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NIRT
NATIONAL INSTITUTE FOR
RESEARCH IN TUBERCULOSIS

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

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

ANNUAL REPORT
2020 - 2021

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

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Report of Research Activities

PREFACE

I am happy to present to you ICMR-NIRT's Annual Report for the year 2020-2021. Amidst the difficult and dark times of COVID-19 pandemic, ICMR-NIRT contributed significantly to the control of this pandemic both by research and service. I take this opportunity to pay my respects to all our beloved colleagues, both current and retired NIRT staff, whom we lost to this disease during this period. I also want to extend my sincere gratitude to each and every Staff of NIRT who worked tirelessly during this pandemic to help ICMR curb this menace.

This edition of the Annual Report highlights the contribution of NIRT to the advancement of COVID-19 and TB research in the last 1-year. Few highlights of our activities during 2020-2021 include:

- Successfully completed enrolment to the country's largest TB Preventive vaccine trial
- Completed 3-rounds of National and 2-rounds of Chennai COVID sero-survey
- Conducted successfully the first Nation-wide state-wise TB prevalence survey
- Conducted study on repurposing of BCG vaccine for elderly to reduce COVID-related morbidity
- Co-ordinated the first COVID-vaccine study in the country
- Initiated studies to identify predictors of COVID disease progression, systems biology of CoV2 in adults and children, pediatric inflammatory multisystem syndrome etc.
- Identification of MIC pattern of newer anti-TB drugs like Bedaquiline and Pretomanid

Our BSL-II Virology facility is an ICMR approved lab for COVID testing and supported Greater Chennai Corporation in COVID-19 testing during the pandemic. NIRT also functioned as ICMR's Central depot for COVID reagents during this period.

NIRT continues to collaborate with other ICMR and non-ICMR institutes for advancement of TB research. NIRT Statistics department is working closely with Institute of Plasma Research, Ahmedabad on developing an Artificial Intelligence tool for interpretation of chest x-ray for TB. Our Health Economics department continues to work with Government of Tamil Nadu on economic evaluation of various health interventions in the state. NIRT continues its contribution to TB control not only to NTEP but also extends support to countries in the South East Asian region through our Supranational Laboratory network. Our quest for early and faster diagnosis, shorter treatment duration, and TB prevention continues as we march towards 2025.

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ABBREVIATIONS

AIC	Airborne Infection Control
ART	Anti –Retroviral Treatment
ATT	Anti-TB Treatment
ATP	Adenosine Triphosphate
AUC	Area Under Curve
BCG	Bacille Calmette-Guérin
BDQ	Bedaquiline
BMI	Body Mass Index
cART	Combinational Antiretroviral Therapy
CBNAAT	Cartridge Based Nucleic Acid Amplification Test
CD	Crohn’s Disease
CHV	Community Health Volunteers
CRT	Co-Receptor Tropism
CSF	Cerebrospinal Fluid
CVL	Cervicovaginal Lavage
DLM	Delamanid
DM	Diabetes Mellitus
DMC	Designated Microscopic Centre
DR-TB	Drug Resistant-TB
DST	Drug Susceptibility Test
EBA	Early Bactericidal Activity
EID	Early Infant Diagnosis
EMB	Ethambutol
EPTB	Extra Pulmonary TB
EQA	External Quality Assurance
ETH	Ethionamide
FDC	Fixed Dose Combination
FDGs	Focus Group Discussions
FQ	Fluoroquinolone
GIS	Geographical Information System
HbA_1C	Glycosylated Hemoglobin
HDL	High Density Lipoprotein
HDTs	Host-Directed Therapies
HHC	Healthy Household Contacts
HIV	Human Immunodeficiency Virus
HTS	High Throughput Sequencing
I-CVI	Item Level Content Validity Index
IGRA	Interferon Gamma Release Assay
INH	Isoniazid
JD	John’s Disease
LAM	Lipoarabinomannan
LAMP	Loop Mediated Isothermal Amplification Assay

LDL	Low Density Lipoprotein
LIMS	Laboratory Information Management System
LLR	Log Likelihood Ratio
LTBI	Latent TB Infection
LRP	Luciferase Reporter Phage
LZD	Linezolid
MDR-TB	Multi-Drug Resistant TB
MGIT	Mycobacterium Growth Indicator Tube
MIC	Minimum Inhibitory Concentration
MOX	Moxifloxacin
MMP	Matrix Metalloproteinases
MSM	Men Having Sex With Men
NAA	Nucleic Acid Amplification
NACO	National Aids Control Organization
NIH-US	National Institute Of Health-United States
NGS	Next Generation Sequencing
NHP	National Health Policies
NTEP	National TB Elimination Programme
NT	Non-Transmitted
OFX	Ofloxacin
OSE	Onsite Evaluation
PBMC	Peripheral Blood Mononuclear Cells
PDB	Protein Data Bank
PBTS	Peripheral Blood Transcriptional Signature
PCR-RFLP	Polymerase Chain Reaction Based Restriction Fragment Length Polymorphism
PK	Pharmacokinetic
PMDT	Programmatic Management Of Drug-Resistant TB
PPV	Positive Predictive Value
PTB	Pulmonary Tuberculosis
PZA	Pyrazinamide
RBT	Rifabutin
RCT	Randomized Clinical Trials
RePORT	Regional Prospective Observational Research In TB
RMP/RIF	Rifampicin
RNTCP	Revised National TB Control Programme
RTPCR	Reverse Transcriptase Polymerase Chain Reaction
SLI	Second Line Injectable
SNPs	Single Nucleotide Polymorphism
STI	Sexually Transmitted Infection
STREAM	Shortening of treatment regimen for MDR-TB Patients
STOI	Standards Of TB Core In India
TAT	Turnaround Time
TBL	Tuberculosis Lymphadenitis

TBM	Tuberculosis Meningitis
TBDM	TB And DM
TDM	Therapeutic Drug Monitoring
TF	Transmitted Founder
TGI	Triglycerides
Tr	Transistmycin
UPHC	Urban Primary Health Centre
VAP	Vaccine Action Programme
VCT	Voluntary Counselling & Testing
VDBP	Vitamin D Binding Protein
VFDB	Virulence Factor Database
VLDL	Very Low Density Lipoprotein
WGS	Whole Genome Sequencing

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 multi-centric collaborative studies with Govt. and private Institutions across India. The department offers support to laboratory studies by facilitating sample collection.

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

Studies in progress

CL -1:The evaluation of a Standard Treatment Regimen of Anti-tuberculosis drugs for patients with MDR-TB - STREAM study stage 2

Principal Investigator	:	Dr. G. Narendran, Scientist ‘E’
Participating Institutes	:	ICMR-NIRT, GHTM, GTHTM, BJMC, RBIMPT
Source of funding	:	USAID, UK DFID, Janssen
Study period	:	2017 - 2022
Category	:	TB
Pillar	:	Treat

Background

TB control worldwide is impeded by two major issues: - the emergence of multidrug resistance (MDR) and (ii) co-existent HIV infection. Preliminary analysis of STREAM Stage I found that 78.1% of participants on Regimen B, the shorter regimen, had a favorable outcome at 132 weeks compared to 80.6% on Regimen A, the 20-24 month long regimen with lesser toxicity and similar adverse events. This Randomised Clinical Trial (RCT) was aimed at not only shortening but also offering an all oral regimen of Bedaquiline for easy translation utility.

Objectives

Currently three regimens have been used for efficacy and safety evaluation

- Reg B: 4KHPMEZC/5MEZC for 9 months. (control regimen – already incorporated into the WHO and NTEP guidelines as shorter version of MDR-TB regimen)
- Reg C: (4-6 Bdq, Lev, Clo, Emb, Z, H, Pro/ 5 Bdq, Lev, Clo, Z, Emb)
- Reg D: (2-3 Bdq, Lev, Clo, Z, H, K/ 4 Bdq, Lev, Clo, Z)

Primary Objectives: Efficacy and safety of regimen C and D as compared to Regimen B which is the control using a non-inferiority margin of 10%.

Study design: Multinational, multi-centric, Randomised Clinical Trial

Study population: Treatment naïve MDR-TB patients without additional resistance to Quinolones or aminoglycosides.

Methodology: Patients with MDR-TB, newly diagnosed who satisfy the eligibility criteria will be randomised to one of the three regimens listed above. They will be followed up for 132 weeks post randomisation with monitoring of blood parameters, ECG and PK for Bedaquiline along with sputum smear and culture at every scheduled visit.

Study progress

ICMR- NIRT has recruited 49 MDR-TB patients of which all have completed 76 weeks follow-upand 30 have completed their 132 weeks follow- up as on date.

The study has very high translational value in determining the optimal regimen for MDR-TB, tailored to cater to the interests of Indian condition and offering an affordable and feasible all oral regimen for MDR-TB that could be easily implemented in field settings. This will assist India’s national TB programme in its efforts to reduce the burden of MDR TB in the country and help achieve the goal of TB elimination by 2025. The study has also supported in bringing the state of art technology for performing BDQ drug susceptibility test (DST) to the NIRT laboratory so that we acquire self-reliance on DSTs for newer drugs.

CL -2:An open-label, non-randomized, two-stage, dose-finding study of Verapamil tablet formulation in adult TB patients in the continuation phase of anti-TB treatment

Principal Investigator	:	Dr.C. Padmapriyadarsini, Scientist ‘F’
Participating Institutes	:	ICMR-NIRT, Kilpauk Medical College, Chennai, Regional Medical Research Centre, Bhubaneswar
Source of funding	:	ICMR
Study period	:	2019 - 2021
Category	:	TB
Pillar	:	Treat

Background

This is a phase 2 open-label dose finding PK study of verapamil given in conjunction with rifampicin (RMP). The goal of this study is to determine the contribution of the efflux pump-mediated tolerance mechanism in delayed or incomplete sterilization in active pulmonary TB (PTB), i.e., verapamil when added to standard TB therapy will accelerate sputum clearance of *M. tb*.

Objectives

1. Determine the compensatory increase in verapamil dose that can offset the increased metabolism of verapamil when it is co-administered with rifampicin.
2. Confirm the safety and tolerability of verapamil in patients with TB without underlying cardiac disease.

Methodology

New sputum smear-positive pulmonary TB patients were enrolled in their sixth month of anti-TB treatment. These patients must have achieved sputum smear negativity during treatment. Patients between the age group of 18 to 55 years and weighing between 45 and 75 kgs, were recruited for each verapamil dose group and PK studies were performed, until the mean AUC of 1000 ng.h/ml is achieved. Once the desired levels of AUC is achieved, 12 participants will be enrolled for the confirmatory PK study. This confirmatory group will provide a check on verapamil dose before testing in later clinical studies.

Study progress

A total of 15 participants (Male- 9, Female-6) were recruited of which 3 participants were recruited in 240 mg dosing, 6 participants in the 480mg and 720 mg dosing respectively. The median verapamil AUC of> 1000 ng.h/ml for AUC 0-t was achieved in two of six participants in 720 mg dose. Recruitment for 12 participants in the confirmatory group is in process (5 participants recruited in confirmatory group) as of March 2021.

CL -3:A phase IIB Open-Label Randomized trial to evaluate the antibacterial activity, pharmacokinetics, safety and tolerability of Metformin when given along with RMP, INH, PZA, and EMB in adults with newly diagnosed sputum positive PTB: an 8-week study

Principal Investigator	:	Dr.C. Padmapriyadarsini, Scientist F
Participating Institutes	:	ICMR-NIRT, ICMR-NARI, Pune AIIMS, New Delhi.
Source of funding	:	ICMR - ITRC
Study period	:	2018 - 2020 (PFT-MTERIF- 2020- 2021)
Category	:	TB
Pillar	:	Treat

Background

Researchers are on the lookout of repurposing of drugs for early sputum conversion to negativity in TB patients. One such drug is metformin that acts by modulating the host immune response. Hence adding metformin to standard anti-tuberculosis treatment will have dual effect – bactericidal with ATT and enhanced killing by boosting immune response. Impaired lung function is common in people with a history of TB and therefore has emerged as a distinct clinical entity. It is therefore important to assess the pulmonary impairment of these patients after treatment completion.

Objectives

1. To evaluate the anti-bacterial activity of Metformin, by measuring the time to sputum culture conversion in liquid media, when given daily for 8-weeks along with standard first-line anti-tuberculosis treatment (ATT) in adults with newly diagnosed sputum positive Pulmonary TB (PTB).
2. (PFT-METRIF) - to assess the pulmonary impairment by spirometry of treated sputum smear positive PTB patients after completion of treatment with 6-months of first-line anti-tuberculosis drugs of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol with or without metformin in the intensive phase of ATT.

Methodology

Randomized, open-label, parallel arm controlled clinical trial with stratified random allocation based on the presence or absence of cavities on chest x-ray and highest sputum smear grading at baseline. Newly diagnosed adult sputum smear positive PTB patients fulfilling the eligibility criteria were included into the study in either the test arm (2Metformin HRZE+2 HRE) or the control arm (2 HRZE+2 HRE) and treated for 6 months. PK, PG and immunologic analysis was done in a subset of the participants.

PFT-METRIF: All study patients from METRIF trial who had successfully completed treatment are screened after 12-month interval following the last dose of their TB treatment. Eligible participants are included in the sub-set for PFT analysis by Spirometry.

