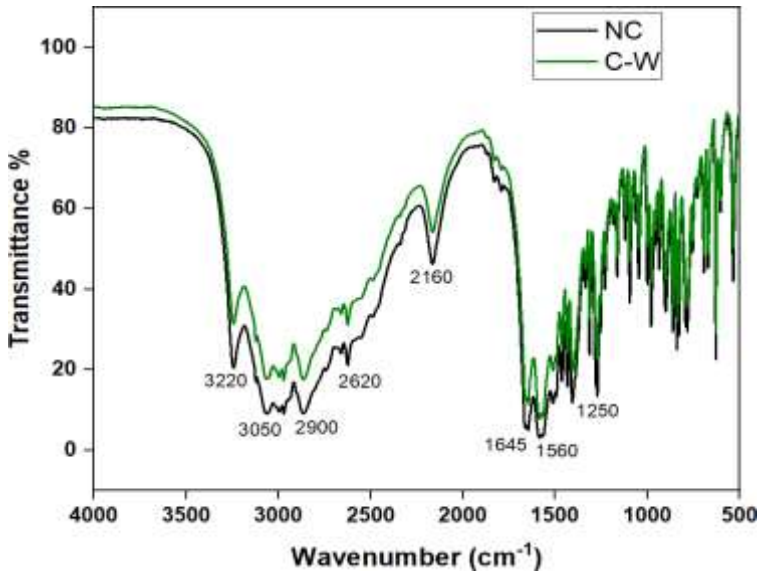
Methodology

In the current proposal, we have planned to develop a carnosine nano-peptide system and explore its effects on the initial intense pro- inflammatory response, immune homeostasis, and excessive inflammation that causes residual lung injury during pulmonary tuberculosis. Further, the immunomodulatory and anti-inflammatory effects of the carnosine nano system will be investigated using *in vitro* models. To comprehend the biological functions of the developed nano system, *in vivo* experiments will be performed

Study progress

As a first part of the study, the development and characterization of carnosine nanostructure were performed; the structural transitions of hydrothermally processed carnosine nanostructure were analysed by recording absorbance, secondary structural information, vibrational spectrum, diffraction data, and the corresponding resonance signals (Figure). The size of the aggregated nano peptide was about ~492 nm (length and width of the particle) and the surface charge was about -11.4 mV. Further, the characteristic hydrophobicity, surface tension, and mesoporosity were recorded using sophisticated techniques. The *in vitro* and *in vivo* experiments will be conducted.

Figure - Fourier transform infrared spectrum of native carnosine (NC) and hydrothermal processed carnosine (C-W)



BC- 3: 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 D
Participating Institutes	:	ICMR-NIRT, Chennai and CSIR-CLRI, 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

1. 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.
2. Validate their medicinal properties using *in vitro* studies
3. To investigate their safety and toxicity as an adjuvant using *in vivo* models.

Methodology

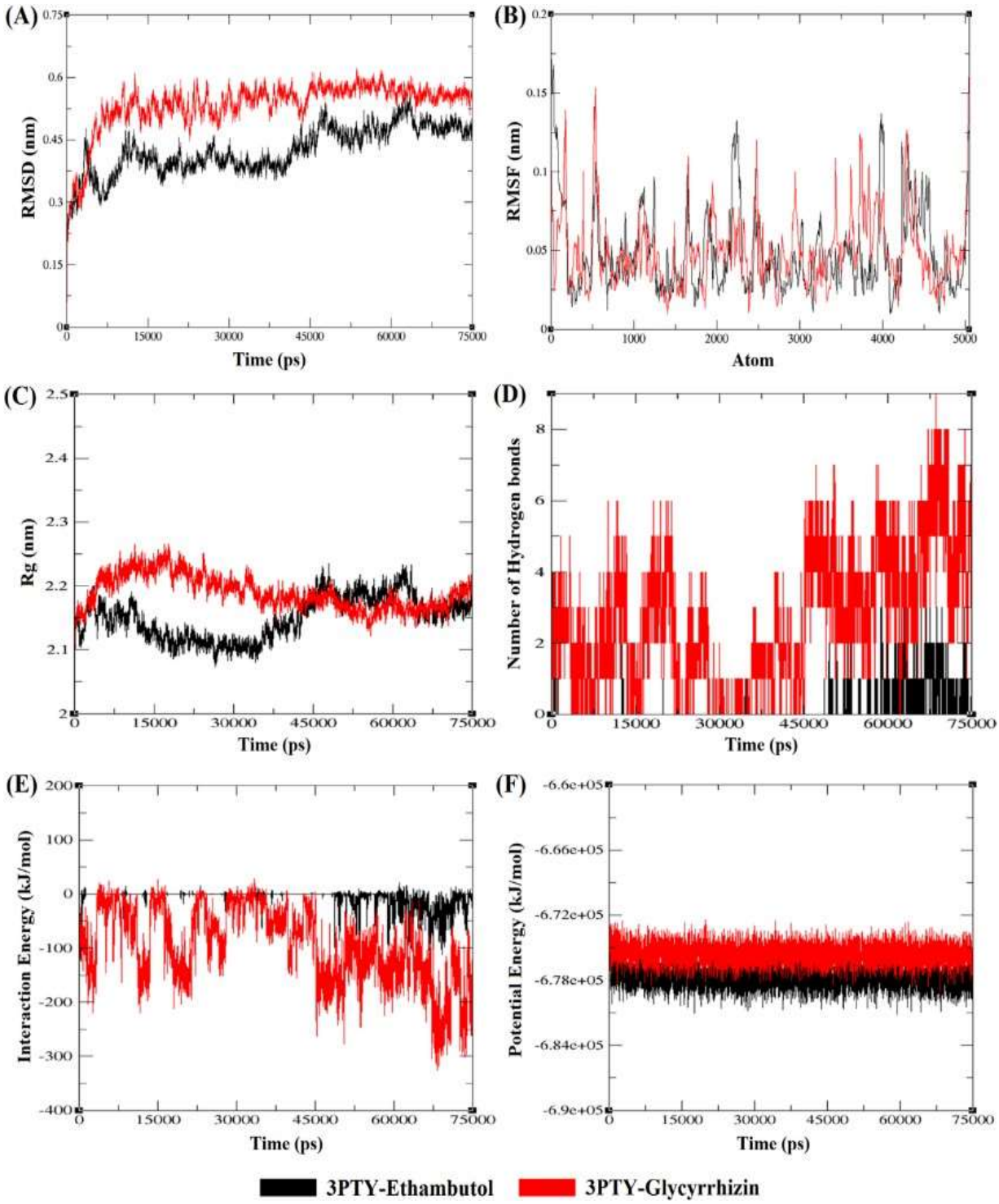
Individual list of phytochemicals for their known effects as (i) antimycobacterial, (ii) immunomodulatory, (iii) hepatoprotective and (iv) pulmonary protective effects will be identified based on scientific evidence and literature in Siddha and Ayurveda. The structure-activity relationship (SAR) of bioactive compounds will be performed through *in silico* experiments further docking and simulation experiments will be conducted for the select phytocompounds. Based on the *in silico* data, promising phytochemicals will be isolated/procured.The minimum inhibitory concentrations (MIC) of the phytochemicals and semisynthetic compounds will be investigated on the *Mtb* H37Rv strain. The cytotoxicity will be checked using cell lines. After successful *in vitro* characterization, select compounds will be investigated for the abovementioned activities in suitable animal models.

Study progress

We have 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 Institute of Technology (VIT), Vellore. The selected proteins for the docking studies are

1. RNA Polymerase subunit C (PDB Id: 5ZX3) AT of RIF, (ii) Enoyl-[acyl-carrier-protein] reductase (PDB Id: 5VRL) AT of INH, (iii) Ribosomal protein S1(PDB Id: 4NNI) AT of PZA, (iv) Arabinosyl transferase (PDB Id: 3PTY) AT of EMB, (v) DNA gyrase subunit A (PDB Id: 4G3N) Active target of Fluoroquinolone, (vi) 2'-O- methyltransferase TlyA (PDB Id: 5KYG) AT of Capreomycin, (vii) F-ATP synthase epsilon chain (PDB Id: 5YIO) AT of Bedaquiline. Selected novel phytochemicals were subjected to molecular dynamics simulation (MDS) experiments (Swertiamarin, Glycyrrhizin, & Laccaic acid) and the preliminary data is published (Figure). These compounds will be further characterized for their beneficial effects through *in vitro* and *in vivo* experiments.

Figure.. MDS analysis of 3PTY with Ethambutol and Glycyrrhizin: (A) Root-mean-square deviation trajectory (B) Root mean square fluctuation trajectory (C) Radius of Gyration plot (D) Number of H-bonds (E) interaction Energy trajectory (F) Potential energy trajectory



DEPARTMENT OF VIROLOGY AND BIOTECHNOLOGY

DEPARTMENT OVERVIEW AND MANDATES

The Department of Virology and Biotechnology provides high quality diagnostic services and research support for various HIV, HIV/TB and other viral studies undertaken by ICMR-NIRT. The Diagnostic Serology division of the Department provides routine clinical safety parameter testing services for clinical trials and other research studies. The Molecular Diagnostic division supports the molecular diagnosis of HIV-1 infection for the National Early Infant Diagnosis Program and HIV-1 viral load testing for the National ART Program. The Cellular Immunology division supports vaccine immunogenicity studies for TB and COVID-19 vaccines. The BSL-II Plus facility supports HIV culture, anti-viral screening and COVID-19 testing.

The Department holds the status of a National Reference Laboratory for HIV-1 drug resistance genotyping for WHO, Regional Reference Laboratory for molecular diagnosis of HIV-1 infection and HIV-1 viral load testing for NACO, ICMR approved laboratory for COVID testing and Central Deport for COVID reagents. The Department offers an in-country external quality assessment (EQA) program for isolation and cryopreservation of peripheral blood mononuclear cells (PBMC), the first and only in-country PBMC EQA Program, for the RePORT India Consortium, and houses a large TB Biorepository. Recently, the Department has received funding to set up a Viral Diagnostic and Research Laboratory (VRDL).

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, identification of cellular and molecular mechanisms that contribute to enhanced risk of mortality among cured TB patients and identification of factors that contribute to increased risk of TB reactivation among HIV/TB co-infected individuals. The Department also undertakes basic research on HIV latency, functional characterization of transmitted/founder (T/F) HIV-1 strains and immune pathogenesis of TB and COVID-19 infections.

Studies in progress

VL -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-NIRT, BJMC - Pune, Johns Hopkins - Baltimore
Source of funding	:	ICMR Adhoc
Study period	:	2019-2023
Category	:	TB
Pillar	:	Detect

Background

Tuberculosis continues to impart significant health and economic setbacks worldwide. 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 the first 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, and target them for prophylactic therapy, thereby contributing in a significant way to TB elimination efforts.

Objectives

1. Multiplexed cytokine analysis of unstimulated (Nil) and stimulated (TB antigen- stimulated) plasma (QuantiFERON supernatant) of TB progressors and non-progressors.
2. MicroRNA profiling of QuantiFERON supernatants of TB progressors and non- progressors
3. Single nucleotide polymorphism (SNP) analysis in TB progressors and non-progressors by genotyping.

Methodology

The QuantiFERON supernatants were analyzed for a panel of 45 soluble analytes using multiplexed cytokine analysis on the Luminex platform. miRNA expression was profiled using Nano String nCounter platform. Genetic polymorphism studies are being performed using Taqman allelic discrimination assays and targeted gene sequencing.

Study progress

Multiplex cytokine/chemokine analysis was performed in 14 progressors (household contacts of TB patients who progressed to TB disease during a two-year follow-up period) and 20 age and sex-matched non-progressors using Luminex Human Magnetic Assay kit 45 Plex (R & D systems). through classification and regression tree analysis, a cut-off of 0.24 for 2qIP10/CCL19 ratio was found to be most sensitive for predicting short-term risk of progression to TB disease with a positive predictive value of 100 (95% CI 85.8-100). Nanostring analysis revealed differential expression of 31 miRNAs between the progressors and non-progressors, among which hsa-miR-223-3p and hsa-miR-451a demonstrated a maximum fold change ratio of 2.05, followed by hsa-miR-423-5p, hsa-miR-92a-3p and hsa-miR-29a-3p.Target gene identification revealed 19 genes related to tuberculosis pathway. Further analysis is ongoing. Genetic polymorphism studies are also ongoing.

VL–2 : Impact of malnutrition on immune responses to tuberculosis in Indian Children

Principal Investigator	:	Dr. Aishwarya Venkataraman Scientist E
Participating Institutes	:	ICMR-NIRT, ICH, Stanley, KKTCH
Source of funding	:	DBT
Study period	:	2018-2022
Category	:	TB
Pillar	:	Treat

Background

The association between malnutrition and TB has been well recognized and is believed to be the result of increased susceptibility to infections due to the immunodeficiency caused by undernutrition. This study aims to evaluate TB-specific immune responses in children with moderate acute malnutrition (MAM) and compare them with that seen in well-nourished children, to assess the impact of malnutrition on dampening of anti-TB immunity. The study also aims to evaluate the impact of a nutritional intervention on *M. tuberculosis* (*M.tb*)-specific immune response.

Objectives

1. To characterize innate and T cell immune responses to *M.tb* in moderately malnourished and well-nourished children with TB disease.
2. To characterize innate and T cell immune responses to *M.tb* in moderately malnourished and well-nourished children with latent TB infection.
3. To assess the impact of a nutritional intervention on host immune response to *M.tb* in children with malnutrition.

Methodology

The study includes 4 groups of children: (i) moderately malnourished children with TB disease, (ii) moderately malnourished children with latent TB infection, (iii) well nourished children with TB disease, and (iv) well-nourished children with latent TB infection. All children were followed up during the 6-month period when the children were on anti-TB treatment or TB chemoprophylaxis. Longitudinal changes in innate and adaptive immune function were evaluated during the period of follow-up.

Study progress

The study has recruited 55 well-nourished and 48 malnourished children with latent TB infection and 28 well-nourished and 34 malnourished children with TB. Immunological evaluations have been performed for all recruited participants. The study is ongoing.

VL–3: 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 C
Participating Institutes	:	ICMR-NIRT
Source of funding	:	Intramural
Study period	:	2021-2022
Category	:	TB/COVID
Pillar	:	Build

Background

Neutrophils are unique in their capacity, both to heal as well as to destroy any tissue in the body, as they are the first cells that reach the site of infection or damage. Through the cytokines produced, neutrophils help to build up an immediate immune response at the early stage of infection. Conversely, excessive cytokine production can contribute to increased inflammation and pathology. NETosis or formation of neutrophil extracellular traps (NETs) is one of the killer functions of neutrophils. While NETs serve to trap the pathogen and destroy them, in the advanced stages of disease, NETs contribute to disease pathogenesis. Recent studies have reported the association of NETs with severe disease in COVID-19 infected individuals. The present study aims to test the hypothesis that underlying TB infection contributes to the pathogenesis of severe COVID-19 disease through increased NETosis.

Objective

To evaluate neutrophil mediated responses in individuals with pulmonary TB (PTB) and SARS- CoV-2 co- infection.

Methodology

Peripheral whole blood is collected from volunteers by trained laboratory personnel and subjected to hematological and biochemical analyses (D-Dimer, C-reactive protein, Ferritin, Lactate dehydrogenase). Neutrophils are isolated from peripheral whole blood using density gradient centrifugation followed by dextran sedimentation procedure. Purified neutrophils are cultured with PMA/Ionomycin overnight in 5% CO2 incubator. Cell culture supernatants are collected and stored at -80^0C for analyzing cytokines (IL1 , IL-6, IL-8, IP-10, MCP-1, MIP-1α and TNF-α). Complement proteins (C3a, C5a and C5b-9 complex) and cell free DNA will be measured in stored sera using commercial ELISA kits (BD biosciences & Invitrogen respectively). Cit-H3 will be quantified in plasma using the Citrullinated Histone H3 (clone 11D3) ELISA Kit (Cayman chemicals, 501620).

Study progress

Participant recruitment is complete. CBC and biochemical test results have been obtained for all participants. For the healthy volunteer cohort, recruitment is currently ongoing. The neutrophils are being isolated from the peripheral blood of participants and cultured with PMA for 2 hours. After culture, NET markers expressed by neutrophils are measured by flow cytometry. The supernatants are stored at -80^0C for cytokine and complement assays. The serum is also stored for quantification of MPO-DNA complexes, Cit-H3 and cell free DNA.

VL – 4: 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-NIRT
Source of funding	:	Intramural
Study period	:	2021-2024
Category	:	HIV

Background

Unprecedented scale-up of antiretroviral therapy (ART) has occurred during the past decade. Nevirapine (NVP) or Efavirenz (EFV)-based regimens were the most frequent ART regimens initiated prior to 2020. High levels of observed pre-treatment drug resistance to NVP and EFV emphasized the need for the transition to an integrase strand-transfer inhibitor (INSTI) -based first- line regimen by the World Health Organisation. As per WHO recommendations, dolutegravir (DTG) based TLD regimen, that is, tenofovir disoproxil, lamivudine and dolutegravir, was introduced in the National ART program as the first line regimen in 2020. As the use of DTG-based first-line ART is being scaled up, it becomes important to conduct periodic pretreatment drug resistance surveys to document any signals of increase in pretreatment 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

1. To determine the prevalence of HIV drug resistance (HIVDR) in treatment-naive individuals, among adults initiating first-line antiretroviral treatment.
2. To document virologic suppression and HIVDR in adults receiving ART for 12 months.
3. To investigate the association between viral failure and drug resistance with specific ART regimen, adherence patterns, and other demographic and clinical factors.

Methodology

This is a prospective study in HIV-1 infected adults newly initiated on first line ART. Blood samples will be collected at baseline (before start of ART) and 12 months after the initiation of ART. HIV-1 viral load testing using the Abbott m2000 real time PCR system and HIV drug resistance genotyping using an in-house protocol will be performed at both time points. Sanger sequencing of HIV-1 protease, reverse transcriptase and integrase genes will be performed using 3500 genetic analyser (Applied Biosystems, Foster City, California, USA). The sequences will be assembled and analyzed by using Seqscape software V2.6 (Applied Biosystems) and DRM interpretation will be done as per HIV Stanford algorithm.

The following survey endpoints will be assessed:

HIVDR: HIV RNA ≥1000 copies/mL at 12 months and ≥1 HIVDR mutation as defined by the standard population-sequencing protocol.

Possible HIVDR: Patients who stopped ART during the 12 months after initiation, patients lost to follow-up and patients with HIV RNA ≥1000 copies/mL at 12 months and no detected HIVDR mutation.

Study progress

Sixteen HIV-1 infected ART naïve participants were screened and enrolled till March 2022. HIV-1 viral load testing has been done for all enrolled participants. HIVDR genotyping was also performed.

VL-5: 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-NIRT
Source of funding	:	Intramural
Study period	:	2022-2023
Category	:	HIV

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. In this scenario, where there is a total lack of HIVDR data on prevailing levels of resistance to the integrase class of drugs in subtype-C prevalent countries like India, it is highly important to screen for the presence of mutations to DTG before initiating the person on a DTG-based first line regimen. This study aims to develop an assay to detect markers of DTG resistance.

Objectives

To develop a simple and affordable HIV drug resistance test specific for the detection of DTG resistance in HIV-1 infected persons.