Study progress

A total of 322 new sputum smear-positive PTB patients were enrolled in New Delhi, Pune and Chennai as of 31st March, 2020. In a subset of 210 participants, pulmonary function test is being conducted of which 118 participants have completed the test from ICMR-NIRT and AIIMS.

Table 1: Characteristics of the study participants with pulmonary Function test

Variables	Overall (n= 118)	Centre	
		NIRT	AIIMS
Gender			
Female	**27**	**19**	**8**
Male	**91**	**63**	**28**
Regimen			
2EHRZ7/4RHE7	**57**	**40**	**17**
2METHRZE7/4RHE7	**61**	**42**	**19**
Age (in years)	34.71 ± 11.9	37.23 ± 12.18	28.97 ± 9.06

CL -4: 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	1. ICMR-NIRT, Govt. hospital of Thoracic Medicine and Govt Ottery TB Hospital, Chennai 2. Rajan Babu Institute of Pulmonary Medicine and Tuberculosis (RBIPMT), New Delhi 3. National Institute of Tuberculosis and Respiratory Disease (NITRD), New Delhi 4. Group of Tuberculosis (GTB) Hospital (GTB Sewri TB hospital), Mumbai 5. 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) 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) endpoint (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.

Objectives

To evaluate the efficacy of a new treatment regimen of 24 - 36 weeks (6-9months) 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 patients were enrolled in New Delhi, Gujarat, Mumbai and Chennai sites. The study is ongoing and all recruited patients are on follow-up.

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

Principal Investigator	:	Dr. V.V. Banu Rekha, Scientist 'E'
Participating Institutes	:	ICMR, Govt. and Private Institutes across India
Source of funding	:	ICMR - ITRC
Study period	:	2018 - 2022
Category	:	TB
Pillar	:	Prevent

Background

Newer vaccines for TB are essential to achieve the End TB targets. Household contacts of sputum smear positive index pulmonary TB (PTB) patients are identified as high risk groups for contracting TB. Prevention of TB among household contacts of PTB patients is a priority. VPM 1002 is a recombinant BCG vaccine from Serum Institute and Immuvac is a heat killed suspension of *Mycobacterium W* from Cadila Pharma.

Objective

To evaluate the efficacy of VPM1002 and Immuvac by comparing the reduction in incidence of TB over 3-year period among Indian healthy household contacts of newly diagnosed sputum positive PTB patients vaccinated with VPM1002 and Immuvac in comparison to placebo.

Methodology

The multicentric, Phase III, double blind, randomized clinical trial is being conducted in ICMR-NIRT sites in Chennai, Thiruvallur, Tambaram, Madurai and Vellore. HIV sero-negative household contacts aged $\geq$ 6 years, without prior or current anti-TB treatment and 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 arm 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 a period of 3 years. Solicited and unsolicited adverse events are documented. The immune responses are studied at baseline, 2 months and 6 months in a sub-set of participants.

Study progress

The trial was initiated in October 2019. A total of 2723 household contacts were screened and 2214 vaccinated. The trial is ongoing.

CL -6: Randomised clinical trial to study the efficacy and tolerability of a 4-month regimen containing ofloxacin compared to the standard 6-month regimen in the treatment of patients with superficial lymph node tuberculosis

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

Background

Tuberculosis lymphadenitis (TBL) is the mostcommon 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

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 ≥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 -7: 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

Principal Investigator : Dr P.K. Bhavani, Scientist 'D'
Participating Institutes : ICMR-NIRT
Source of funding : ICMR Extramural Funds
Study period : 2018 - 2021
Category : TB
Pillar : Treat/Build

Background

Technical and Operational guidelines 2016 & Standards of TB care in India recommends that every TB death should be notified and a competent authority should do a death audit of every TB death irrespective of treatment initiation in order to prevent avoidable deaths. WHO and National TB programme defines TB deaths as the number of TB patients dying during treatment, irrespective of cause.

Most studies have used all-cause mortality as a surrogate marker of mortality attributable to TB. With the available practice of Death reporting we hypothesis that the TB deaths are misclassified (overestimated/under estimated).

Objectives

To identify the cause of death among TB patients registered for treatment under the TB program of India in Chennai using Verbal autopsy.

Methodology

This cross sectional study was conducted to ascertain the cause of death in patients initiated on treatment under the NTEP in Chennai district from January 2020 till July 2021.All the deaths that occurred were notified to NIRT study staff by the staff of Greater Chennai Corporation on a daily basis. Trained study physician and staff conducted the verbal autopsy interview within 15 days of the event after approval from the relatives of the deceased. Coding of Deaths is done using ICD-11 for Mortality and Morbidity Statistics (ICD-11 MMS) dated 18th June 2018. Data from TB treatment drug cards, lab registers, hospital records, laboratory tests done are documented and available death certificates are included in review process.

Study progress

Out of 180 deaths notified, Verbal autopsy (VA) was conducted for 177. 30% of the respondents were spouses of the deceased. The median time taken to notify the deaths was 5[IQR: 2 – 11] days from the event and 4 [IQR: 2 – 11] days from notification to conduct of VA.

Details about Deceased**:** 50 % were males and 70 % were initiated on treatment for Pulmonary TB. The median time to death from time of treatment initiation was 48 (20 – 87) days.

Underlying cause of death for patients who died during TB treatment. Out of 177 deaths notified, 99 (56 %) deaths were due to TB causes and 78 (44%) were due to Non-TB causes. Among TB Deaths, 40.6% were Pulmonary TB. The commonest cause of death among Non-TB deaths were heart diseases followed by deaths due to Kidney diseases and Cancer. 9 out of 78 deaths were due to COVID 19.

CL -8:Sentinel surveillance for measuring the TB burden and trends in high risk group for TB

Principal Investigator	Dr Shrinivasa B M, Scientist ‘B’
Participating Institutes	Government Medical College Tirunelveli, TN Andhra medical college Vishakhapatnam AP Dr. Rajendra Prasad Government Medical College Tanda HP Dr. Radhakrishnan Government Medical College, Hamirpur HP
Source of funding	Global Fund
Study period	2019-2021
Category	TB
Pillar	Detect/Build

Background

Early detection of TB is essential to improve health outcomes for people with TB, and to reduce TB transmission effectively. The available evidence suggest that screening for TB, if done in the right way and targeting the right people, may reduce suffering and death due to TB.

Objective

1. To establish a national hospital based surveillance to examine trends and pattern of TB attributable to selected high risk groups/clinically vulnerable population attending tertiary care hospitals in India.
2. To estimate the prevalence of TB in selected clinically vulnerable population attending tertiary care Hospitals in India.

Methodology

Study Design:

Phase 1: Retrospective Secondary data analysis of TB program registers

Phase 2: Prospective multi-centric Surveillance study.

Study progress

The enrolment of 7376 participants in the four high risk group namely ANC/PNC, Immuno-supressed (apart from HIV), health care worker and chronic kidney disease patients has been completed. Males constituted 2789 (37.8%)of the study population and known case of TB was 111. A total of 4522 chest x-ray was done and 3783 sputum samples were tested for TB bacilli.

CL -9:Improving Airborne Infection Control (AIC) practices in health care facilities involved in the management of Tuberculosis in Chennai.

Principal Investigator	:	Dr. D. Bella Devaleenal, Scientist ‘D’
Participating Institutes	:	NIRT-ICMR, 25 UPHCs in Zone V and Zone VI
Source of funding	:	ICMR Extramural
Study period	:	2019 - 2021
Category	:	TB
Pillar	:	Prevent

Background

Airborne Infection Control **(**AIC), though a most important strategy in preventing the transmission of TB, is the least practiced. Our study aims to study AIC practices based on administrative, environmental control and personal protective environments in facilities and among the Health care workers (HCWs) and patients. The identification of strengths and gaps of the AIC practices would help to strengthen the Programme towards the goal of TB elimination.

Objectives

- To describe the AIC practices at Urban Primary Health Centres (UPHCs) and centres providing TB care services in Chennai between 2019 and 2020.
- To describe the awareness and practices of AIC among health care providers in UPHCs involved in TB care in Chennai
- To describe the awareness and practices of AIC among patients who are diagnosed with TB and registered in RNTCP in Chennai
- To train the HCWs in AIC practices and develop AIC plan in the identified institutes involved with the management of TB patients.

Methodology

Quasi Experimental Study Design (Pre and Post intervention) Pre intervention and post intervention AIC assessments:

Health care facilities: UPHCs providing TB care services in eastern division of Chennai Corporation will be included in the Survey. This will be done using an observation check list.

Health care workers: HCWs in the above UPHCs will be included in the Survey. This will be done using a pretested validated questionnaire.

Patients: The patient population will be also recruited from the same UPHCs. The minimum required sample size will be 260 patients during pre and post intervention assessment. This will be done using a pretested validated questionnaire.

Study progress

The study was initiated in October 2019. The pre intervention assessments were initiated in December 2019 and completed by July 2020. A total of 23 UPHCs, 351 HCWs and 260 patient recruitments were done during the pandemic period. Interventional activities included pre intervention assessment report generation and sharing with Medical Officers & Programme Managers, creating and sharing IEC materials on AIC and general infection control practices, sharing of National AIC guidelines and National guidelines for infection prevention and control, assisting the facility-in-charge of the UPHCs in preparation of AIC plan for the UPHCs. It also included patient group and individual counselling regarding respiratory etiquettes and AIC practices. Two day online training programme was conducted in AIC for HCWs in the UPHCs assessed. It will be followed by post-intervention assessment.

CL -10: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	:	2019 - 2022
Category	:	TB
Pillar	:	Build

Background

Studies from India have documented that the private sector often deviates from the standard, internationally recommended, TB management practices. National Strategic Plan (2012-17) urges to extend the umbrella of quality TB care and control to include those provided by the private sector. There is very little information about the TB population managed in the private sector in South Tamil Nadu and little is known about their quality of diagnosis and treatment, including treatment outcomes. This study will be conducted among private practitioners in semi urban cities who treat TB with the objective of assessing the practices in the diagnosis and treatment of TB and drug-resistant tuberculosis to standards set in the Standards of TB care in India (STCI) and National TB guidelines.

Objective

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

Methodology

Study Design: This is a cross sectional survey of Private Practitioners in Theni, Dindigul, Virudhunagar and Sivagangai districts of Tamil Nadu, India.

Study Population and Study Period: All allopathic practitioners with private practice irrespective of their association with the government health services were 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 based on the STCI guidelines and National TB guidelines. Eleven standards pertaining to diagnosis and treatment from the STCI (2014) was considered. Data on PPs' self-reported socio-demographic information, patient volume, TB disease knowledge, diagnostic and treatment practices were collected. PPs were 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

This study is ongoing. Data has been collected from 170 PPs.

CL -11:The impact of HIV infection on molecular diagnosis of drug resistant tuberculosis

Principal Investigator	Dr. B.M.Shrinivasa, Scientist ‘B’
Participating Institutes	ICMR – NIRT, Govt. Hospital of Thoracic Medicine, Tambaram
Source of funding	Global Fund
Study period	2020-2022
Category	TB/HIV
Pillar	Detect

Background

In recent years, the emergence and spread of drug-resistant forms of TB seriously threaten our ability to treat the disease. Early diagnosis of drug-resistant (DR-TB) and appropriate therapy are critical for successful treatment outcomes. Whole-genome sequencing (WGS) is a new approach for diagnosis of DR-TB that overcomes limitations of current tests. We hypothesize that HIV infection reduces the sensitivity in the detection of drug resistant genetic mutations by current diagnostic tests. The goal of the proposed pilot research study is to investigate the impact of HIV infection on molecular diagnosis of DR-TB in India**.**

Objective

To identify novel resistance –conferring mutations among HIV – infected TB patients.

To estimate the population-level impact of WGS-based diagnosis and management of DR-TB compared to the concurrent standard in India using mathematical modelling.

Methodology

This is a prospective cross-sectional study of 79 HIV- infected TB patients. We will collect sputum specimens at baseline. Culture-based DST and WGS will be done on all specimens. Culture-based DST will be used to determine INH and RIF’s resistance at baseline.WGS will be performed at the NIRT sequencing facility using an established pipeline currently used in NIRT (ILLUMINA Miseq instrument).. Baseline WGS results will be compared between patients with and without DR-TB, in TB/HIV Co-infected people to identify possible resistance-associated mutations.

Study progress

10 participants were screened and 4 sputum samples were collected.

CL -12: Predictors of resistance emergence evaluation in MDR-TB patients on treatment – PREEMPT

Principal Investigator	Dr.C. Padmapriyadarsini, Scientist ‘F’
Participating Institutes	ICMR-NIRT
Source of funding	NIH (RO1)
Study period	2018-2022
Category	TB
Pillar	Detect

Background

The emergence of multidrug-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 fail to cure 30%-50% of patients, leading to continued spread of drug-resistant organisms in the community Moreover resistance to the two new anti-tuberculosis drugs for MDR- and XDR-TB, Bedaquiline and Delamanid, is already emerging. This problem will continue to worsen unless the mechanisms 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 sero positivity 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) patientswith pulmonary TBwho 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 12 months post completion of treatment. Sputum samples and PK samples will be collected as per study schedule.

Study progress

In India, the study is done in Chennai, Pondicherry, Mumbai and Pune. The study has been initiated in January 2019 and is currently enrolling the participants. A total of 44 participants (Male-28, Female-16) were enrolled as on March 2021.

CL -13: 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	2018 -2023
Category	TB
Pillar	Detect

Background

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

Objectives

- To evaluate Novel Diagnostics & Biomarkers of Diverse States of *M.tb* Infection
- To identify markers Of Treatment Response
- To identify Markers of Lung Injury and impairment associated with Unfavourable TB Treatment Outcomes.
- Resistance To Infection: Mechanisms of Protection Against TB in Exposed Persons
- Progression To Disease: Identify Immunologic Markers of Persons at Highest Risk of Progress of Latent TB Infection to TB

Methodology

Study Design: Prospective Observational Cohort study

Study Population: Adult and child Participants will be enrolled into

- Diagnostic (Dx) Cohort: presumptive TB patients of all age groups
- Cohort A: active TB patients (> 18years)

Study size: New enrolments include:

- Diagnostic Cohort - 325 (Aim 1) - Adult TB -150, Paediatric TB -100, EPTB-75
- Cohort A – 90 New adult (>18years) PTB participants

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

Study progress

Study staff training is currently ongoing. Individual site initiation and patient recruitment will commence after training.

CL -14: Study to evaluate the effectiveness of BCG vaccine in reducing morbidity and mortality in elderly individuals in COVID-19 hotspots in India

Principal Investigator	Dr.C. Padmapriyadarsini, Scientist ‘F’
Participating Institutes	ICMR-NIRT, AIIMS- New Delhi, NIREH- Bhopal, NIOH-Ahmedabad, NIIRNCD- Jodhpur, KEM- Mumbai, JSS- Mysore, RRMCH- Bangalore, MMC- Mysore, NH- Bangalore,Amrita Institute – Cochin.
Source of funding	ICMR-ITRC
Study period	2020-2021
Category	COVID-19

Background

Bacille Calmette-Guérin (BCG) is a vaccine against TB, with protective non-specific effects against other respiratory tract infections including COVID-19 in in-vitro and in-vivo studies, and therefore could potentiate significant reductions in morbidity and mortality in high-risk, elderly individuals.

Objectives

To evaluate the effectiveness of BCG vaccination in preventing morbidity and mortality due to COVID-19 in elderly individuals between 60 to 80 years of age living in COVID-19 hotspots in India.

Methodology

1555 individuals will be screened and eligible participants between 60 -95 years of age will receive BCG vaccination while 778 individuals will be controls without vaccination. All participants will be followed up for a period of 6 months.

Study progress

The study is ongoing and all recruited patients are on follow-up as of March 2021.

Table 2:**Site wise enrolment data**

S.No	Site	Screened	Enrolment	Gender	
				Male	**Female**
1.	**NIRT**	595	231	131	100
2.	**AIIMS- New Delhi**	184	82	55	27
3.	**NIREH- Bhopal**	310	157	105	52
4.	**NIOH- Ahmedabad**	427	183	73	110
5.	**NIIRNCD- Jodhpur**	691	301	141	160
6.	**KEM- Mumbai**	384	112	63	49
7.	**JSS- Mysore**	303	201	121	80
8.	**RRMCH- Bangalore**	225	144	65	79
9.	**MMC- Mysore**	209	103	63	40
10.	**NH- Bangalore**	21	9	8	1
11.	**Amrita Institute – Cochin**	281	43	16	27
Total		3630	1566	841	725

CL -15: Clinical, radiological and laboratory predictors of disease progression and mortality among patients with proven COVID-19 infection hospitalized to a tertiary care center – a retrospective data analysis from Chengalpattu.

Principal Investigator	Dr. G. Narendran, Scientist 'E'
Participating Institutes	ICMR-NIRT, GCMCH
Study period	2020-2021
Category	COVID-19

Background

With specific antiviral and targeted immunomodulatory therapy being still defunct and vaccination coverage catching up, a lucrative approach would be rational allocation of resources by early identification of vulnerable population for early referral to tertiary care centre without undue delay but importantly, without straining the health system.

Objectives

To develop predictors for progression to severe COVID 19 infection and mortality using clinical, radiological and laboratory data available from a retrospective analysis of records among hospitalised patients in the tertiary care centre of Govt. Chengalpattu Medical College Hospital.

To derive and formulate meaningful scores for risk stratification or model with a combination of risk factors/predictors, after achieving the primary objectives.

Methodology

Retrospective analysis of case records with complete data available from RTPCR confirmed COVID 19 patients admitted at Govt. Chengalpattu Medical college, a tertiary centre for COVID care between 1st May, 2020 to 30th November, 2020, the period coinciding with the raising slope of the pandemic in this region, were transcribed into electronic after deletion of patients' identifiers. The primary analysis was determination of prognostic predictors for disease progression and mortality at baseline while the secondary analysis would probe into intra- parameter correlation between laboratory and clinical manifestations. Comparisons would be done among patients who uneventfully recover and those who progress to severe disease and succumbto COVID-19. This comparative analysis will be used in determination of predictors of mortality using multivariate/binary logistic regression. Based on the regression coefficients, a risk score would be formulated. This would help to rationalise health resources so that the patient gets the best care while the health system is strained in no way.

Study progress

Data collection, and cleaning has been completed and final analysis is in progress

Completed studies

S.No.	Title of the project	Principal Investigator	Source of funding	Category /Pillar
CL -16	Phase II b open label, parallel arm, randomized controlled clinical trial to evaluate the safety, tolerability, pharmacokinetics and anti-bacterial activity of High dose rifampicin versus Conventional dose of Rifampicin along with standard anti-tubercular therapy (ATT) in drug sensitive adult patients of pulmonary tuberculosis (HICON-R)	Dr P.K. Bhavani, Scientist 'D'	ICMR- India TB Research Consortium	TB/ Treat
CL -17	A Phase I/II Randomized, Open-label trial to evaluate the pharmacokinetics, safety, and treatment outcomes of multidrug treatment including high dose RMP with or without Levofloxacin versus standard treatment for paediatric tuberculous meningitis	Dr. Bella Devaleenal, Scientist 'D'	NICHD	TB/ Treat
CL -18	C-TRIUMPh: Cohort for TB research by the Indo-US medical partnership multicentric prospective observational study	Dr. C. Padmapriyadarsini, Scientist 'F'	Department of Biotechnology	TB/Build
CL -19	Species identification and response to the appropriate treatment of symptomatic pulmonary non-tuberculous mycobacterial disease among patients treated for TB in Tamil Nadu	Dr.C. Padmapriyadarsini, Scientist 'F'	ICMR Task Force	TB/Detect, Treat

DEPARTMENT OF SOCIO-BEHAVIORAL RESEARCH

DEPARTMENT OVERVIEW AND MANDATES

Department of Social and Behavioural Research (DSBR) remains integral to the vision and mission of ICMR- NIRT .DSBR plays a key supportive role in the clinical trials which are undertaken at ICMR-NIRT and other research studies which require effective patient support activities. The department had undertaken multiple social behavioural studies in TB and HIV at the state and national level which have policy implications. Qualitative and quantitative research studies in assessing the psycho-social factors which drive TB patient health seeking-behaviour, treatment adherence and completions are undertaken by the department. DSBR has conducted Randomised control trials to test the effectiveness of psychosocial interventions on various target groups. The department had also implemented operational and implementation research projects for TB at the national and sub national level and had been contributing to the NTEP program in various aspects. In addition to its research contribution, DSBR is known for its active community outreach towards the vulnerable sections of society that are affected by TB and HIV. DSBR also routinely organises Information, Education and Communications intervention to various sections of society to improve the knowledge, attitude and practices of the community with respect to TB prevention, diagnosis and treatment. DSBR had developed a range of research tools, interventions materials and research findings which are actively disseminated to the policymakers and stakeholders to facilitate translation of research output into practice.

Ongoing studies

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
Source of funding	:	Intramural
Study period	:	2020-2021
Category	:	TB
Pillar	:	Detect

Background

Public transportation may facilitate TB transmission due to problems of limited airspace, overcrowding, and poor ventilation, as drivers do not have any control in deciding whom they can take as their passengers. They are at high risk for TB infection. With millions of people using public transport, these transport services may be hotspots of increased TB transmission. However, 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 prevalent stigma in TB, it is difficult to decide on what type of intervention is feasible and acceptable among drivers to advocate for TB screening.

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

- Phase-I 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 sites 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.
- Phase II Quantitative phase: A total of 454 quantitative interviews will be done, with 277 from each site. The quantitative data collection will be done through a semi-structured interview schedule.

Study progress

The study was initiated in February 2020. We have completed a total of 12 FGDs, 20 In-depth interviews, 172 quantitative interviews in Chennai site. The study is ongoing.

Completed studies

S.No.	**Title of the project**	**Principal Investigator**	**Source of funding**	**Category /Pillar**
DSBR- 2	Patients' Perception on Quality of Care in TB Care Settings in Chennai	Mr. Murugesan Periyasamy, Senior Technical officer 2	ICMR-(Extramural) New Delhi	TB/Detect, Treat
DSBR- 3	Utilization of School Students as Ambassadors in TB Sensitization in Chennai city	Mrs. Priscilla Rebecca, Technical Officer A	The United Nations Office for Project Services	TB/ Prevent, Build
DSBR- 4	Mental Health and Social Stigma among Healthcare Personnel Involved in the Management of Covid-19 Patients in India.	Mr. Murugesan Periyasamy, Senior Technical officer 2	ICMR-(Extramural) New Delhi	COVID-19
DSBR- 5	Factors Related To Covid-19 Stigma: A Mixed-Methodology Study	Dr. A. Stephen, Scientist B	ICMR (Extramural)	COVID-19

LABORATORY STUDIES DEPARTMENT OF BACTERIOLOGY

DEPARTMENT OVERVIEW AND MANDATES

The Department of Bacteriology supports the clinical trials and operational research studies carried out at NIRT, including setting up of drug susceptibility testing for newer anti-TB drugs The Department also contributes to 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 had contributed to studies of public health importance with significant findings. The studies on Whole Genome Sequencing has assessed the added value in drug resistance prediction, transmission dynamics, and recurrent TB infection. Host Directed Therapy through autophagy stimulation research have shown promising adjunct therapy candidates for TB by the autophagy enhancing molecules. The studies on tribal population across India have revealed the presence of Beijing strains. The department had highlighted the use of Resuscitation Promoting Factors to enhance the sensitivity of TB diagnosis by liquid culture. Changes in the critical concentration of anti-TB drugs (Rifampicin, moxifloxacin, ethambutol, and PAS)was observed and reported by the department. The department has facility for screening anti-TB compounds. The other key research focus areas of the department are Prevalence of non-resolving pneumonia in children suspected with TB and the development of non-sputum based assay for paediatric TB. Development of Semi-Automated Device for detection of primary MTB and drug resistance using Luciferase Reporter Phage Assay has been undertaken. Recently, studies are being conducted to understand the effect of SARS-COV2 virus and TB co-infection.

Bacteriology laboratory is a National Reference Laboratory under the National Tuberculosis Elimination programme (NTEP) and provides technical support for the TB laboratory activities to five states and five Union territories in India for NTEP activities. As part of the Supra National Reference Laboratory (SNRL), Department of Bacteriology conducts External Quality Assurance (EQA) for culture and DST (Drug susceptibility testing) under the NTEP. This activity is also extended to other SEARO member’s courtiers namely Myanmar and Timor Leste. Support to conduct drug resistance surveillance in Timor Leste has been provided. Line probe assay for 1 st line and 2 nd line anti-tuberculosis drugs and other diagnostic services to Tamilnadu under Programmatic Management of Drug-Resistant TB (PMDT) are being offered by the department.

Studies in progress

B-1: Prediction of treatment failure among diabetes-TB patients by peripheral blood transcriptional signature

Principal Investigator	: Dr. S Siva Kumar, Scientist ‘C’
Participating Institutes	: IBMS, Madras University, Chennai
Source of funding	: DBT
Study period	: 2017-2021
Category	: TB
Pillar	: Detect

Background

India currently has 61 million people with diabetes mellitus (DM) and will soon become the “diabetic capital” of the world. Diabetes in Asian Indians is characterized by the younger age of onset, lower body mass index, and increased insulin resistance which has been described as “Asian-Indian Phenotype”. The current pandemic of DM is accelerating in a world where approximately one-third of the population is latently infected with *M. tb.* The consequences of these converging epidemics are likely to be substantial. Several studies indicate that patients with TB, who have DM, present a higher bacillary load in the sputum, delayed mycobacterial clearance, and higher rates of multidrug-resistant infection. Recent epidemiological surveys have clearly shown the possibility of diabetes-TB (DM-TB) nexus in near future. Thus, these issues require urgent attention.

Hypothesis

Can peripheral blood transcriptional signature (PBTS) predict sputum smear conversion after the intense phase of anti-TB treatment among patients with diabetes and TB.