Methodology

The study will be carried out in three phases, Pre-validation or assay development phase, validation phase and study completion phase. In assay development phase, we will carry out the designing of specialized primers and probes and evaluate their binding efficiency to synthetically designed DNA fragments. In the assay validation phase, we will test the assay on actual reference panel plasma samples with known genotypes of interest and the results will be compared with the Sanger sequencing data. As per WHO guidelines, accuracy, precision, reproducibility and amplification sensitivity will be evaluated for the newly developed genotypic test. In the study completion phase, compiling of data and data analysis will be carried out and agreement of test results between the newly developed assay and the gold standard Sanger sequencing method will be evaluated (Sensitivity, specificity and LOD).

Study progress

In silico analyses of HIV-1 integrase gene sequences (>28,000) from all HIV-1 subtypes, including recombinants were carried out. Multiple sequence alignments were constructed using MUSCLE program in Jalview 2.11.0 and checked manually. The DRM SNP positions were identified using the Stanford University HIV Drug Resistance Database (http://www.hivdb.stanford.edu). Allele frequencies for each primer and probe binding position were calculated and a signature profile dataset was generated for each DRM position with subtype-specific and combined subtype data for "pan-primer and probe design". The study is ongoing.

VL- 6: Impact of HIV infection and antiretroviral therapy on premature onset of aging-associated disorders

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
	:	Dr. A. Nusrath Unissa
Participating Institutes	:	ICMR-NIRT, YRG CARE
Source of funding	:	Intramural
Study period	:	2019-2022
Category	:	HIV

Background

Availability of antiretroviral therapy (ART) has transformed HIV infection from a fatal disease to a chronic manageable disease. Despite the significant decline in mortality associated with HIV infection in the recent years, 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 carried out in our department 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 metabolite profile with risk factors for aging associated co morbidities like cardiovascular disease (CVD), diabetes mellitus (DM), liver and kidney diseases.

Objectives

1. To identify abnormalities in immunological and biochemical parameters in HIV- infected individuals on ART.
2. To correlate cellular and immunological abnormalities with biochemical markers indicative of risk for metabolic disorder and age-related comorbidities.

Methodology

41 participants have been recruited to the study. , Immune activation levels were determined in whole blood. PBMC were isolated, stored and analysed for the state of immunosenescence, memory differentiation and cytotoxic function of T cells. Further, T cells were characterized for immune exhaustion and proliferation flow cytometry. Telomere length was measured using RT-PCR and the plasma samples were screened for presence of other viral co-infections.

Study progress

Preliminary analysis revealed lower levels of immune activation, higher levels of immune senescence, lower levels of Tregs, and moderate levels of immune exhaustion and proliferation in HIV infected individuals. Majority of the HIV-infected individuals were positive for Cytomegalovirus (CMV) antigen though none of them had evidence of clinical disease, suggesting the effect of ART in suppressing the clinical complications of CMV infection. On the other hand, there was a very low prevalence of other viral co-infections among HIV-infected individuals on suppressive ART. Analysis of biochemical and immunological data are ongoing.

VL–7: 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-NIRT
Source of funding	:	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.

Objectives

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

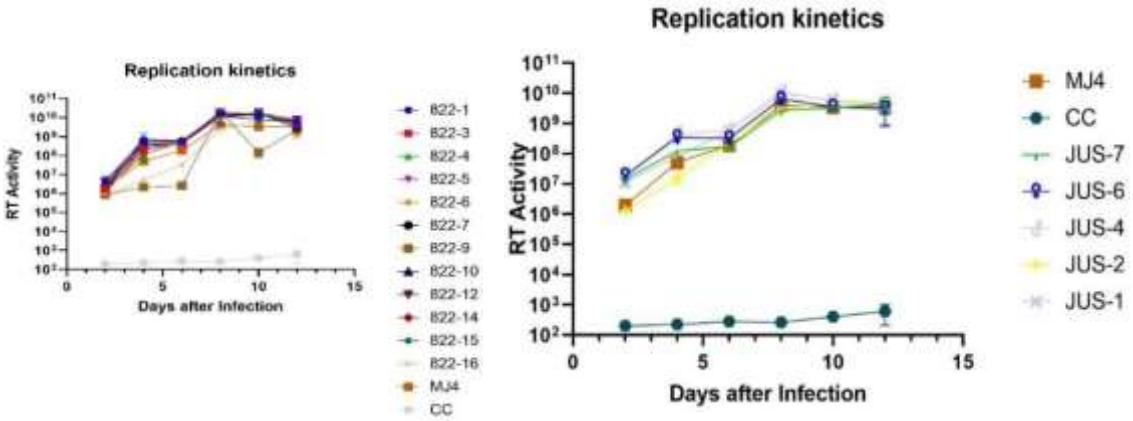
Methodology

Near full length genome (NFLG) of HIV was amplified from the plasma of HIV-infected infants (aged <6 months). The 5' and 3'LTR fragments were amplified separately from the proviral DNA and cloned with the 9 kb NFLG through ligation independent cloning method to generate full length HIV-1 clones. The full-length infectious clones were sequenced using Illumina NGS sequencing, and the sequences were analyzed to identify full length intact TF and CC viruses. The full-length clones were characterized for infectivity, replication kinetics, coreceptor usage, neutralization sensitivity and resistance to innate immune factors. Representative TF and CC clones were tagged with GFP and used for viral transmission and infection studies.

Study progress

We generated 23 full-length HIV-1 clones from the plasma virus of three HIV-1 positive infants. The clones were sequenced and the sequences were analyzed to identify molecular differences in the envelope that distinguish TF from CC viruses. The viruses were tested for replication kinetics, per particle infectivity, tropism, co-receptor use and sensitivity/resistance to innate immune factors and broadly neutralizing antibodies using relevant cells lines and primary cells. Replication kinetics of the IMCs is shown in Figure. 1. Further characterization is ongoing.

Figure: Replication kinetics of the IMCs



VL–8 : Introduction of point mutations in the *gag* gene of HIV-1 using Adenosine Deaminase acting on RNA (ADAR)

Principal Investigator	:	Dr Luke Elizabeth Hanna, Scientist F
Research Scholar	:	Mr. Balakumaran S
Participating Institutes	:	ICMR-NIRT
Source of funding	:	Intramural
Study period	:	2020-2023
Category	:	HIV

Background

HIV uses the host machinery to translate its mRNA, and any alteration to 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 exploit the gene editing activity of ADAR-1 to inhibit HIV-1 protein synthesis.

Objectives

1. To construct an ADAR-1 p150 guide RNA cassette.
2. To analyze the gene editing efficiency of the cassette and its ability to inhibit protein synthesis *in vitro*.
3. To analyze expression of ADAR-1 p150 isoform upon stimulation with IFN-α.

Methodology

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

Study progress:

Guide RNA oligos were designed and prepared for cloning into the Block-it U6 entry vector system. The ssOligos were annealed using TE buffer at 95°C for 2 minutes and cooled at room temperature. pSilencer 2.1 U6 hygro vector was digested with Bam HI and Hind III enzymes. The digested backbone and annealed oligoes were purified using Machery Nagel clean-up kit. The purified gRNA will be cloned into the digested pSilencer backbone using T4 DNA ligase. *In vitro* characterization of gRNA will be carried out after confirmation of the clones. The work is ongoing.

VL – 9: HIV-1 transmission pairs: genetic variability and clinical implications

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Participating Institutes	:	ICMR-NIRT
Source of funding	:	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 on the sequence of the HIV-1 *env*. Further, the *env* sequence also determines the course of disease in the recipient. HIV-infected persons who make significant amounts of neutralizing antibodies, demonstrate better control over infection and disease progression, and are referred to as elite neutralizers. This study aims to identify key mutations in the *env* gene of HIV-1 transmission pairs and analyze the clinical impact of these mutations.

Objectives

1. To amplify the envelope gene of HIV from the plasma samples of transmission pairs (couples who are both HIV positive), of which one is an elite neutralizer and the other is a non-neutralizer.
2. To identify key mutations in the HIV-1 *env* gene and correlate them with the clinical data.
3. To deduce the amino acid sequence from the gene sequence and look for variations in key neutralization epitopes.

Methodology

Viral RNA was extraction from the plasma of HIV-1-infected transmission pairs and reverse transcribed into cDNA. The *env* gene was amplified by semi-nested PCR. The amplified products were sequenced and analyzed for the presence of key mutations in the neutralizing antibody epitopes. This data was correlated with the *in vitro* neutralization profile and clinical data.

Study progress

The study included two pairs of elite neutralizers and four pairs where one among the transmission pairs in an elite neutralizer while the other is a non-neutralizer. Sequence analysis and clinical correlation analysis is currently ongoing.

VL-10: Molecular and immune profiling in adults affected with COVID-19 disease

Principal Investigator	:	Dr. N.Sudhakar, Scientist B
Participating Institutes	:	ICMR-NIRT, Government Corona Hospital (GCH), Guindy, Chennai
Source of funding	:	Intramural
Study period	:	2020-2022
Category	:	COVID-19

Background

Angiotension converting enzyme 2 (ACE2) is an entry receptor for the binding of SARS CoV-2 to 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. This study aims to understand the significance of ACE-2 and TMPRSS-2 gene expression in COVID-19 affected adults and correlate it with variations in host immune responses as mild, moderate and severe.

Objectives

1. 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.
2. To investigate immune dysregulation and to assess the magnitude of cytokine and chemokine response in COVID-19 infected adults with varying disease severity.
3. To quantify the viral load in COVID-19 affected adults and to correlate it with the immune response and clinical outcome.
4. To decode the transcriptome in PBMC of COVID-19 affected adults and identify altered genes and pathways for the purpose of identifying novel drug targets.

Methodology
This is a prospective study carried out among COVID-19 infected adults. All enrolled participants are 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 is determined using real-time RT-PCR. Levels of cytokines and chemokines is estimated using a multiplex assay on the Luminex platform.