Methodology:

A total of 10 ml blood, 5 ml of peripheral blood in PAXgene tubes and 5 ml of blood will be collected for estimating biochemical parameters. The smear conversion in DM-TB patients using “Blood Transcriptional Signature” will be predicted using the Whole blood RNA which will be extracted from stored samples by following ABI kit protocol. The expression of specific genes will be quantified using RT-PCR. Based on the expression pattern a heat map would be generated. The serum biomarkers in DM-TB patients will also be assessed by estimating the Serum levels of insulin, glucagon, leptin and adiponectin and also the same will be estimated before, during and after the completion of therapy using ELISA method following kit protocol. Further fasting blood sugar, HbA1c, LDL, HDL, VLDL, TGL, urea, creatinine, SGOPT, SGPT, albumin and bilirubin would be estimated using an auto analyser.

Study progress

The recruitment for the study is completed and we are currently performing the Gene expression assays for the Insilco shortlisted genes for treatment failure

B-2: Prevalence of Resistance to Newer Anti-tubercular Treatment (ATT) drugs in Treatment-Naive Tuberculosis Patients from Tamil Nadu: 2021-2023

Principal Investigator	: Dr. S Siva Kumar, Scientist ‘C’
Participating Institutes	: NTEP Tamil Nadu
Source of funding	: ICMR
Study period	: 2021-2023
Category	: TB
Pillar	: Detect

Background

Drug resistance TB (DR-TB) is a global public health threat when the world is striving towards TB elimination. Bedaquiline, Delamanid, and Pretomanid are considered to be the newer ATT drugs that may be used to treat DR-TB patients. In 2014, Bedaquiline (Bdq) was approved to be used under PMDT for MDR-TB treatment and in 2019, it was incorporated into the All Oral Longer Regimen for the eligible patient. In June 2017, Delamanid (Dlm) was approved to be part of the PMDT MDR-TB regimen for adults aged 18 and above, currently Dlm use has been expanded in age group 6-17 years. Whilst we are adopting policies with the inclusion of newer ATT drugs, 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 drug resistant 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 DR-TB patients(Treatment-Naïve, not started on any newer ATT containing regimen)to determine the resistance if any to the newer and repurposed drugs. Sample size will be 300 MDR/RR-TB with FQ/SLI resistant DR-TB patients from Tamil Nadu.

Study progress

All the permissions and ethical approvals have been obtained, a database of mutation for the newer drugs have been created and presently sample collection is in progress.

B-3: Deciphering the role of biofilms in conferring drug tolerance among clinical *Mycobacterium tuberculosis* isolates

Principal Investigator : Dr. S Siva Kumar, Scientist ‘C’
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 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

- Characterization of differential phenotypic and in vitro drug tolerance between the planktonic and biofilm forms of *M. tb* and quantitate the biofilm formation from different lineages
- Compare the infectivity, immunological parameters, and drug tolerance of planktonic and biofilm forms of *M. tb* isolates in macrophages
- 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 would 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 *M. 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 would 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 would 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 would be analysed and statistical significance would be assessed.

Study progress. All the permissions and ethical approvals have been obtained. Study yet to be initiated.

B-4: A Study on the Strain specific Modulation of Tuberculosis granulomatous reaction using *in-vitro* 3D granuloma model

Principal Investigator	: Dr. Azger Dusthackeer, Scientist ‘C’
Participating Institutes	: ICMR-NIRT
Source of funding	: ICMR-PDF
Study period	: 2020 - 2022
Category	: TB
Pillar	: Treat

Background

Granuloma is the hallmark of TB infection comprising blood-derived macrophages, epithelioid cells and multinucleated giant cells that are surrounded by T lymphocyte. The protective nature of granuloma is depended on its architecture and in certain cases, the granuloma may become disseminative to cause spreading of the infection inside the host.Various factors of host and pathogen origin influence the architecture of granuloma. In this study we are interested to find whether granuloma architecture could be modulated by *Mycobacterium tuberculosis* (*M. tb*) in a strain specific manner.

Objectives

1.To study the strain-specific modulation of TB granuloma formation using in-vitro 3D granuloma model by stimulating the PBMCs isolated from the healthy volunteers.
2. To analyse the pattern of granuloma formation in TB patients using in-vitro 3D granuloma model by stimulating the PBMCs and to look for any correlation with the disease progression and treatment response.
3. To explore the available immunomodulators through ex-vivo studies to direct the host immune response towards the formation of protective granuloma.

Methodology

M. tb clinical isolates belonging to the different family will be obtained from the NIRT repository to induce the PBMCs from healthy volunteers to form granuloma. The development of *in-vitro* 3D granuloma will be performed using Seitzer and Gerdes (2013) protocol using the PBMCs.*M.tb* clinical isolates from the pulmonary TB patients collected before treatment initiation will be used to induce the PBMCs from the same patients to form granuloma. The induced PBMCs will be treated with immunomodulators to check for the modulation of the immune response towards the protective direction. Polarization towards protection will be assessed by the presence of markers for M1 macrophages.

Study progress

Methodology for the development of In-vitro 3D granuloma were standardized and the primer to perform molecular characterization of macrophage polarization and immune activation was designed.

B-5: Role of Membrane proteins responsible for drug efflux mechanisms in *Mycobacterium tuberculosis.*

Principal Investigator	: Dr. Azger Dusthackeer, Scientist ‘C’
Participating Institute	: ICMR-NIRT
Source of funding	: ICMR-RA
Study period	: 2021 - 2023
Category	: TB
Pillar	: Treat

Background

Mycobacterium tuberculosis is a pathogen difficult to control mostly due to its impenetrable cell wall coupled with a long generation time, a plastic metabolism, and a remarkable ability to establish persistent infections. The mechanisms associated with this resistance could involve mutations in genes coding for target proteins, decreased permeability, increased efflux mechanism, etc. Efflux pump activity contributes to drug resistance by allowing the bacteria to survive for a longer period of time in the presence of subinhibitory concentrations of antibiotics, until chances for acquiring chromosomal mutations for resistance emerge and are established in the bacterial population. In this study, we will evaluate Rv0194 and Rv0933 drug efflux proteins from *M. tb* for studying the mechanism of resistance and synthesising a potent drug target for efflux mediated resistance.

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 carried out by Rv0933 and Rv0194

Methodology

The DNA will be isolated from drug resistance TB clinical isolates. The efflux pump genes Rv0933 and Rv0194 will be amplified, cloned, and overexpressed in *Mycobacterium smegmatis*. The identified active compounds via *in silico* screening will be validated against the recombinant Rv0933 and Rv0194 for MIC validation.

Study progress

The crystal structure of Rv0933 and Rv0194 was selected from Protein Data Bank (PDB) database. The small molecule inhibitors were selected and downloaded from ZINC natural and synthetic databases. Docking will be carried out using Auto dock. The DNA from MDR TB clinical isolate was isolated. The shuttle vector PMV261 with kanamycin backbone was propagated from a glycerol stock.

B-6: Isolation and Analysis of *Mycobacterium tuberculosis*-Induced-MMPs directly from sputum samples: Inhibitor synthesizing and validation

Principal Investigator	: Dr. Azger Dusthackeer, Scientist 'C'
Participating Institutes	: ICMR-NIRT
Source of funding	: ICMR-RA
Study period	: 2021 - 2023
Category	: TB
Pillar	: Treat

Background

TB caused by *Mycobacterium tuberculosis (M.tb)* still remains a major threat to human life. For patients who suffer from active pulmonary TB, there is a high chance of tissue damage in the lungs, which is characterized by cavitation. Lung tissue damage facilitates the dissemination of *M.tb*. Matrix metalloprotease (MMP) 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.

Objectives

- To identifyand determine the concentration of *M. tb* induced MMP expression directly from the smear positive sputum samples
- To identify small molecule inhibitors for *M. tb*-induced MMPs using *In silico* virtual screening.
- To analyze the MMP inhibitory activity of lead molecules by *in-vivo* methodology using peripheral blood mononuclear cells.

Methodology

The concentration of the MMPs in the sputum samples will be analysed using substrate gel Sodium Dodecyl Sulfate Poly-Acrylamide Gel Electrophoresis (SDS-PAGE) Zymography method.. MMP 1,2,3,8 and 9 will be analysed by using gelatin as a substrate. Duke's database will be used for the identification of small molecule lead inhibitors. The MMP inhibitory activity will be validated by *ex-vivo* Methodology using peripheral blood mononuclear cells.

Study progress

The crystal structure of selected MMPs was selected from Protein Data Bank (PDB) database. The small molecule inhibitors were selected and downloaded from ZINC natural and synthetic databases. Docking will be carried out using Auto dock. TB patient sputum samples were collected and stored for MMP isolation by Zymography method.

B-7: Molecular manipulation and hybrid strategy in design and discovery of Cytochrome bc1 inhibitors as potent leads for drug resistant tuberculosis

Principal Investigators	: Dr. Azger Dusthackeer, Scientist 'C'
Participating Institutes	: Raghavendra Institute of Pharmaceutical Education and Research
Source of funding	: SERB
Study period	: 2020 - 2021
Category	: TB
Pillar	: Treat

Background

The unknown resistant behaviour of *Mycobacterium tuberculosis* $H_{37}Rv$ has resulted in various forms of drug resistant TB (MDR, XDR, Mono, and PolyResistant TB). Treatment of drug resistant TBis challenging due to prolonged duration, less effective and toxic drugs. In accordance with the need for newer TB drugs, this research proposal has been designed to discover new Cytochrome bc1 (Cyt bc1) inhibitors as lead molecules for MDR/XDR-TB. Here, the proposed hybrid strategy in the design and development of novel anti-TB agents will focus on discovering potent hits as Cyt bc1 inhibitors.

Objectives

The objective of this project is to discover a new potent and safer anti-TB molecule with a novel mechanism of action to treat MDR-TB/XDR-TB.

Methodology

The database will be created for Cytochrome bc1, using literature /Preliminary studies. In-silico design, docking, and 3D QSAR studies on cytochrome bc1 complex at active sites. *In vitro* screening of compounds against *M. smegmatis* and *M. bovis* will be validated.

Study progress

Screening for 100 synthesized compounds for their anti-tubercular activity on $H_{37}RV$ and drug-resistant isolates has been undertaken. The potent compounds from the preliminary screening were further screened for their synergistic activity on drug-resistant isolates along with anti-TB drugs such as rifampicin (RMP) and Isoniazid (INH). This exercise resulted in two potent novel lead molecules which exhibited synergistic anti-TB activity with both RMP and INH and was found to reduce the MICs of these drugs below that of their critical concentrations. A patent is filed towards these potent new lead molecules.

B-8: MIC distributions of Bedaquiline, Delamanid, Pretomanid, Linezolid, clofazimine, moxifloxacin and levofloxacinamong wild-type, MDR and XDR isolates of *M. tuberculosis* among South Indian population

Principal Investigators	: Dr. Azger Dusthackeer, Scientist 'C'
Participating Institutes	: ICMR-NIRT
Source of funding	: ICMR Intra-mural
Study period	: 2021 - 2021
Category	: TB
Pillar	: Detect

Background

Drug susceptibility testing (DST) is crucial in the treatment of TB. Critical concentration or breakpoint concentration plays an important role in determining whether the strain is susceptible or resistant to a particular antibiotic. Growing evidences suggest that there might be changes in critical concentration of drugs in different populations based on their pharmacokinetic and pharmacodynamics profiles. Bedaquiline, Delamanid, Pretomanid, Linezolid, clofazimine, moxifloxacin and levofloxacin are important second line anti-TB drugs to treat drug resistant TB.

Objective

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

Minimum inhibitory concentration (MIC) will be determined using MGIT960 as per the manufacturer's protocol and broth microdilution Methodology (for Bedaquiline, Delamanid, Pretomanid, Linezolid, clofazimine, moxifloxacin, and levofloxacin.

Study progress

A total of 16 drug-resistant cultures have been subjected to MIC determination for Bedaquiline, Delamanid, Pretomanid, Linezolid, clofazimine, moxifloxacin, and levofloxacin by MGIT960.Determination of MIC for Bedaquiline, Linezolid, clofazimine, and levofloxacin using broth microdilution Methodology has been completed for 14 drug-resistant TB clinical isolates.

B-9:A study to evaluate the endometrial samples for asymptomatic *Mycobacterium tuberculosis* infection in unexplained infertility

Principal Investigators	:	Dr. Azger Dusthackeer, Scientist C Dr. D. Bella Devaleenal, Scientist D Dr. T. Radha Bai Prabhu, Professor
Participating Institutes	:	Sri Muthukumaran Medical College, Chennai-600029
Source of funding	:	ICMR Intra-mural
Study period	:	2020 - 2022
Category	:	TB
Pillar	:	Diagnosis

Background

The predilection for TB is pulmonary disease, however, TB infection also occurs with increasing frequency in extra-pulmonary locations such as the genitourinary tract. Genital tuberculosis (GTB) is nearly always secondary to primary elsewhere in the body. The clinical features develop 10-15 years after the primary infection unless it is an acute miliary spread. Reactivation of these bacilli can occur around the time of puberty when the vascularity of the pelvic organs increase.

Objectives

1. To estimate the prevalence of asymptomatic TB of the endometrium in women presenting with unexplained infertility.
2. To associate the endometrial thickness with MTB positivity by HPE/culture / PCR results to see whether MTB causes endometrial thinning leading to implantation failure.

Methodology

The endometrium samples from women with unexplained infertility will be screened for diagnosis of TB via smear, culture, and Gene Xpert.

Study progress

Around five endometrial specimens have been received and all of them were negative for *M. tuberculosis*, the study is ongoing.

B-10: Prevalence of non-resolving pneumonia in children suspected with TB

Principal Investigator : Dr. R. Priya, Scientist C
Participating Institutes : ICMR NIRT
Source of funding : ICMR- Intramural
Study period : 2018 – 2021
Category : TB
Pillar : Detect

Background

Studies have emphasized the potential importance of *M. tuberculosis* in acute severe pneumonia in children as a primary cause or underlying co-morbidity. It has been reported that pneumonia in infants and young children has underestimated the contribution of TB as a direct cause or co-morbidity of acute community-acquired pneumonia in children because of the difficulties of microbiological confirmation in this age group, especially in resource-restricted TB endemic settings. There is an urge for an extensive study on the association of TB with community-acquired pneumonia in children by strengthening the microbiological confirmation Methodology in this age group which in turn would help in improving clinical management. In this study, we hypothesize that among children with respiratory diseases, simultaneous diagnosis of TB and other pneumonia-causing organisms will depict the factual representation of the etiology and help inappropriate treatment.

Primary objective

(i) To estimate the prevalence of non-resolving pneumonia and co-infection of TB and bacterial/viral causative agents of pneumonia in children treated with ATT (in Group- A)

Secondary objectives

(i) To determine the bacterial and viral cause of pneumonia in children (in Group-B);
(ii) To estimate the sensitivity and specificity of the molecular detection of cause of pneumonia
(iii) To estimate the prevalence of bacteriologically confirmed and un-confirmed paediatric PTB

Methods

The following microbiological investigations will be done in respiratory specimens / gastric aspirate:

(i) Smear microscopy, Culture and identification: Detection of Mycobacterium tuberculosis and other bacteria
(ii) Xpert® MTB/RIF: Detection of Mycobacterium tuberculosis
(iii) DNA extraction and real-time PCR: For a panel of Bacteria and viruses

Study progress

We have received 190 paediatric pulmonary samples. The standardized multiplex real-time PCR for the detection of bacteria was carried out on 100 samples. The bacterial multiplex PCR has detected a wide panel of organisms in these samples that includes *Streptococcus pneumoniae*, *Legionella pneumophila*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Bordetella species,* and

Mycobacterium spp. The viral multiplex PCR was also standardized and 50 samples have been screened so far. These samples were positive for the target genes of Parainfluenza type I, II, and III, adenovirus, and Influenza virus. Out of these 190 screened for TB, 9 samples were positive for *M. tuberculosis* by Xpert® MTB/RIF and culture.

B-11: Evaluation of stool concentration Methodology for detection of *M.tuberculosis* in children

Principal Investigator	: Dr. R. Priya, Scientist 'C'
Participating Institutes	: ICMR NIRT
Source of funding	: ICMR- Intramural
Study period	: 2020 – 2021
Category	: TB
Pillar	: Detect

Background

The inability of the children to expectorate sputum and the paucibacillary status of the pathogen increases the diagnostic complexity of MTB in paediatric population. Since stool is easily collected from children, it can be used for the detection of *M.tuberculosis*which is present in the swallowed sputum.Culture and molecular methods can be utilised for the detection of *M.tuberculosis*. In this study, we aim to standardize an in-house protocol for the processing of stool specimens and subject the DNA extracted from them to LPA for detection of MTB and its drug resistance.

Objectives

Stage I: To measure the isolation rate of MTB from stool samples spiked with $H_{37}RV$ using concentration techniques - Determination of Limit of detection (LOD).

Stage II: To assess the feasibility of concentration technique in isolation of MTB from stool samples of paediatric patients with confirmed TB.

Stage III: To validate the concentration technique for TB detection in stool from the presumptive paediatric TB population.

Methodology

For stage I, the stool from control children was spiked with $H_{37}Rv$ in 5 different dilutions (1:1, 1:10, 1:100, 1:1000, and 1:10,000). The spiked samples (50) were subjected to 1 % chlorhexidine treatment and concentrated with Brij 35 solution. The concentrated solution was washed twice and filtered using glass wool syringe filters. All filtrates were subjected to smear microscopy, solid culture (LJ), Xpert Ultra testing, and DNA extraction for Line probe assay. For stage II and Stage III, the chlorhexidine treatment and concentration technique will be carried out with the stool samples obtained from confirmed and presumptive TB cases.

Study progress

We have received 10 control samples so far. In smear microscopy, bacilli could be seen in 8 samples in 1:1 and 1:10 dilutions. Growth in LJ was seen in 4 samples (1:1) at the 3rd week of inoculation with 3-8 colonies in two samples and 1+ growth in two samples. No results were obtained for other dilutions and samples in smear and culture. Xpert ultra testing could detect MTB in all dilutions of stool with "MTB detected low" in 1:1 and 1:10, "MTB detected very low" in 1:100 and 1:1000 and "MTB detected trace" in 1:10,000 dilutions. Similarly, line probe assay could detect MTB in all samples and dilutions in addition to rifampicin and isoniazid sensitivity. We are yet to receive samples from confirmed TB and the presumptive TB population.

Completed studies

S.No.	**Title of the project**	**Principal Investigator**	**Source of funding**	**Category /Pillar**
B-12	Genomic characterization of severe acute respiratory syndrome corona virus-2 (SARC-COV-2) strains circulating in Chennai	Dr. C Padmapriyadarsini, Scientist F	Greater Chennai Corporation	COVID-19
B-13	Identification of Inhibitors for Multidrug Efflux Pumps of *Mycobacterium tuberculosis* from medicinal plants, Using In Silico High-Throughput Virtual Screening and In Vitro Validation	Dr. Azger Dusthackeer, Scientist ‘C’	ICMR-PDF	TB/Treat
B-14	Evaluation of Truenat MTB INH, an indigenous molecular test for rapid direct detection of isoniazid resistance from sputum samples	Dr. N.S. Gomathi, Principal Technical Officer	ICMR intramural	TB/Detect

DEPARTMENT OF IMMUNOLOGY

DEPARTMENT OVERVIEW AND MANDATES

The Department of Immunology primarily conducts research on the biological, immunological and molecular biological aspects of mycobacterial infections. The department is involved in studies on basic pathogenic mechanisms that may lead to better diagnostic tools and development of vaccines and other immune interventions for 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 immunodiagnosis are other major areas of research which the department undertakes. More recently, the department has added a facility for Next generation sequencing of mycobacterial clinical isolates and performing research activities in understanding the drug resistance, transmission dynamics and novel mutation identification in TB. The department is also focused on understanding the Zoonotic and reverse zoonotic transmission of TB between human and cattle.

Studies in progress

I-1: Early bactericidal activity of anti-TB drugs

Principal Investigator	:	Dr. K. R. Uma Devi, Scientist E
Participating Institute	:	ICMR NIRT & CDC, Atlanta.
Source of funding	:	CRDF (CDC)
Study Period	:	2017-2020
Category	:	TB
Pillar	:	Treat

Background

Several MDR-TB treatment patients have DST results showing resistance to one drug within a class of drugs but susceptibility to other drugs in the same class. Experts agree there are no solid clinical data for evidence-based treatment decisions in these situations.

Objectives

(i) To determine the bactericidal activity of Rifabutin (RBT) in patients whose baseline DST results demonstrate susceptibility to RBT and resistance to RMP.

(ii) To determine the bactericidal activity of high-dose INH in patients whose baseline DST results demonstrate susceptibility to high concentrations of INH and resistance to low concentrations of INH

Methodology

Potential patients are screened with an approved rapid, molecular test to confirm the species as *M. tuberculosis* and detect mutations associated with RMP resistance and possibly INH resistance. Among those found to have RMP or INH resistance, DST is carried out in liquid media by the direct method, which yields results in 7-14 days. Drugs to be tested include at least RMP, RBT, and 3 concentrations of INH. Quantitative bacteriology is carried out on days 0, 2, and 4, using a 16-hour overnight sputum specimen. In addition, rapid direct method DST using MGIT 960 was performed for initial screening. Standard phenotypic DST using the indirect method for the drug used during the period of monotherapy is repeated on specimens collected in the morning after the last day of monotherapy and again 2 months later for all patients who remain culture positive at those points in time.

Study progress

The recruitment to the study with 17 patients in the high dose isoniazid arm is completed and data analysis is in progress.

I-2: Accurate, Rapid, Robust & Economical Diagnostic Technologies for Tuberculosis (ARREST-TB)

Principal Investigator	:	Dr. K. R. Uma Devi, Scientist E
Participating Institutes	:	ICMR-NIRT, GHTM
Source of funding	:	DBT
Study period	:	2020-2022
Category	:	TB
Pillar	:	Detect

Background

The massive increase in the incidence of antimicrobial-resistant infections is a global concern and it is important to consider TB in this context. The rapid selection and spread of antimicrobial resistance (AMR) is compromising the efficacy of even the 'last resort' antibiotics, as seen in extensively drug resistant (XDR) TB. Although improvements have been realized in the diagnosis of MDR TB using technologies such as GeneXpert™, 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

1. 1. Evaluation and validation of the 'No Wash' probe and the image device (Objective 1) that will be developed in this project will be evaluated and validated as per the methodology developed by the collaborating partners using the mycobacterial culture followed by using the sputum smear for validation of the probe and the device.
2. The evaluation and validation of the spin tube device for detection of MTB Vs NTM and for MDR TB (Objective 2) developed in this project will be carried out with DNA extracted from culture followed by DNA extracted from sputum using the Truenat device as per the developer's protocol. The comparator testing will be done with Xpert/LPA and or MGIT culture and DST.
3. The miRNA detection(Objective 3) will be carried out in blood samples collected for the study using the DestiNA Optoi device developed in this project and the testing will be done based on the Standard operating procedures provided by the collaborators.

Study progress

A total of 166 sputum samples have been collected and processed across NIRT sites.

Table 3: **Current Status**

Sample Collection and sample processing done at NIRT from Jan to Mar 2021				
Sites	**Vellore**	**Madurai**	**Chennai**	**Total**
Sample Collection Initiation Date	13-01-2021	04-03-2021	11-03-2021	
Presumptive Pulmonary TB	47	52	20	**139**
Multidrug Resistant TB	6	32	9	**56**
Total	**53**	**84**	**29**	**166**

I-3:Attenuated Mycobacteria based vaccine with a novel strategy for T cell priming

Principal Investigator	:	Dr. K. R. Uma Devi, Scientist ‘E’
Research scholar	:	J S V Soundarya
Participating Institutes	:	ICMR-NIRT
Source of Funding	:	ICMR Intra-mural
Study period	:	2017-2022
Category	:	TB
Pillar	**:**	Prevention

Background

Currently available BCG vaccine has shown to have varying efficacy in adult population in different parts of the world**.** Therefore, in the current scenario, development of new vaccine candidates is a priority. rBCG co-expressing Ag85A-ESAT6 fusion protein of *M.tb* elicited more long lasting and stronger Th 1 type cellular responses in BALB/c mice. Published study illustrated that rBCG:: Ag85B-ESAT6-Rv2608 is a potential candidate against *M. tuberculosis* in C57BL/6 mice. In the present study, additional modifications will be carried out in the mc^{2}6206 and BCG to provide enhanced immune response by a two-prong approach. First approach is to add an additional deletion of ChoD or Tgs4 to mc^{2}6206 and BCG and the second is to provide a targeted delivery of T cell specific mycobacterial antigens to the dendritic cells using these knock out strains.

Objectives

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

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.
   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

Cloning of the fusion protein in the mycobacterial shuttle vector has been accomplished. Recombinant mycobacterial strain selection incorporating the mycobacterial vector and their expression is in progress.

I-4: CRISPR mediated platform for diagnosis and rapid detection of drug resistance pattern in *Mycobacterium tuberculosis*

Principal Investigator	:	Dr.K.R.Uma Devi, Scientist 'E'
Research scholar	:	Mr. P. Venkatesan
Participating Institutes	:	ICMR-NIRT, GHTM
Source of funding	:	ICMR Intra-mural
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 of more precise and reliable diagnosis method for TB. Currently, several nucleic acid based amplification techniques such as XpertMTB/RIF assay and Line probe assay are available to diagnose and detect the drug resistant pattern of pulmonary clinical specimens. However these techniques are limited in identifying drug resistant pattern for few drugs. In this context, it is important to develop tools using newer technologies like CRISPR based tool for diagnosis and detection of drug resistance in *Mycobacterium tuberculosis* with less turnaround time and high sensitivity and specificity.

Objectives

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

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 DNA with appended T7 promoter sequence. Using Hiscribe T7 quick high yield RNA synthesis Kit, crRNA was synthesized and purified.

Step 3: RNA isolation: The RNA isolation 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 achieved our goal of designing a CRISPR Cas 13a tool for identifying *M.tb* in this project. Its specificity, LOD, and live dead bacteria discrimination have been evaluated. We are currently testing for identifications of mutations in drug-resistant *M.tb*.