Study progress
The study has recruited 160 adults with mild, 46 with moderate and 34 with severe COVID-19. Twelve milliliters of blood and nasal swab sample were collected from study participants. The results revealed a significant difference in expression of ACE-2 gene in nasal swabs of moderate/severe COVID-19 cases as compared to those with mild COVID-19 disease. In contrast, there was no difference in the expression of TMPRSS2 gene between the different groups. ACE-2/TMPRSS-2 gene expression, immune markers and hematology/biochemical parameters in COVID-19 affected individuals were correlated with clinical outcome. The study is in progress.

VL – 11: 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
Source of funding	:	Intramural
Study period	:	2021-2022
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 against acutely viral infections. An earlier study revealed an impaired anti-SARS-CoV-2 antibody response in non- severe COVID-19 patients with diabetes mellitus. This study aims to compare the immunogenicity of Covishield SARS-CoV-2 vaccine between healthy controls and people with diabetes mellitus.

Objective
To compare the kinetics of anti-spike IgG antibody and neutralizing antibody response to Covishield vaccine between healthy controls and people with diabetes.

Methodology
This is a prospective observational cohort study among individuals with known diabetes mellitus. Healthy controls without

diabetes are included as controls. After recording basic demographic profile, vital signs, and history of diabetes, a prime-boost regimen of Covishield vaccine with two doses was given 12 weeks apart. Venous blood samples were collected at baseline, 14, 28 days after the prime (first) dose, during second dose (booster), one-month post-booster, 3rd. and 6th month post-booster, and at COVID-19 breakdown. The anti-spike IgG antibody and neutralizing antibody levels were measured in plasma samples using commercial kits and the kinetics of the antibody responses were compared with the diabetic and non-diabetic groups.

Study progress

Currently recruitment to the study is still ongoing. 86 participants have been recruited under Diabetic Cohort. 102 participants have been recruited under Non-Diabetic Cohort.

Bioinformatics Division

The research activities of the division are outlined below.

- Establishment of Adult Retinal Pigment Epithelial (Are) Cell lines for transcriptomics studies.
- Structural Analysis and Molecular Dynamics simulation studies of HIV-1 Antisense Protein (ASP).
- *In silico* design and development of oligopeptide mimetics of broadly neutralizing antibodies against HIV.
- Configuration and deployment of small scale GPU based Molecular Dynamics simulations with available Hardware infrastructure.

COMPLETED STUDIES

Title of the project	Name of PI Designation	Source of funding	Category
Development and validation of a diagnostic kit for early detection of HPV infection in cervical cancer	Dr. N. Sudhakar Scientist B	DST-Scheme for Young Scientists and Technologists (SYST)	Cervical cancer

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 field of public health and medicine, and by contributing to the academic, research and professional committees.

Studies in progress

S-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-NIRT
Source of funding	:	ICMR -Adhoc
Study period	:	2020 – 2022
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, Thiruvallur 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 Thiruvallur 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 (Table 1). The study is on-going.

Table 1: Distribution of TB patients interviewed in Chennai and Thiruvallur districts

Time points	Chennai		Thiruvallur	
	New TB patients	MDR-TB patients	New patients	MDR-TB patients
Sample size	80	42	80	42
Initiation of treatment (Baseline)	80	42	80	24
At the end of Intensive Phase of treatment	80	20	80	14
At the end of Continuous phase of Treatment	76	8	78	4
After 3 months of completion of treatment	68	4	67	1

S–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 E
Participating Institutes : ICMR-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

1. To develop a computer assisted screening system to differentiate clinically normal chest x ray from clinically abnormal types.
2. To develop a computer aided detection system that enables auto differentiation of TB from other chest diseases/ other lung diseases using Chest X-rays
3. 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, NIRT must provide 6500 x-ray images to be distributed among the several categories. These x-ray images can be either retrospective or prospective, but we have only gathered retrospective images from the NIRT clinical trials and the national TB prevalence research. Once gathered, these need to go through various processes, like image pre-processing to unify the size, clarity, and quality. We are now pre-processing the images, 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

Title of the project	Name of PI Designation	Source of funding	Category
Development of a Database of Clinical Study X-rays at NIRT, Chennai	Dr C Ponnuraja C Scientist E	ICMR	TB/Build
ICMR-IPR Project of AI tool for Survey X-rays: Phase-I X-Rays Annotation at NIRT, Chennai	Dr C Ponnuraja Scientist E	IPR (Institute of Plasma Research)	X-Ray image Annotation for AI tool for TB diagnosis
A Monte Carlo Simulation approach to compare binary regression models for clinical trials	Dr Adhin Bhaskar, Scientist B	Nil	Biostatistics

DEPARTMENT OF EPIDEMIOLOGY

Studies in progress

E-1: District wise prevalence of microbiologically confirmed pulmonary tuberculosis in Tamil Nadu

Principal Investigator	:	Dr. G. Prathiksha, Scientist C
Participating Institutes	:	State TB Cell, Tamilnadu
Source of funding	:	National Health Mission, Tamilnadu
Study period	:	2021-2022
Category	:	TB
Pillar	:	Detect

Background

The National level TB prevalence survey to estimate the prevalence of microbiologically confirmed pulmonary TB at the National and 20 state/state group levels was recently completed. Estimating the prevalence of TB at District level is equally important to understand the epidemiology of TB locally and for monitoring the activities taken for control of Tuberculosis at the district level. With this background, NIRT in partnership with the Tamil Nadu government has planned to estimate the district level TB burden to monitor the effectiveness of TB control activities.

Objectives

1. To estimate the point prevalence of microbiologically confirmed pulmonary TB among persons aged ≥15 years in all districts of Tamil Nadu.
2. To explore the health seeking behavior of survey participants who are symptomatic and currently on TB treatment
3. To determine the proportion of those currently on TB treatment who were notified to the NTEP surveillance system
4. To estimate the expenditure incurred by survey participants who are currently on TB treatment

Methodology

Cross-sectional study among individuals aged ≥15 years in the selected village / urban census enumeration block. A total of 143 clusters will be surveyed in the state using 5 teams. Each cluster will have a sample size of 800. Eligible participants after obtaining consent will be interviewed at the cluster site. All participants will be offered chest X ray using mobile X- ray vans except pregnant women. Participants who have TB symptoms and/or abnormal chest X-ray will undergo sputum examination. First sample will be tested by CBNAAT and the second specimen by smear and liquid culture to detect TB. Tablets will be used to collect the survey information and the geo- coordinates of the surveyed households. The data collected in the field will be monitored at the central level using the monitoring dashboards

Study progress

Study was initiated in Chennai on February 25th 2021. As of March 2022, 101 were completed and 6 were clusters ongoing.

E–2: Evaluation of information slip method in case finding among contacts of tuberculosis cases at household and community under Programme settings in Tamil Nadu.

Principal Investigator	:	Dr. G. Prathiksha Scientist C
Participating Institutes	:	District TB Cell, Kanchipuram
Source of funding	:	DHR, Grant-in-aid scheme
Study period	:	2020-2022
Category	:	TB
Pillar	:	Detect

Background: Currently the NTEP recommends screening household and close contacts of TB index cases. Close contacts are those who are not in the household but shared an enclosed space, such as a social gathering place, workplace or facility, for extended periods. Close contacts remain a challenging group to be screened in the Programme. It is very difficult to screen these close contacts through the existing system. "Information slips'' have been routinely used in sexually transmitted infections (STI) for contact tracing. The use of such slips in the context of TB case finding is new and it will be a very practical and cost-effective way to screen TB contacts especially, the community contacts which otherwise is very difficult to be captured in the Programme setting.

Objectives

To evaluate the effectiveness of the information slip method in improving the contact tracing and TB case detection among contacts of TB cases at household and community level.

Methodology

This is a Quasi experimental community interventional trial in 2 selected Tuberculosis units (TU) of Kanchipuram district. The sample size is 634 (317 per group). In the intervention TU, TB patients who are willing will be offered small information slips to take to their household and close contacts. These slips will contain a message about symptoms of TB, availability of tests and treatment free of cost in the Programme, importance of testing themselves for TB and inviting the contacts to test for TB. The contacts who report to the centers for screening with the information slips will be interviewed and routine TB testing will be done through the Programme. In the control TU, data from routine contact screening in the Programme will be collected.

Study progress

Study was initiated in October 2020. As of March 2022, 312 cases were recruited in the intervention site and 307 cases were recruited in the control TU. Proportion of contacts screened in the intervention and control arm was 29% (N=91) and 12% (N=307) respectively. The interim analysis show that the contact tracing was higher in the intervention arm than the control arm but the yield of cases due to the intervention did not change much between the two groups.

E–3: **Development and deployment of Artificial Intelligence (AI) aided tool for screening of chest x-ray for enhanced detection of Pulmonary Tuberculosis**

Principal Investigator	:	Dr. Sriram Selvaraju, Scientist D
Participating Institutes	:	Central TB Division, National Informatics Centre, New Delhi
Study period	:	2020-2022
Category	:	TB
Pillar	:	Detect

Background

ICMR-NIRT, CTD and NIC has planned to develop an Artificial Intelligence (AI) tool which could be used in the program and other developing countries for the early diagnosis and treatment of TB and thereby reduce transmission, morbidity and mortality.

Objectives

1. To develop an AI tool for automated reading of chest x-ray to detect abnormalities on radiograph so that more individuals eligible for rapid molecular testing can be identified.
2. To design and integrate the AI tool with Collaborative Digital Diagnosis System (CollabDDS), an NIC developed system.
3. To offer the integrated service in the peripheral public health system free of cost so that any eligible individual with chest x-ray abnormality is automatically linked with appropriate tests and medical care.

Methodology

The methodology involves 4 steps

1. Mobilization of annotated Chest X-Ray
2. Product Development (AI algorithm development and training)
3. Assessment of accuracy (validation and testing tool)
4. Deployment of AI tool Expected outcomes include
    1. Third party validated AI tool with minimum sensitivity of >90% to detect abnormality on digital chest x-ray image; integrated with CollabDDS, ready to use in public sector health facilities.
    2. Joint patent filed for this AI based automated reading of Chest X-ray tool for TB screening by CTD, NIC and ICMR-NIRT.
    3. Validated 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.