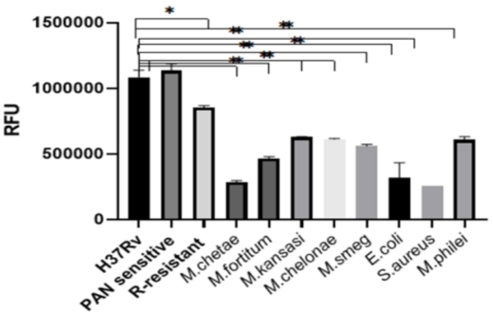


Figure 1: Detection of M.tb

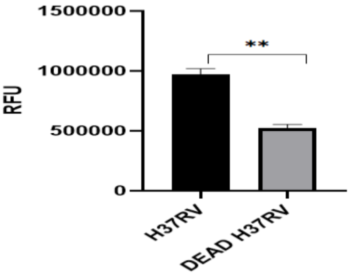


Figure 2: Live and Dead bacilli differentiation

I-5: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 and CBST, VIT, Vellore
Source of funding : DST SERB
Study period : 2019-2021
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 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.

Objectives

The objective of the study is 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.

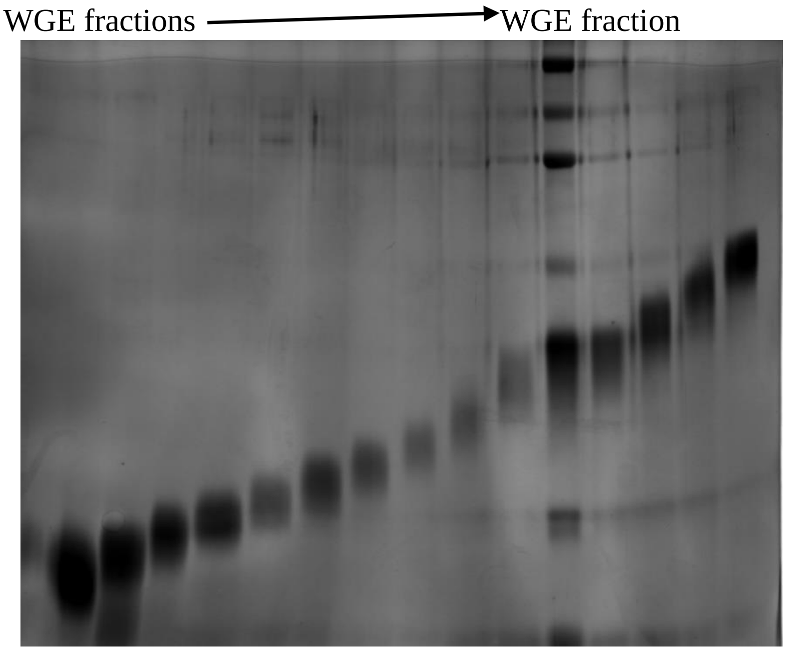
Methodology

The clinical strain of *M. tuberculosis* (S7 strain) was isolated from culture by centrifugation. Isolated cell pellet was lysed by the sonication. From the whole cell lysate, cell wall and cell membrane proteins were isolated by ultra-centrifugation method. Cell wall and cell membrane proteins of *M. tuberculosis* were initially separated based on their iso electric point by preparative IEF using Rotofor instrument. The Rotofor separated fractions were subjected to a second dimensional separation based on molecular weight by preparative SDS-PAGE. Separated proteins were 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 be assessed.

Study progress

M. tuberculosis (S7), a well characterized Drug sensitive Clinical isolate, was grown as bulk culture (20 litres). *M. tuberculosis* bacterial cells were separated from the culture and were lysed by sonication process to obtain around 2 gram of whole cell lysate protein. By subjecting to differential ultracentrifugation process, we separated the cell wall and cell membrane proteins of 300mg to 100mg respectively. Three hundred mg of the cell wall proteins were subjected to 3 individual IEF runs with 100 mgs of protein in each run. 20 fractions could be obtained from every preparative IEF run. 300 mg cell wall proteins were separated into 60 fractions. Fractions with similar pI value and similar proteins profile were pooled together. By this approach, we were able to pool the 60 IEF fractions into 6 pooled IEF fractions. Six pooled rotofor separated cell wall fractions were subjected to 7 runs on preparative SDS-PAGE followed by whole gel elution. This procedure separated cell wall proteins into 210 fractions. Proteins concentration in the separated fractions ranged from 25µg to 650 µg. similar approach was used for the separation of cell membrane proteins which separated cell membrane proteins into 270 fractions. Proteins concentration in the separated fractions ranged from 20 µg to 650 µg. The SDS-PAGE analysis of whole gel eluted cell membrane fractions showed in the figure 1.

Fig 3: SDS-PAGE analysis of whole gel eluted cell membrane fractions



I-6:Molecular Analysis of Monocyte Subsets from Humans Infected with *Mycobacterium tuberculosis*

Principal Investigator : Dr.B.Ramalingam, Scientist E
Participating Institutes : ICMR - NIRT
Source of funding : DBT Ramalingaswami Fellowship
Study period : 2015-2021
Category : TB
Pillar : Detect, Treat

Background

The mechanisms for mononuclear phagocyte mediated protective immunity against *M.tuberculosis* infection have not yet been completely deciphered. Reports with modulated frequencies in the subsets of mononuclear cells influenced us to study their phenotypic and genotypic differences and to elucidate their functional role against TB infection.

Objectives

1. To phenotypically characterize and analyze the different monocyte subsets from whole blood of the TB patients, by immunophenotyping based on cell surface marker expression and comparison to normal healthy subjects.
2. To study the transcriptome profiles of monocytes within the study participants and to validate the differentially expressed genes by quantitative real time PCR.
3. To identify the most promising candidate biomarker genes and pathway networks by comparing the transcriptomic profile of the monocyte subsets from active TB patients to the healthy participants.

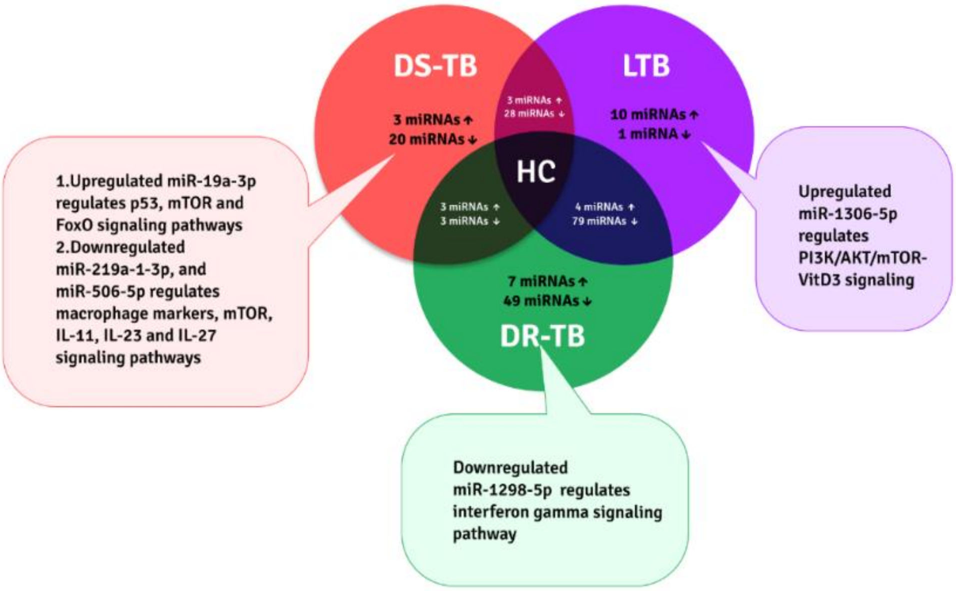
Methodology

FACS sorted monocytes (HLA-DR+ CD14+ CD16+), (N-24) were subjected to Nano string nCounter miRNA profiling assay, representing four groups [healthy individuals (HC), latently infected (LTB), drug sensitive TB (DS-TB) and single or multi-drug resistant TB (DR-TB)] with 6 samples each. Differentially regulated miRNAs and their targeted mRNAs and pathways were identified using nSolver, miR-DB and Webgestalt softwares.

Study Progress

- Identified upregulated and downregulated miRNAs among the study groups
- TB specific targeted mRNA pathways identified for the differentially regulated miRNAs

Fig 4: Differentially regulated miRNAs (upregulated as ↑ and downregulated as ↓) among LTB, DS-TB and DR-TB compared to HC and their TB specific targeted pathways



1.Upregulated miR-19a-3p regulates p53, mTOR and FoxO signaling pathways
2.Downregulated miR-219a-1-3p, and miR-506-5p regulates macrophage markers, mTOR, IL-11, IL-23 and IL-27 signaling pathways

Upregulated miR-1306-5p regulates PI3K/AKT/mTOR-VitD3 signaling

Downregulated miR-1298-5p regulates interferon gamma signaling pathway

I-7: *CYP27b1* gene promoter polymorphisms in pulmonary tuberculosis

Principal Investigators : Dr. Harishanker M, Technical Officer C
Dr. Ramalingam B, Scientist E
Participating Institutes : ICMR-NIRT
Source of funding : ICMRIntra-mural
Study period : 2020-2021
Category : TB
Pillar : Detect, 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 disease.

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.

Study progress

The table shows number of study participants and genotype details using PCR-RFLP method

<u>Table 4:</u> 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)	45	30	666	*TaqI*	CC-single band CT-3 bands GG-2 bands	436bp 436+182+48bp 182+48bp
-1260 (A/C)	45	30	666	*TfiI*	AA-single band AG-3 bands CC-2 bands	423bp 423+177+66bp 177+66bp

Genotypic associations, p-values with OR adjusted for gender and age will be calculated by logistic regression under codominant, dominant, recessive and over dominant models using the online SNPstats 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. A p-value ≤0.05 will be considered statistically significant.The study is in progress.

I-8:Identification of Mycobacterium tuberculosis complex (MTBC) organisms in the lymphnode samples of slaughtered cattle in Chennai

Principal Investigator : Dr. P. Kannan, Scientist ‘D’
Participating Institutes : ICMR- NIRT, Tamilnadu Veterinary and AnimalSciences University
Source of funding : ICMR Extra-mural
Study period : 2019-2022
Category : TB
Pillar : Detect

Background

Bovine tuberculosis (bTB) is one of the important areas of concern because of its serious impact it causes on economic losses and public health. 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. Slaughter house 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 shown any visible lesions during post-mortem depicting the status of latent infection in human.

Objectives

The primary objective of the study is to isolate, identify and understand the MTBC organisms from the lymph node samples of slaughtered cattle with and without visible lesions.

To achieve that aim the following objectives are to be carried out.

1. Isolation and identification the MTBC from the lymph node samples of the cattle with and without visible lesions.
2. Identification of drug susceptibility patterns for the MTBC isolates obtained from the lymph nodes.
3. Analysing the genomic patterns of MTBC isolates obtained from the lymph node samples using whole genome sequencing.

Methodology

A Cross sectional study is being 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 lymphnode samples were collected from the slaughtered cattle with or without visible lesions of TB. The samples were decontaminated and inoculated into liquid and solid medium for MTBC isolation.. Whole genome sequencing (WGS) is being performed to identify the genetic relatedness of the MTBC. A total of 186 Lymphnode samples have been collected in two batches, from 19/09/2020 to 27/09/2020 and on 04/04/2020. Of these, 101 samples have been processed and inoculated in solid and liquid media.

Study progress

- Six samples out of the 101 samples have been identified to belong to MTBC by phenotypic Methodology (colony morphology, microscopy) and using immunochromatographic test in MGIT cultures.
- 15 samples were Non Tuberculous Mycobacteria culture positive.
- IS6110 PCR was performed, which confirmed that all these isolates belonged to MTBC organisms.
- WGS analysis further revealed that all the six isolates belong to *M.orygis*

I-9:Study on Mutations Associated with Pyrazinamide Resistance in *Mycobacterium tuberculosis*

Principal Investigator	:	Dr. P. Kannan, Scientist 'D'
Co-Investigator	:	Ms. R. Ananthi
Participating Institutes	:	ICMR-NIRT
Source of funding	:	ICMR (under SRF Program)
Study period	:	2019-2022
Category	:	TB
Pillar	:	Treat

Background

Pyrazinamide (PZA) is an important first line drug in TB therapy. It is active against semi-dormant *M. tuberculosis* which is not killed by other TB drugs. 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, it is not included in the group of antimycobacterial drugs to be routinely tested for resistance because PZA drug susceptibility testing (DST) is notoriously difficult and often inaccurate. Resistance to PZA will severely affect the treatment outcome in TB cases. In India no major studies have been conducted to understand PZA resistance among various clinical strains from presumptive drug resistant patients. This study will provide a unique opportunity to understand the genotype mutations and phenotypic correlation with PZA resistance in clinical strains.

Objective

The objective of this study is to understand the Pyrazinamide resistance in *M. tuberculosis* strain isolated from presumptive drug resistant TB patients from Chennai.

Methodology

Drug Susceptibility Testing (DST) for RMP, INH and PZA were performed on BACTEC MGIT 960. Total number of 226 clinical isolates were revived from stored cultures among which 176 isolates were MGIT positive for *M. tuberculosis* and remaining stored isolates either did not grow or got contaminated. DST assay was carried out with MGIT positive cultures. The aliquots of the bacterial cultures were stored as glycerol stocks at -80 °C.