Study progress

The study was initiated in 2022 and the software development is ongoing

COMPLETED STUDIES

Title of the project	Name of PI Designation	Source of funding	Category/Pillar
Sentinel surveillance for measuring the TB burden and trends in high-risk group for TB	Dr Shrinivasa B M, Scientist 'C'	Central TB Division and Global Fund to fight AIDS, Tuberculosis and Malaria.	TB/ Detect and Build
National Survey for state-wise prevalence of microbiologically confirmed pulmonary tuberculosis in India	Dr.Sriram Selvaraju Scientist D	Central TB Division through DHR-ICMR	TB / Detect

DEPARTMENT OF HEALTH ECONOMICS

DEPARTMENT OVERVIEW AND MANDATES

Health Economics is increasingly recognized in public health and health research settings. Health Economics is now foundational and integral to healthcare decision-making at every level. In this background a Department of Health Economics was established in ICMR-NIRT, Chennai in 2018. The mandate of the department is to conduct research on economic aspects of diseases with focus on tuberculosis. In addition, the department is providing their technical support to generate Evidence from Health Economics to make policy decisions relating to drugs, devices, treatment pathways, and preventative health intervention strategies. One of the key mandates of the 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.

Studies in progress

HE - 1: The Evaluation of a standard treatment regimen of anti-tuberculosis drugs for patients with MDR-TB Stage II (STREAM II) – Health Economics Component

Principal Investigator	:	Dr. M Muniyandi Scientist D
Participating institutes	:	ICMR-NIRT
Source of funding	:	Liverpool School of Tropical Medicine, UK
Study period	:	2018-2022
Category	:	TB
Pillar	:	Treat

Background

Despite the widespread availability of an efficacious and affordable regimen and strategy for managing drug-susceptible tuberculosis (TB), the emergence of multidrug-resistant TB (MDR-TB) remains a major challenge for global TB control efforts. The STREAM II trial is assessing the efficacy of shorter MDR-TB regimens. The health economics component of the STREAM II trial in India is aiming to assess the impact of four alternative MDR-TB regimens.

Objectives

1. To assess the costs (direct and indirect) imposed on patients enrolled in the study based on MDR- TB treatment regimen.
2. To assess changes to employment, socioeconomic status and financial well-being on patients enrolled in the study by MDR-TB treatment regimen.
3. To assess health-related quality of life during treatment, and its relation to regimen and adverse events.
4. To assess the health system resources required to provide MDR-TB treatment and associated patient care by MDR-TB treatment regimen.

Methodology

A societal perspective will be taken, so that health systems and patient costs are included. The participants of this study will be patients with MDR-TB in the STREAM II trial and caregivers. Data related to the health system and patient costs will be collected. For the health system, we need to estimate costs based on the quantities of resources consumed in the system for delivering different treatment regimens and the prices of those resources. For patients, we need to understand the economic benefits, if any that one regimen has over the other through estimating the costs patients incur throughout the treatment period and how such expense affects the lives and livelihoods of patients of different socio-economic status. An additional analysis of health-related quality of life (HRQoL) will also be conducted; data for this will be collected using the EQ5D-5L tool at the same time as the health system and patient cost data. The main health economics-related outcomes will be mean incremental costs incurred by patients, the incremental cost to the health system by the study regimen compared with the control regimen.

Study progress

We have collected information from a total of 49 patients enrolled in the main STEAM trail. Basic information on socio-economic status is completed for all patients. Data collection on costs for treatment, follow-up, health status and quality of life is in progress.

HE-2 : The potential impact of COVID-19 pandemic on tuberculosis epidemic

Principal Investigator	:	Dr. M Muniyandi Scientist D
Participating institutes	:	ICMR-NIRT
Source of funding	:	Operational Research Program – Tamil Nadu Health System Reform Program (TNHSRP) Coordinated by IITM, Chennai
Study period	:	2021-2022
Category	:	TB
Pillar	:	Treat

Background

The novel coronavirus (COVID-19) pandemic is a major source of disaster in the 21st century and it has caused enormous health, demographic, social and economic impacts. In the absence of pharmaceutical interventions, many countries have resorted to population wide lockdowns to slow the spread of the virus and to allow their health systems to cope. These lockdowns have had an important effect on SARS-CoV-2 transmission. However, unintended consequences are inevitable with such sweeping measures. In low- and middle-income countries with health systems already under strain, the adverse effects of disruptions in health services Include ongoing transmission of infectious diseases. India has one of the largest numbers of people with latent TB infection and the large burden of active TB an estimated 354 million persons across all ages. The COVID-19 pandemic has resulted in both a health shock and an economic shock. The lockdown in response to the pandemic and the events related to it can have an adverse epidemiologic impact on TB incidence.

Objectives

1. To estimate the prevalence and incidence of TB before and after Covid-19 pandemic in Tamil Nadu
2. To find out the notification trend of pulmonary TB cases before and after Covid-19 pandemic in Tamil Nadu

Methodology

A mathematical modelling approach will be used for this study. This mathematical framework will represent variables and their interrelationships to describe observed phenomena in the TB cascade during the COVID–19 pandemic. We will collect both primary data points from the national level and state level surveys and secondary data points from the published reports and literatures. We will adapt mathematical model of TB transmission to incorporate lockdown associated disruptions in the TB care cascade.. It is planned to model the impact of disruptions on TB incidence, prevalence and mortality and we will consider potential interventions to curtail this impact.

Study Progress: Data collection is in progress.

HE–3: Establishment of Regional Resource Centre for Health Technology Assessment in India (HTA-In)

Principal Investigator	:	Dr. M Muniyandi Scientist D
Participating institutes	:	ICMR-NIRT
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 HTAIn is to design and institutionalize best international practice which features transparent, inclusive, fair, and evidence-based decisions. HTA evidence would serve as an important tool in prioritizing 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, HTAIn is making evidence-based recommendations to the Government of 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 patient's clinical needs and circumstances.

Activities of ICMR-NIRT

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 the introduction and assessment of new and existing health technologies in the system and provide support for the adoption of health technologies.
3. This resource center will undertake HTA in terms of medical effectiveness, cost- effectiveness, appropriateness, efficacy, and 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 the public health domain.

Study Progress

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

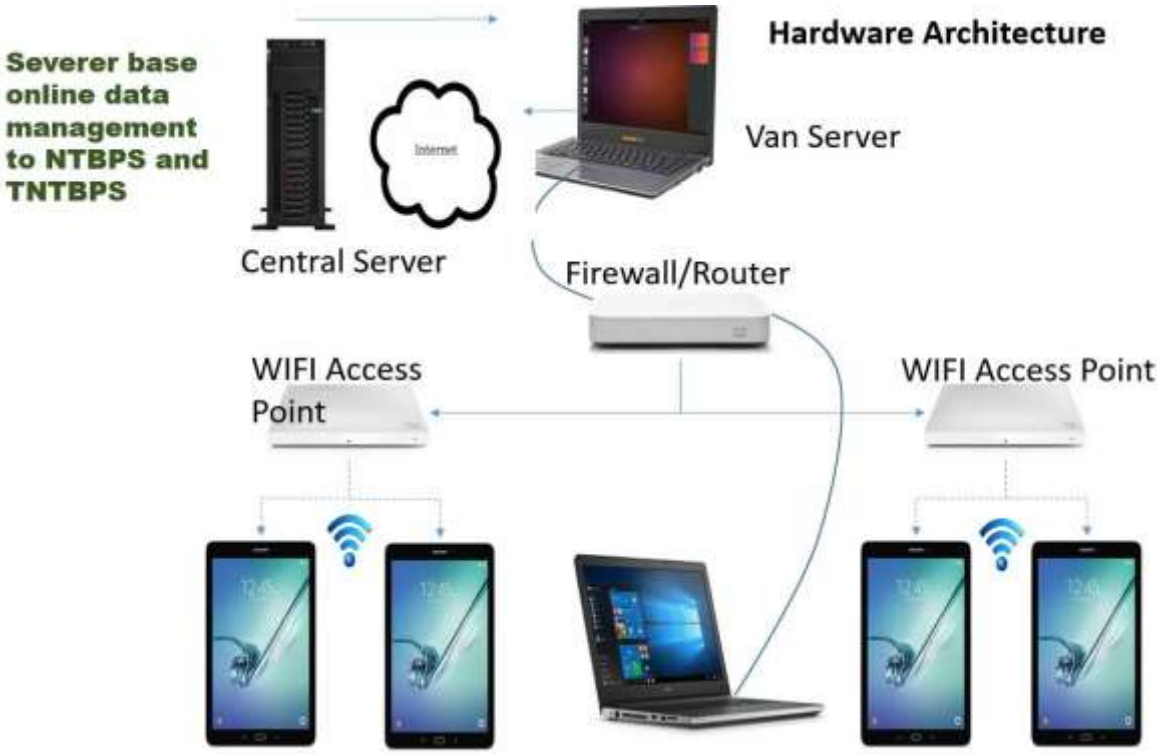
ELECTRONIC DATA PROCESSING DIVISION

DIVISION OVERVIEW AND ACTIVITIES

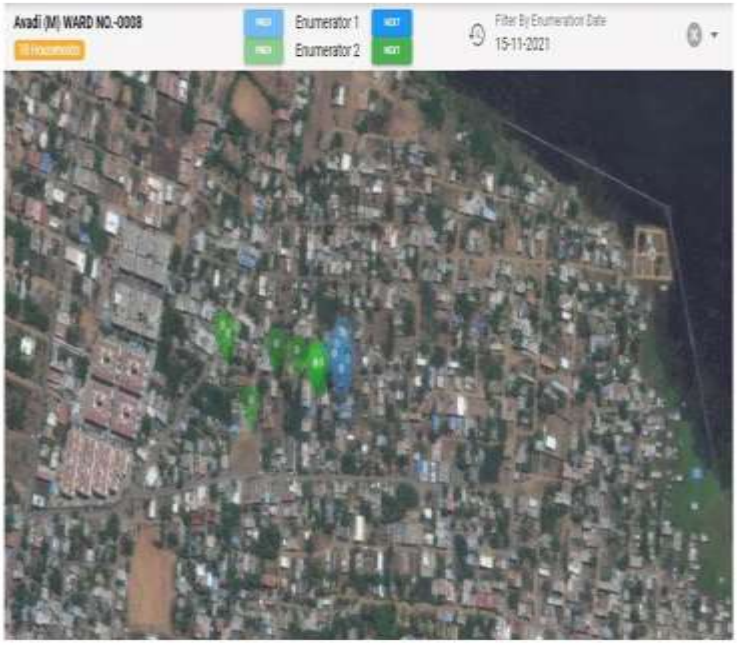
The Division is primarily involved in the quality control of the data collection process in prevalence surveys and data management. During the period, the division has taken part in server setup, server monitoring, and data management for the TB prevalence survey, which included continuous monitoring of the fieldwork, data flow, data quality check, positivity intimation, and data consolidation report. It aims to function as a resource center and to render high-quality statistical analytical support for epidemiological health research, and thereby strengthening the mission of TB elimination in India.

Online data management of the following projects

1. District wise prevalence of microbiologically confirmed pulmonary tuberculosis in Tamil Nadu.
2. The RATIONS (Reducing Activation of Tuberculosis by Improvement of Nutritional Status) study
3. Regional Prospective Observational Research for Tuberculosis (RePORT) Consortium (RePORT International Common Protocol)



Day – 1 [Starting New Cluster]



Last Day [Before closing the cluster]

GIS Team monitoring process

INTERNATIONAL CENTRE FOR EXCELLENCE IN RESEARCH (ICER)

DEPARTMENT OVERVIEW AND MANDATES

The India ICER program in Chennai, is a formal collaboration between the NIAID-NIH, USA and the ICMR-NIRT, India with the following mandates

1. To develop a sustained research program in areas of high infectious disease burden through partnerships with scientists and physicians in US and India.

2. To partner with in-country scientists to address major endemic diseases and foster research in areas such as helminth infections, HIV, COVID-19 and tuberculosis.

3. To build capacity of scientists to tackle emerging and re-emerging infectious diseases in the future

Studies in progress

ICER - 1: Title: 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	:	NIH-NIAID
Source of funding	:	NIH-ICER
Study period	:	2020-2025
Category	:	TB
Pillar	:	Detect

Background

Approximately 2 billion people worldwide are infected with *Mycobacterium tuberculosis*, with 90% of individuals having a latent tuberculosis infection (LTBI). Among the various risk factors that are known to play a role in promoting active TB, HIV is the most studied and described. However, in low-HIV-endemic countries like India, other risk factors might play a more prominent role in active TB pathogenesis. 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, it is imperative to study the pathogenesis of TB infection and disease in these "at-risk" populations.

Objectives

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

Methodology

This is a cross-sectional study to identify individuals with LTBI and coinfections/ comorbidities: malnutrition; DM; and helminth infections Approximately, 5000 individuals in the age group of 14- 65 years from Thiruvallur district 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 for active TB will be screened for LTBI by interferon-gamma (IFNγ) release assay (IGRA), screened for SARS-CoV2 antibodies, assessed for malnutrition (by body mass index [BMI]), evaluated for DM status (by hemoglobin A1c [HbA1c] levels), and evaluated for helminth infection (by serology and stool quantitative polymerase chain reaction [qPCR]). 300 individuals who are eligible will be assigned to one of six study groups based on LTBI status and presence of coinfections/comorbidities. Participants will have an additional study visit within 6 months of screening for clinical assessment and collection of blood, urine, and stool samples for experimental studies and storage for future research. Key evaluations will include gene expression analyses and immunophenotyping on blood samples.

Study progress

We have screened 632 and enrolled 13 participants in the study. The study is ongoing.

ICER–2 : Title: Regional Prospective Observational Research in Tuberculosis (RePORT) - Phase 2

Principal Investigator	:	Dr. Subash Babu, Scientific-Director
Participating institutes	:	MVDRC
Source of funding	:	Department of Biotechnology and NIAID
Study period	:	2021-2026
Category	:	TB
Pillar	:	Detect/Prevent

Background

India ranks number one in global tuberculosis (TB) burden and accounts for 26% of all cases—2.7 million occurring annually. Furthermore, 27% of India's 1.3 billion population is estimated to be latently infected with *Mycobacterium tuberculosis* and at risk of developing active TB disease. To accomplish the target of TB elimination, research is warranted in the development of rapid, sensitive, low-cost TB diagnostics; identification of biomarkers to assess the response to TB treatment and the risk of developing disease, and a deeper understanding of TB immunology and pathogenesis to inform vaccine development.

Objectives

1. Evaluate novel diagnostics and biomarkers of diverse states of *Mycobacterium tuberculosis* infection.
2. Identify markers for TB treatment response.
3. Identify markers of lung injury associated with unfavorable TB treatment outcomes
4. Examine mechanisms of protection against TB in exposed persons.
5. Identify immunologic markers of persons at highest risk of progression from latent TB infection to TB disease.

Methodology

The study design involves establishment of two prospective, observational cohorts for collection of specimens and associated data; and analysis of stored specimens and relevant data. Study population involves adult participants enrolled in the following study cohorts [1] Diagnostic (Dx) Cohort: participants with suspected TB (all age groups) [n=200] [2] Cohort A: active TB patients (> 15years) [n=60]. From the enrolled study participants, we will compare blood RNA and plasma cytokine biomarkers that assess inflammation, indirectly reflect bacterial burden and show promise for predicting cure. Candidate methods will be tested with existing Parent and Common Protocol RNA and plasma samples, along with 400 of the 588 newly recruited adult PTB participants to fill gaps in the prior study design and develop new resources in India. Testing several methods in parallel allows comparison of accuracy and potential for advancement to a point-of-care (POC) diagnostic test. Cases of microbiologically confirmed treatment failure and TB recurrence within 12 months after treatment will be compared to controls with lasting cure, matched for sex, age, and site. We will also perform an exploratory plasma proteomics study of TB recurrence prediction in 30 recurrence cases and 30 age and sex-matched controls.

Study progress

We have recruited 11 individuals in the diagnostic cohort and 2 individuals in cohort A.

ICER- 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	:	NIH-NIAID
Source of funding	:	NIH-ICER
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. It is currently thought that the severe inflammation is primarily driven by the host response and the result of a dysregulated "cytokine storm" that persists after activation by the virus. Whether this 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.

Methodology

This is a pilot, community-based, cross-sectional study, to characterize the immune response and intestinal microbiota in people with and without SARS-CoV-2 antibodies and helminth infection. Approximately, 1500 individuals (aged ≥5 years) from Thiruvallur district with or without severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies and helminth infection will be screened. Participants will undergo a one-time blood and stool collection SARS-CoV-2 antibody testing and experimental studies including transcriptomics will be done in collected blood samples. Stool will be used to diagnose parasitic infections and to conduct microbiome 16S sequencing and meta transcriptomics. PBMCs will be assessed by multipara meter (N>40 parameters) flow cytometry for cytokine responses in innate and adaptive immune cells after stimulation with lipopolysaccharide- and SARS-CoV-2–specific T-cell epitopes. PBMC samples will be used for single-cell RNA sequencing approaches of batched and hash-tagged samples to determine transcriptional profiles, cell surface marker expression, and T-cell receptor usage in the T-cell populations. Plasma samples will be measured by Luminex to determine levels of circulating cytokines and chemokines.

Study progress

We have screened 822 and enrolled 625 participants. The study is ongoing.

COMPLETED STUDIES

Title of the project	Name of PI Designation	Source of funding	Category
Humoral and cellular immune response among recovered COVID-19 patients: A cross-sectional study, Thiruvallur district and Chennai, Tamil Nadu, India.	Dr. Subash Babu, Scientific Director, Dr N Pavan Kumar, Scientist C Dr Jeromie Wesley Vivian Thangaraj Scientist C.	NIH-ICER and ICMR-NIE	COVID-19
Study to evaluate the effectiveness of BCG vaccine in reducing morbidity and mortality in elderly individuals in COVID-19 hotspots in India.	Dr. C. Padma Priyadarshini, Director Dr. Subash Babu, Scientific Director.	ICMR	COVID-19
An observational study of clinical and immunological features of children with SARS-COV-2 (COVID-19) infection.	Dr. Aishwarya Venkataraman, Scientist E Dr. Subash Babu, Scientific Director	NIH-ICER	COVID-19
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 Dr. V. Aishwarya, Scientist E	NIH-ICER	COVID-19

LIBRARY AND INFORMATION CENTRE

NIRT LIBRARY

NIRT Hybrid Library continues to expand with exciting new digital tools for the scientists of NIRT to expand their research. Our electronic collection of journals, books, and archives is unique in respiratory health areas. The library has always been instrumental in supporting research. Our Valued Services provide excellence and commitment to quality information services to our researchers and scholars.