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. The known susceptible control strains ($H_{37}Rv$) produced PZase and were susceptible by MGIT 960 method.

Study progress

176 MGIT positive strains were used for further studies. They were screened for resistance to INH, RMP and PZA and the results are provided in the table.

Table 5: Screening of first line drug resistance along with PZA resistance

Total no of MGIT positive isolates	INH Resistant	INH+RMP Resistant	INH+PZA Resistant	RMP+PZA Resistant	INH+RMP +PZA Resistant	PZA alone Resistant
176	56	12	16	01	10	15

I-10:Dereplication guided bio-prospecting of cyclic lipopeptides from marine *Bacillus* sp. for inhibition of *Mycobacterium tuberculosis*

Mentor	:	Dr P.Kannan, Scientist'E'
Principal Investigator	:	Dr. Sagarika Devi
Participating Institute	:	ICMR - NIRT
Source of funding	:	DST, Govt. of India, New Delhi
Study period	:	2019-2022
Category	:	TB
Pillar	:	Treat

Background

The lack of drug compliance, appearance of multiple-drug-resistant strains are a few factors that have led to the resurgence in TB. This emphasizes the need for additional novel antibiotics and massive scale probing of their novel process chemistry from existing biosphere. There are fewer published reports, which have evaluated and validated the potential of the marine *Bacillus* sp. that act against clinically important mycobacterial strains. This proposed investigation is aimed towards whole cell screening and bio-guided isolation of potent marine *Bacillus* cyclic lipopeptides with antimycobacterial activity.

Objective

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.

Methodology

In discussion with Zoological Survey of India, Jamnagar, marine sponge samples were collected from Mithapur and Poshitra in Gulf of Kachchh, Gujarat. Non-calcareous marine sponges belonging to the taxonomic Class Demospongiae were collected from 4 mts deep water by snorkelling following the Okha tide table. The samples were processed for taxonomic study and microbiological analysis. The sponge samples used in the study have been taxonomically identified by Zoological Survey of India, Chennai.

Bacterial colonies isolated from each sponge was cultured on Zobell Marine Agar (ZMA) and pure cultures obtained by streaking on ZMA after incubation at 25 ± 2º C for 3-5 days. The individual slant cultures maintained on ZMA were studied for Gram staining. Currently, each gram positive bacteria is being cultivated in bulk on Zobell Marine Agar plates for plug extraction. Plugs are harvested from 72 hr bacterial culture and extracted in isopropanol-ethyl acetate-1% formic acid followed by 15 min ultra-sonication. The supernatant is collected, dried utilizing nitrogen evaporator and stored for bioactivity study.

Study progress

1. Marine sponges, 12 no's (non – calcareous, Demospongiae) collected from Gulf of Kutch, Gujarat and identified by Marine Biology Regional Centre, Zoological Survey of India, Chennai
2. Sponge samples have been processed microbiologically and 79 associated marine bacteria have been isolated.
3. In preliminary identification of the 79 bacterial cultures, 21 have been identified as gram positive rods, 34 gram positive cocci, 10 gram negative rods and 14 gram negative cocci.
4. Each gram positive bacteria is being cultivated on Zobell Marine Agar plates and harvested in bulk after 72 hr of growth by micro plug extraction. The plug extract is processed. The supernatant is collected, dried utilizing nitrogen evaporator and stored for bioactivity studies (ongoing).

I-11: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
Source of funding	:	DHR-ICMR
Study period	:	2019-2022
Category	:	TB
Pillar	:	Detect

Background

Newer diagnostic methodology are urgently needed for the diagnosis of childhood TB. Identification of TB specific biomarkers will be helpful in the development of the newer diagnostic method in diagnosing childhood TB. MS-based biomarker identification in urine of childhood TB participants has not been studied. Hence, in the present study we are using MS-based proteomic approach to identify the biomarker specific for childhood TB in urine samples.

Objectives

i. To identify disease-specific biomarker for childhood TB in urine.
ii. 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 children was 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 participant recruitment was initiated in October 2019. We have recruited 58 Children with respiratory infection other than TB (Group B) and 16 Children with Confirmed TB (Group A) and 46 healthy children (Total of 120 children). We extracted urine proteins from 30 children and sent the mass spectrometry analysis to Rajiv Gandhi centre for Biotechnology, Thiruvananthapuram. Initially protein profile of 3 children (one from each study group) has been analysed. In healthy children urine high resolution proteomic analysis identified 172 proteins. In the children with respiratory disease other than TB we had identified 190 proteins by the high resolution proteomic analysis. In the TB infection confirmed children mass spectrometry analysis identified 575 proteins. Proteomic analysis of the other samples is ongoing.

I-12:Protecting and improving public health globally: Building laboratory, surveillance and workforce capacity to detect, respond to and prevent DR-TB in India

Principal Investigator	:	Dr K R Uma Devi, Scientist ‘E’
Participating Institutes	:	ICMR- NIRT
Source of funding	:	CDC (GHSA), Atlanta.
Study period	:	2015 – 2021
Category	:	TB
Pillar	:	Build, Detect and Prevent

Background

Detection of drug resistant TB (DR-TB) by current Methodology is reported to have limitations. Early detection of drug resistance is crucial for patient's management. Whole genome sequencing (WGS) is the key for rapid detection of DR-TB, to understand the molecular epidemiology of DR-TB, to develop new molecular Methodology for detection of DR-TB and to assist in TB outbreak investigations.

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 and prevent antimicrobial resistance, and strengthen surveillance systems, national laboratory systems, and workforce development.

Methodology

- ❖ DR-TB strains were collected prospectively from various IRLs as identified by CTD for a national representative based on quota sampling as MDR-TB burden reported for each state.
- ❖ The WGS facility was established for TB isolates genome sequencing and capabilities for detection of DR-TB mutations by computational analytic pipeline at NIRT. Quality assurance was done externally for WGS.
- ❖ Phenotype by MGIT DST for a panel of 14 first-line and second-line drugs was performed and the genotypic detection by WGS was compared for each isolates.

Sensititre MYCOTB MIC plate based assay is being done for the isolates having discrepant phenotypic and genotypic results for different drugs, in order to identify the mutation specific variations in MIC.

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

Principal Investigator	:	Dr. Syed Hissar, Scientist 'D' Dr. N. Pavan Kumar, Scientist C
Participating Institutes	:	GHTM, KMC and RGGH.
Source of funding	:	ICMR
Study period	:	2021-2024
Category	:	TB and HIV
Pillar	:	Detect

Background

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

Objectives

- Characterize systems biology of the effect of TB chemoprophylaxis in HIV
- Characterize immunology response of the effect of TB chemoprophylaxis in HIV

Methodology

HIV sero-positive individuals attending NIRT clinics at Madras Medical College Hospital, Chennai; Stanley Medical College Hospital, Chennai; and Government Hospital of Thoracic Medicine (GHTM), Tambaram, Chennai, will be screened for latent TB by Quantiferon TB gold plus (QFT) and recruited before administration of INH prophylaxis. We will then examine the groups at baseline (pre-treatment) and after 6 months of INH prophylaxis. Characterization of the blood transcriptome, urinary proteome, gut microbiome, microbial translocation, Characterization of NK cell responses, monocyte responses, dendritic cell (DC) responses and systemic immune activation in HIV patients with or without latent TB will be done. Correlation of the above with HIV parameters including CD4 count and viral loads will be done.

Study progress

Recruitment and experimental phase is underway.

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’
Dr.S. Subash Babu, Scientific Director, ICER
Participating Institutes : ICH, Rainbow Children’s Hospital,
Dr. Mehta’s Children Hospital
Source of funding : NIRT-ICER
Study period : 2020-2021
Category : COVID-19

Background

Severe Acute Respiratory Syndrome – Coronavirus – 2 (SARS-CoV2) and its related Coronavirus Disease – 19 (COVID-19) 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. Unfortunately, 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

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

Methodology

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 and 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

Recruitment and experimental phase is underway

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

Principal Investigator : Dr.N. Pavan Kumar, Scientist C
Dr. Banu Rekha, Scientist E
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 what are 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. Published studies offered a strong evidence that T cell immune responses are sustained, even in the face of declining or undetectable antibodies, implying that some immunity persists. The evidence from new studies, interim results from phase III vaccine trials, and previous data from phase I and phase II trials support the notion that memory T cell responses to the vaccines, along with B cell antibody responses, should provide good and possibly enduring immunity to SARS-Cov-2. 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

- To estimate the neutralizing antibodies titre against SARS CoV-2 by vaccine type (Covaxin or Covishield) in healthcare/frontline workers.
- To estimate the proportion of vaccine recipients developing effective antibody response for SARS-CoV-2 specific IgG, IgM, and total IgE and IgA antibodies pre- and post-COVID-19 vaccination on day zero, day 28, month 2, 3, 6, 12, 18 and 24 by vaccine type.
- To identify and characterize the immune biomarkers for long term innate and adaptive immune response by vaccine type.
- To estimate the ratio of immune biomarker levels between pre- and post-COVID-19 vaccination at days 28, month 2, 3, 6, 12, 18 and 24 by vaccine type

Methodology

Study design: Prospective Cohort study

Exposure: Participants will 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.

Study population: Healthcare/frontline workers working in the ICMR-NIRT and ICMR-NIE aged 18 to 60 years

Study Sample size: This study aims to recruit ~150 participants at the time of first dose of vaccination (75 each who received Covaxin or Covishield).

Study procedure: 10 ml of whole blood 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 COVID-19 first dose of vaccine. In addition to above time points blood will also be collected at the time when the participant develops COVID-19 disease. For all the enrolled participants during all the time points blood sample collection, processing and storage will be done at ICMR-NIRT.

Study progress

Recruitment and immunological experimental phase is underway.

Completed studies

S.No.	**Title of the project**	**Principal Investigator**	**Source of funding**	**Category /Pillar**
I-16	CYP27b1gene polymorphisms in pulmonary tuberculosis	Dr. Harishanker M, Technical officer C and Dr. Ramalingam B, Scientist 'E'	Intramural ICMR-NIRT	TB/Detect
I-17	CYP27b1 gene polymorphisms in pulmonary tuberculosis	Dr. P. Kannan Scientist 'D'	ICMR Intramural and DST INSPIRE Fellowship	TB/Detect
I-18	Gene knockout characterization of Rv2159, an alkyl hydroperoxidase of Mycobacterium tuberculosis	Dr. P. Kannan Scientist 'D'	DST INSPIRE Fellowship and ICMR Intramural	TB/ Treat
I-19	Whole Genome Sequencing and Transcriptome analysis of Mycobacterium tuberculosis clinical isolates from Bovine and Human Origin	Dr. P. Kannan Scientist 'D'	Extramural – DST- SERB (N-PDF)	TB/Detect

DEPARTMENT OF
CLINICAL PHARMACOLOGY

DEPARTMENT OVERVIEW AND MANDATES

The Department of Clinical Pharmacology primarily undertakes pharmacokinetic profiling of anti-tuberculosis drugs and anti-retroviral drugs for patients participating in clinical trials of ICMR-NIRT and other studies conducted in various organisations of the country. The department also renders support in therapeutic drug monitoring (TDM) of anti-TB drugs for patients undergoing treatment at Government Research Institutes & Hospitals at the State and National level. The department is part of the International Quality Assurance Program (Netherlands) for proficiency testing of anti-TB drugs. We provided evidence on the therapeutic concentration of first- and second-line anti-TB drugs and drug-drug interactions. Our mandate is also to develop new, simple, and novel HPLC-based Methodology for measuring newer anti-TB, anti-viral, anti-diabetic drugs and vitamins in various biological fluids.

Studies in progress

BCP-1:Therapeutic Drug Monitoring in drug sensitive, non-responding pulmonary TB patients

Principal Investigator	:	Dr. A.K. Hemanth Kumar, Scientist D
Participating Institutes	:	Goa Medical College
Source of funding	:	NTEP
Study period	:	2018-2020
Category	:	TB
Pillar	:	Treat

Background

Therapeutic drug monitoring (TDM) has been used to ensure optimal dosing for maximizing the therapeutic benefit while minimizing toxicity. TDM is not routinely done for the active management of TB. Although published reports describe patients for whom slow response or no response to treatment was attributable to low drug levels, there is a gap in understanding how best to implement TDM on a programmatic scale. Definitions of slow response to treatment vary and recommendations to prioritize TDM for specific medications are lacking. However, identification of patients at risk for slow response is critical for improving the treatment outcomes. Programmatic implementation of TDM has been less studied.

Objectives

- To estimate plasma concentrations of first-line anti-TB drugs (RMP, INH, PZA) in pulmonary TB patients not responding or slowly responding to treatment under NTEP after ruling out drug resistance in these patients by culture or molecular Methodology
- In those patients detected to be having sub-therapeutic anti-TB drug levels, to assess the clinical, radiological, and bacteriological response by increasing doses of drugs

Methodology

This is a prospective study conducted in the department of Pulmonary Medicine, Goa Medical College. The study participants comprise of adult pulmonary TB patients who are receiving TB treatment in the NTEP centres in Goa. Patients with positive smear at 2 months of ATT were identified and therapeutic drug monitoring (TDM) was performed at this point of time. The sub-therapeutic cut-off values will be taken as <8µg/ml for RMP, <3µg/ml for INH and < 20µg/ml for PZA. If any of the drug concentrations are found sub-therapeutic, the dose of only those drugs will be increased for a month, after which TDM will be repeated. If the repeat smear is negative, the increased drug doses will be continued till the end of anti-TB treatment. The study aimsto to enrol 20 patients during the study period.