VALUED SERVICES

Digital Library *(established in 2001)*Portal has been updated

1. Annual Reports
2. Catalogue (OPAC)
3. E-Books
4. E-Journals (*including Archives*)
5. Library Forms
6. E-Office interlink for File Management System (Firefox)
7. ICMR e-Consortium
8. Impact Factor (*by Clarivate Analytics - a Web of Science Group)*
9. **Institutional Scholarship Repository***(it keeps getting updated/uploaded with full-text publications with copyright policy)*
10. IRINS *(Indian Research Information Network System),*
11. iThenticate *(plagiarism software)*
12. NIH Library
13. Open Access Resources
14. Predatory Journals
15. Science Citation Index
16. Specialised Databases
17. STHIRA (*a tool for*
18. Tamizh Books
19. Tuberculosis Links

1. **Automation**: Electronic Check-in and Check-out services since 2002
2. NIRT Library took initiative for NIRT to become the part of **IRINS** (Indian Research Information Network System) database. This portal facilitates the NIRT Scientists to collect, curate and showcase their scholarly communication activities and provides an opportunity to create a scholarly network.

Selective **D**issemination of **I**nformation (**SDI**) Service

1. e-Publications
2. Information Resources/Journal Articles Published (*on Tuberculosis, COVID-19, HIV*)
3. Digital Document Delivery Service *(DDDS)*
4. Literature search

5. Reference Assistance (*Face-to-face, Telephone, E-Mail*)
6. Resource Sharing (*ICMR; NIH*)

Current **A**wareness **S**ervice (**CAS**) – Daily Service**:**
Digital Information Alert Services on
Press Clippings New Article(s) Alert Online First Article Accepted Manuscript(s) online In Press High Impact Articles Table of Contents Weekly Updates Monthly Updates
Information about Awards, Conferences, Seminars, Workshops, Webinars etc.

E-PUBLICATIONS

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

CONTRIBUTION TO NATIONAL PROGRAMME

NATIONAL TB ELIMINATION PROGRAM ACTIVITIES IN ICMR-NIRT NATIONAL REFERENCE LABORATORY

Contact person: Dr. Padmapriyadarsini. C and Dr. Sivakumar. S
Source of Funding: Central TB Division, Ministry of Health & Family Welfare, New Delhi

National Institute for Research in Tuberculosis (NIRT), Chennai is one of the National Reference Laboratory (NRL) for Tuberculosis, which closely monitors five states (Andhra Pradesh, Gujarat, Kerala, Tamil Nadu, Telangana state) and five Union territories (Andaman & Nicobar, Puducherry, Lakshadweep, Daman & Diu and Dadra & Nagar Haveli) in India for NTEP activities.

Microbiologists visit the assigned states at least once a year for onsite evaluation (OSE) for monitoring human resource, BSL facilities, EQA activities of NAAT, smear microscopy, culture and DST by both phenotypic and genotypic methods as per the NTEP protocol. During OSE visit, NRL microbiologist provides technical support for establishing quality assured smear microscopy, NAAT facilities, 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 for patient management under NTEP. NRL also undertakes yearly proficiency testing of IRL and Culture and Drug susceptibility testing labs as part of the certification and renewal process under NTEP.

Seven IRLs, 13 C & DST labs have been certified and 7 C& DST labs certification is in progress for diagnosis of DR-TB patients from aforementioned states.

During 2021-2022, the Institute conducted 13th round of proficiency testing for 26 labs including Five NRLs in India, with panel of 20 cultures for susceptibility testing for both first and second-line anti-TB drugs (including newer drugs) by genotypic and phenotypic methods. Based on the proficiency results, three Culture and DST laboratories (RDT Bathalapalli, AP, GMC, Surat, Gujarat and CMC Vellore and GHTM Tambaram, Tamil Nadu) received the first certification for LPA and Liquid culture. Retesting process has been completed for two Culture and DST laboratories (GHTM, Tambaram and CMC, Vellore, Tamil Nadu) for certification by both Liquid and LPA. Assessment visit has been conducted for three Culture and DST labs as part of certification process.

As part of PMDT activities, the Institute is supporting 10 districts of Tamil Nadu for diagnosis of DR-TB patients by both first and second-line DST in NTEP settings. A total of 5458 samples were received for DR-TB diagnosis and 1379 samples received for follow up cultures from 10 districts of Tamil Nadu. As part of NRL EQA activities, On Site Evaluation (OSE) of sputum microscopy, NAAT sites and Culture and DST lab have been conducted by NRL team for three states, Tamil Nadu, Kerala, Puducherry and 165 panel slides were used to assess the proficiency of 33 laboratory personnel for smear microscopy. The training on

NAAT and Culture and DST by LPA and Liquid were provided (Virtual, campus and on-site) for 516 laboratory personnel from four states of India.

Regional Reference Lab for the National AIDS Control Organization

The Regional Reference Lab for NACO, which is a part of the Department of Virology and Biotechnology, has continued to provide support for NACO's Early Infant Diagnosis (EID) program and National ART program. For the EID program, the lab has received and tested a total of 2968 DBS samples for HIV-1 total nucleic acid by PCR 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 5577 samples for HIV-1 viral load from various districts of Tamil Nadu as well as from Andamans during the period of report.

COVID-19 response

NIRT responded to Coronavirus Pandemic by providing services and support in several fronts during the last year, including COVID-19 testing during the 2nd and 3rd waves of the pandemic, SARS-CoV-2 genomic surveillance, COVID vaccine trial and basic research. NIRT also served as one of the four Central Depots for COVID reagents for ICMR.

BUILDING COHORTS, BIOREPOSITORY AND LABORATORY CAPACITY

Studies in progress

LC-1 : Central TB Biorepository for Regional Prospective observational Research in TB (RePORT) India Phase II

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Participating institutes	:	ICMR-NIRT
Source of funding	:	DBT
Study period	:	2022-2026
Category	:	TB
Pillar	:	Build

Background

The RePORT India Consortium is a bi-lateral, multi-organizational collaborative effort that was established under the Indo-U.S. Vaccine Action Program (VAP) to address the threat of TB that affects the lives and well-being of people in India and across the globe, and poses an increased risk for persons living with HIV. As part of this program, well characterized biological specimens collected longitudinally from cohorts of TB patients and their household contacts is being stored in the Central TB Biorepository which was set up at ICMR-NIRT in 2017. The specimens stored in the Biorepository will be utilized for undertaking path breaking TB research under 5 specific aims listed below.

Objectives

1. To evaluate novel diagnostics and biomarkers for diverse states of *Mycobacterium tuberculosis* infection.
2. To identify markers of treatment response.
3. To identify markers of lung injury associated with unfavorable TB treatment outcomes.
4. To examine mechanisms of protection against TB in exposed persons.
5. To identify immunologic markers of progression of latent TB infection to active TB disease.

Methodology

Various types of biospecimens including whole blood for DNA, PBMC, plasma, urine, saliva, sputum, *M. tuberculosis* isolates, QuantiFERON supernatants, whole blood in PAXgene tubes for RNA, as well as linked data are collected from cohorts of presumptive TB cases (Diagnostic cohort), newly diagnosed TB patients (Cohort A) and healthy household contacts of TB patients (Cohort B), using harmonized standard operating procedures and data collection forms. The samples are shipped from the clinical research sites (CRS) to the Central Biorepository in dry ice for long term storage.

Study progress

Nine CRS spread throughout India are working in collaboration to implement the Common Protocol of the RePORT India Consortium. Biospecimens sent to the Central Biorepository from the CRS are stored at appropriate temperatures in calibrated storage equipment. Sample inventory and chain of custody of the samples in the Biorepository is maintained through a cloud-based specimen inventory management system called the Freezer PRO. Investigators with protocols approved by the RePORT India Executive Committee can submit their request for specimens to the Biorepository in the specified format along with required regulatory approvals and the Biorepository will disburse the specimens after signing of MTA between the two parties.

LC- 2: Cohorts for HIV Resistance and Progression in Indian Children and Adults (CoHRPICA)/National HIV Cohort Program

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Participating institutes	:	ICMR-NIRT, ICMR-NIE, ICMR-NARI, YRG CARE,
IGICH Source of funding	:	ICMR/DBT/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.

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.

Methodology

The study targets 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). Collection of data and biological specimens from enrolled participants is as per well-standardized templates and procedures that have been harmonized across the participating sites.

Study progress

The study has enrolled 125 participants into the HIV-uninfected (MSM/TG) cohort and 47 participants into the HIV-infected cohort, of which, 33 had no co-morbidities, 9 had tuberculosis and 5 had diabetes. Recruitment into both cohorts is ongoing.

LC- 3 : NIRT BMC (Peripheral Blood Mononuclear Cells) Cryopreservation Proficiency Testing Program

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Participating institutes	:	ICMR-NIRT
Source of funding	:	NIH-CRDF
Study period	:	2017-2022
Category	:	TB
Pillar	:	Build

Background
The quality of cryopreserved PBMC is of utmost importance for the successful conduct of meaningful immunological studies. Hence ongoing proficiency testing of labs involved in preparation and cryopreservation of PBMC is very crucial. NIRT has been successfully implementing the in-country PBMC PT program since 2017 for the clinical research sites preparing and storing PBMC for the RePORT India TB Consortium.

Objectives
1. To assess a laboratory's ability to provide good quality PBMC for future research.
2. To respond quickly and appropriately to poor performance.

Methodology
Six laboratories processing PBMC for the RePORT India Consortium - CMC, MVDRC, JIPMER, BJMC, BMMRC and NIRT, are enrolled in this program. Four quarterly surveys are rolled out each year. For every quarter, the participating lab is required to prepare and send two aliquots of frozen PBMC (each containing ~5.0x10^6 cells/ml) from each of two donors. The NIRT PT Laboratory receives the PBMC, stores them in liquid nitrogen (-196°C) for a week, thaws them and scores them for viability as well as recovery. The performance scores are shared with the respective labs as well site PIs.

Study progress
The Program successfully administered 4 quarterly surveys during the last year to the 6 participating sites. Scores were shared with the sites, and sites requiring refresher training or assistance with trouble shooting were provided the required support.

LC- 4 : Virus Research and Diagnostic Laboratory (VRDL)

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist F
Participating institutes	:	ICMR-NIRT
Source of funding	:	DHR
Study period	:	2021-2026
Category	:	Viruses

Background
In the year 2000, a separate HIV/AIDS Department was established at ICMR-NIRT to support clinical trials for the management and prevention of TB in HIV/AIDS patients and to undertake basic research in the immunopathogenesis of HIV-TB co infection. Since then, the Department expanded its activities into HIV virology research and developed adequate infrastructure for virology work including a BSL-II plus laboratory, molecular biology laboratory, viral load testing facility, sequencing facility, diagnostic serology laboratory and cellular immunology laboratory. Given our longstanding expertise in viral research, we submitted an application for a medical college level VRDL at the NIRT Thiruvallur site, which was considered favorably and approved for funding.

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

Progress
The old lab building at NIRT-Thiruvallur is being renovated and refurbished as the new VRDL. Staff recruitment and procurement of equipment are in process. The VRDL is expected to become fully functional by the end of this year.

TRANSLATIONAL VALUE OF RESEARCH PROJECTS

Translational value of Research projects – 2021-22

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.

National TB Prevalence Survey in India

ICMR-NIRT coordinated one of the world's largest TB prevalence survey from 2019 to 2021. The survey estimated the point prevalence of microbiologically confirmed pulmonary TB (PTB) among persons aged ≥15 years in India at the national level and for 20 individual states / state groups. In addition, the health-seeking behaviour and the prevalence of TB infection were studied. Prevalence of microbiologically confirmed pulmonary TB among 15 years and above in India was 316/lakh population for the period 2021. Prevalence of TB was associated with past history of TB treatment, older age group, malnourished, known diabetics, smokers and alcohol users. Majority (64%) of symptomatic population did not seek health care. Among the 36% of survey participants who sought care for their symptoms, there was equal preference for government and private facilities. The findings from this survey have implications for focussed interventions to reduce TB disease burden in India.

TB diagnosis

1. 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.

2. 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.

3. 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.

4. 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.

TB treatment

1. The multi-country SHINE Study in which our Centre participated concluded that the four-month treatment was as good as the standard six-month treatment for children with minimal TB and this is incorporated in the WHO treatment guidelines.

2. HICON-R study which was initiated and coordinated by our Centre observed early and faster sputum culture conversion, with similar adverse events as compared to conventional dose, suggesting 25mg/kg/day rifampicin containing regimen can be considered in the treatment of pulmonary TB patients.

3. Evidence for shorter regimen will be provided from the ongoing study with 4 -month moxifloxacin containing regimen in drug sensitive pulmonary TB.

4. The results from the following ongoing studies will have implications in the treatment of drug resistant TB patients

    a. 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.

    b. 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

    c. Evaluation of a Standard Treatment Regimen of Anti-tuberculosis drugs for patients with MDR-TB (STREAM – Stage 2)

    d. A quantitative scale for measuring the patient-perceived quality of care in public and public-private mix care settings for TB has been developed and validated. The tool could be used for evaluating the quality of services for TB patients from a patient perspective.

    e. Filed patent titled “Efficay enhancement of quinone molecules in combination with isoniazid and rifampcin”; Application number 202141033473 dated 26 July 2021. The present invention relates in the field of pharmaceuticals in particularly drug discovery for the treatment of drug resistant tuberculosis. More particularly, it relates to the efficacy of the quinone compounds in combination with isoniazid (INH) and rifampicin (RIF) for the treatment of multidrug resistant tuberculosis (MDR-TB).

    f. Adequate blood drug levels are essential to achieve the desired effect of the drug. Bioavailability of fixed-dose combination (FDC) of first-line anti-TB drugs in patients will provide evidence for drug levels with the currently used FDC.

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.

APPENDICES

LIST OF PUBLICATION FOR THE YEAR 2021-2022

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Workshop(s)/Symposium/OtherEvents

DetailsavailableatNIRTWebpage: http://www.nirt.res.in/html/events.htm

StaffList

DetailsavailableatNIRTWebpage: 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	Y Mary Rebecca	Hemanth Kumar AK Clinical Research	Dr.M.G.R. Medical University	Ph.D.	Full-time	Pharmacokinetic drug-drug interactions between first-line anti-TB and anti-diabetic drugs	Intramural	Completed
2	V Sudha	Hemanth Kumar AK Biochemistry	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
3	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
4	A Vijayakumar	Hemanth Kumar AK Microbiology	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

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	Kadar Moideen. A	Dr. Ramalingam ICER	University of Madras	Ph.D	Full-time	Exploration of immunological biomarkers for pulmonary Tuberculosis	ICER	Ongoing
6.	Arul Nancy. P	Dr. Ramalingam ICER	University of Madras	Ph.D	Full-time	Characterization of host immune response to unfavourable outcomes in Tuberculosis.	ICER	Ongoing
7.	Bindu. D	Dr. Subash Babu ICER	NA	Post Doc	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	ICER	Ongoing
8.	Saravanan. M	Dr. Subash Babu ICER	NA	Post Doc	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
9.	Gokul Raj. K	Dr. Subash Babu ICER	NA	RA	Full-time	Effect of Pre-Diabetes on Immune responses in Latent and Active Tuberculosis.	DBT	Completed
10.	Dr. A. Nusrath Unissa	Dr. LE Hanna Dept. of Virology & Biotechnology	NA	RA	Full time	Impact of HIV infection and antiretroviral therapy on biomarkers for premature onset of aging-associated disorders	ICMR	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
11.	Mr. B. Aanand Sonawane	Dr. LE Hanna Dept.of immunology	University of Madras	PhD	Full time	Molecular mechanisms of HIV pathogenesis in target cells	CSIR	Ongoing
12.	Mr. Deepak Selvam	Dr. LE Hanna Dept.of immunology	University of Madras	PhD	Full time	Generation of stable lactic acid bacteria strains for enhanced DNA stability and protein expression	ICMR	Ongoing
13.	Ms. Evangeline Ann Daniel	Dr. LE Hanna Dept.of immunology	University of Madras	PhD	Full time	Identification of biomarkers that can predict progression from latent tuberculosis infection to active disease	DST INSPIRE	Ongoing
14.	Mr. S. Balakumaran	Dr. LE Hanna Dept.of immunology		PhD	Full time	Pre-mRNA editing of HIV-1 using adenosine deaminase acting on RNA (ADAR)	ICMR	Ongoing
15.	Ms. Sandhya V	Dr. LE Hanna Dept.of immunology	University of Madras	PhD	Full time	Isolation and characterisation of broadly neutralising antibodies from HIV infected elite neutralizers	DBT	Ongoing
16.	Mr. Michel Premkumar	Dr Sivakumar Bacteriology	University of Madras	PhD	Part-time	Rapid Diagnosis and drug susceptibility testing of Mycobacterium tuberculosis	Intramural	Ongoing
17.	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
18.	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
19.	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

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
20.	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
21.	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
22.	Dr. Sam Ebenezer	Dr. V. N. Azger Dusthackeer Bacteriology	NA	ICMR-PDF	Full time	AStudyontheStrainspecificModulationofTuberculosisgranulomatousreactionusing*in-vitro* 3D granuloma model	ICMR	Completed
23.	Dr.Christy Rosaline	Dr. V. N. Azger Dusthackeer Bacteriology	NA.	ICMR-RA	Full time	Isolation and Analysis of *Mycobacterium tuberculosis*-Induced-MMPs directly fromsputum samples: Inhibitorsynthesizing and validation	ICMR	Ongoing
24.	Dr. E. Padmasini	Dr. V. N. Azger Dusthackeer Bacteriology	NA	ICMR-RA	Full time	Role of membrane proteins responsible for drug efflux mechanisms in Mycobacterium tuberculosis	ICMR	Ongoing
25.	Shaik Fayaz Ahamed	Dr. C. Ponnuraja Statistics	Madras university	Ph.D	Full Time	Flexible machine learning methods for survival analysis of high dimensional clinical trial health care data	Abricot	Ongoing
26.	JSV Soundarya	Dr.K.R. Uma Devi Immunology	University of Madras	Ph.D	Full time	Attenuated Mycobacterial based vaccine against tuberculosis with a novel strategy for T cell priming	ICMR	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
27.	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
28.	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
29.	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
30.	Arul Nancy	Dr. Ramalingam B Immunology	University of Madras	Ph.D	Full Time	Characterization of host immune response to unfavourable treatment outcomes in tuberculosis	ICER	Ongoing
31.	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
32.	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
33.	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

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
34.	Ms. Bhargavi	Dr. P. Kannan Immunology	Madras University	PhD	Full time	Functional Characterisation of oxidoreductase Rv 0148 and Alkylhydroperoxidase Rv2159 of Mycobacterium tuberculosis'	DST Inspire	Ongoing
35.	Mrs. Ananthi	Dr. P. Kannan Immunology	Madras University	PhD	Full time	Study on Mutations Associated with Pyrazinamide Resistance in Mycobacterium tuberculosis	ICMR	Ongoing
36.	Ms. R. Harini	Dr. P. Kannan Immunology	Madras University	PhD	Full time	Comparative genomics of Mycobacterium tuberculosis complex isolates from animals	ICMR	Ongoing
37.	Dr.S.Sriram	Dr.N.Gopalan Immunology & Public health	Central University of TamilNadu	PhD	Part time	To be finalised	To be finalised	To be initiated
38.	Mr. T. Kannan	Dr. K Rajendran Department of Statistics Section, Epidemiology Unit	Madras University	PhD	Part time	An evaluation of predictive statistical data mining techniques	ICMR	Ongoing

OBITUARY

NAME AND THE DESIGNATION	DEPARTMENT	DATE OF DEATH
Mr. S. Sriramachandran, Ex-Senior Technician (2)	Transport	19.04.2021
Mr. B. Vijayakumar, Ex-Senior Technician (3)	Transport	21.04.2021
Mr. V. Partheeban, Ex-Senior Technician (3)	Field Unit, Epidemiology	24.05.2021
Mr. D. Sukumar, Ex- UDC	Administration	11.06.2021

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