Study progress

So far five patients have been recruited and the study is in progress.

BCP-2:Impact of pregnancy on Tuberculosis

Principal Investigator : Jerrold J. Ellner (USA) & Sonali Sarkar (India)
Dr. A.K.Hemanth Kumar, Scientist D, NIRT
Participating Institutes : Goa Medical College and ICMR - NIRT
Source of funding : Goa Medical College
Study period : 2017-2020
Category : TB
Pillar : Detect, Treat

Background

Standard doses of first-line anti-TB drugs are recommended by the World Health Organization to treat pregnant women with active TB. Although the available data does not suggest any significant adverse maternal-fetal effects or need for dose adjustment in pregnancy, the PK of TB drugs in pregnant women has not been systematically studied, even for drugs that comprise the basic first-line regimen.

Objectives

- To determine the impact of pregnancy on diagnostic biomarkers of LTBI and on host biomarkers that may predict the risk of progression to TB.
- To determine the risk of TB in pregnancy and to describe the severity of disease, the response to treatment, and pregnancy outcomes.
- To evaluate the pharmacokinetics of TB drugs during pregnancy and assess the exposure of the fetus to anti-tuberculous TB drugs.

Methodology

The profile of anti-tuberculous drug metabolism between pregnant and non-pregnant TB patients will be compared by conducting PK studies every 2 months during the TB treatment. This will include drug level measurements (at 1 hour, 2 hours, and 6 hours post-drug administration) and will determine appropriate dose adjustments for pregnant women.

Study progress

. A total of 8 patients have been recruited and the study is in progress

BCP-3:Pharmacokinetics of second-line anti-TB drugs in children and adolescents with MDR TB

Principal Investigator : Dr.A.K.Hemanth Kumar, Scientist D
Participating Institutes : NIRT, ICH, LHMC, NITRD
Source of funding : ICMR-ITRC
Study period : 2019-2022
Category : TB
Pillar : Treat

Background

Drug-resistant TB (DR TB) is an important health issue which needs to be addressed especially among children. There is a paucity of pharmacokinetic data of ATT in children with MDR TB. A prospective, observational study was conducted to determine the pharmacokinetics of Levofloxacin (LFX), Pyrazinamide (PZA), Ethionamide (ETH), and Cycloserine (CS) in 25 children with MDR TB being treated according to NTEP guidelines at the Sarojini Naidu Medical College, Agra. The study results showed that the second-line anti TB drug levels were within the therapeutic range. Till date, only few studies have evaluated the pharmacokinetics of second line anti-TB drugs in children, however, with modest sample size. Therefore, there is a need to evaluate the safety and pharmacokinetics of second-line ATT in children with MDR-TB.

Objectives

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

Methodology

A prospective, cross-sectional PK study is being conducted at the Institute of Child Health, Chennai, BJ Wadia Hospital for Children, Mumbai, Lady Hardinge Medical College, New Delhi, and National Institute for Tuberculosis and Respiratory Diseases, New Delhi. The sample size is 200 children.

Study progress with Interim Findings:

Presently, 91 children have been recruited of which 69 is in Mumbai and 22 in Chennai. The study is ongoing

BCP-4:Bioavailability of fixed dose combination of first line anti-TB drugs in patients with pulmonary tuberculosis

Principal Investigator : Dr. A. K. Hemanth Kumar, Scientist D
Participating Institutes : NIRT, ICH, MMC, GHTM
Source of funding : ICMR Intra-mural
Study period : 2020-2022
Category : TB
Pillar : Treat

Background:

Fixed-dose combination (FDC) of drugs is one of the Methodology to improve compliance and reduce errors. The rationale of FDC is that the presence of all drugs combined in one tablet can facilitate dosage calculation, prevent prescribing errors, increase patient’s acceptance, and decrease pill burden. In India, FDC’s are recommended for TB patients under the National Tuberculosis Elimination Programme (NTEP) during daily treatment both in the intensive and continuation phase. There are 5 weight bands for adult TB patients receiving INH, RMP, PZA, and EMB (75/150/400/275mg) and 6 weight bands for children receiving dispersible FDC’s (50/75/150/100) in addition to streptomycin for 2 months in the intensive phase. Till date there a lack of assessment of the combined use of 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

The study will be conducted in adult TB patients who receive treatment at the Govt Hospital for Thoracic Medicine, Tambaram, and children at the Institute for Child Health, Egmore, Chennai. These patients will be receiving FDC formulation of anti-TB drugs based on their body weight as per NTEP recommendation for a week. The patients will be requested to report to the treatment centre in the morning without taking any anti-TB medication, under fasting conditions. Serial blood samples will be collected at 2, 4, 6, 8 & 12 hours after drug administration. Plasma RMP, INH, and PZA concentrations will be estimated by validated HPLC Methodology. Based on the plasma concentrations at different time points, certain pharmacokinetic parameters such as peak concentration, Tmax, exposure (area under the time concentration curve), and half-life will be calculated.

Study progress with Interim Findings: Necessary approvals for the conduct of the study have been obtained and the recruitment of patients is initiated. It will be conducted in 12 patients each of adults receiving treatment under 5 different weight bands and paediatric population receiving treatment under 6 different weight bands. This study is in progress.

Completed studies

S.No.	**Title of the project**	**Principal Investigator**	**Source of funding**	**Category /Pillar**
BCP-5	Pharmacokinetic drug-drug interactions between first line anti-TB and anti-diabetic drugs	Dr. A.K. Hemanth Kumar Scientist ‘D’	ICMR Intra-mural	TB / Treat

DEPARTMENT OF BIOCHEMISTRY

DEPARTMENT OVERVIEW AND MANDATES

The Department of Biochemistry contributes to the following major activities of ICMR-NIRT.

Clinical Biochemistry Laboratory Activity:The Clinical Biochemistry Laboratory (CBL) plays a vital role in providing high-quality diagnostic and research support to various research projects conducted at NIRT. Currently, about 18 clinical trials and few research studies are utilizing the analytical service of CBL. In the year 2020-21, around 3500 clinical samples from various trials were analysed at CBL. The launch of the Laboratory Information System by CBL has been much useful and advantageous in terms of decreasing the turnaround time (TAT) which in turn improved clinical care management of study participants. Presently the laboratory is in the process of getting accreditation with the National Accreditation Board for Testing and Calibration Laboratories (*NABL*). Estimating the active content of the ATT drugs and reporting the data to the Drug Procurement Committee of NIRT is another important regular activity of the Department of Biochemistry

The focus of research of the department are as follows:

To establish newer point of care (POC)diagnostic tools: Studies have been initiated to establish POC diagnostic procedures which are effective in terms of (a) increasing the specificity and sensitivity of screening procedures and (b) decreasing costs of implementing intensified case finding processes of TB diagnosis.

To explore adjuvant therapeutic leads from functional foods and natural compounds: Efforts are initiated to explore potential natural compounds with immunomodulatory potential and anti-inflammatory properties for therapeutic application.

To develop nano delivery of nutrients along with ATT: The focus is on investigating novel therapeutic approaches using nano-mediated delivery of nutraceuticals and pharmaceuticals.

To establish lipidomics and metabolomics facility: To address various basic research aspects and biomarker discovery we have initiated a process to establish lipidomics facility (LC/MSMS) in the Department of Biochemistry.

Studies in progress

BC-1:Evaluation and characterization of potential therapeutic leads form AYUSH system of medicine for adjuvant therapy during anti-tuberculosis treatment.

Principal Investigator	:	Dr.N Saravanan, Scientist D
Participating Institutes	:	ICMR-NIRT, Chetpet, Chennai Vellore Institute of Technology (VIT), Vellore Foundation for Neglected Research, Bangalore
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 persons on ATT, the adverse drug reaction caused in the host and the altered inflammatory homeostasis may reflect in 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 *M.tb*, (ii) to aid pulmonary health to withstand the necrotic effects of *M.tb* infection and to (iii) preserve liver function during treatment to avoid anti-tubercular drugs induced adverse effects.

Objectives

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

Methodology:

To meet the first objective we have conducted in silico studies in collaboration with the Medical and Biological Computing Laboratory, School of Biosciences and Technology, Vellore Institute of Technology (VIT), Vellore.

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, RMP, PZA, and EMB) and second-line (Fluoroquinolones, Bedaquilline and Capreomycin) ATT. The selected proteins for the docking studies are (i) 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.

Study progress

The results showed that seven novel phytochemicals namely Gardenin-A, Swertiamarin, Glycyrrhizin, Alizarin, Mangiferin, Laccaic acid, and Aloe-emodin are binding efficiently with active targets of ATT drugs as evidenced by the number of hydrogen bond formation and C-score. These compounds will be further characterized for their other beneficial effects before initiating *in vitro* and *in vivo* studies for which an application has been submitted for funding.

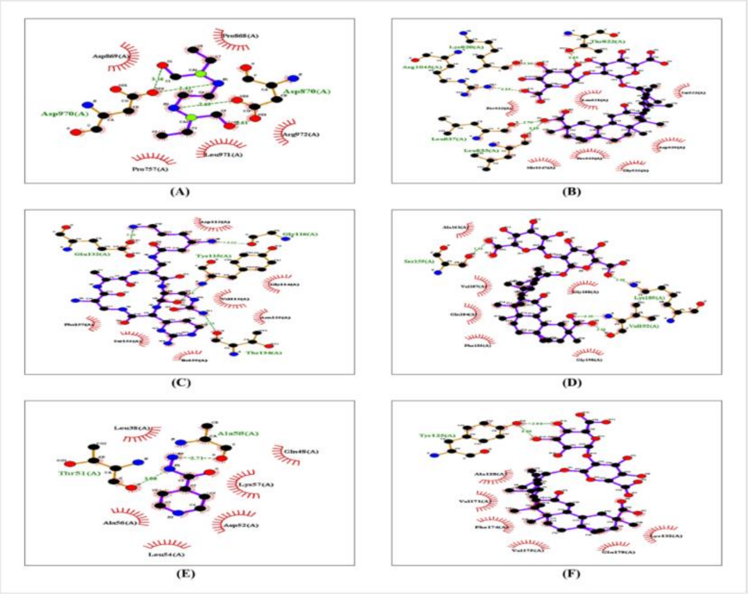


Fig 5: Comparison of protein-ligand binding in protein-glycyrrhizin complex and the proteins with other anti-TB drugs (Ethambutol, Capreomycin, and Isoniazid). (A) 3PTY with Ethambutol (B) 3PTY with Glycyrrhizin (C) 5KYG with Capreomycin (D) 5KYG with Glycyrrhizin (E) 5VRL with Isoniazid and (F) 5VRL with Glycyrrhizin

BC-2:Point of care estimation of Vitamin D and C-Reactive Protein for tuberculosis screening in household contacts of active pulmonary tuberculosis patients in Chennai, India: A pilot study

Principal Investigator : Dr.N Saravanan, Scientist D
Participating Institutes : ICMR-NIRT
Source of funding : ICMR Intra-mural
Study period : 2020-2021
Category : TB
Pillar : Detect

Background

To achieve elimination of TB,the Worlds Health Organisation stressed the importance of ‘systematic screening’ of high-risk populations such as household contacts (HHC) of index cases to detect TB early and thereby decrease the risk of (a) transmission (b) adverse social and economic consequences and (c) adverse treatment outcomes. It is established that the serum vitamin D concentration ≤25 nmol/L is significantly associated with increased risk of active TB while an increase in the levels of C Reactive Protein (CRP; ≥8 mg/L) is been used as predictive marker for active TB. We herewith proposed to employ point of care testing of both Vitamin D and CRP levels in HHC of pulmonary TB patients as a strategy to increase specificity and sensitivity of the screening procedure further”

Objectives

To compare the diagnostic accuracy (sensitivity and specificity) and the predictive value (negative and positive predictive value) of point-of-care (POC) estimation of C-reactive protein and Vitamin D with WHO symptom-based screening for active TB in the household contacts of PTB patients.

Methodology

Serum samples of 200 household contacts were identified from the repository of RePORT India (Regional Prospective Observational Research for Tuberculosis) database and subjected to the POC test for Vitamin D and CRP. CRP and Vitamin D are fairly stable in proper storage conditions. The data on liquid culture, chest X-ray, gene Xpert, and demographic information will be accessed for the respective household contacts.

The diagnostic accuracy and the predictive value POC estimation of CRP & Vitamin D will be compared with symptoms and chest X-Ray (CXR) for active TB in household contacts of PTB patients with reference to culture results and Xpert MTB/RIF data independently.

Study progress

We have completed the POC estimation of Vitamin D and CRP. The data will be analysed.

BC-3:Development and Characterization of a Novel Nanopeptide System for Therapeutic Application in Residual Lung Injury caused by Pulmonary Tuberculosis

Principal Investigator	:	Dr. N Usha Rani (ICMR-RA)
Mentor	:	Dr N Saravanan
Participating Institutes	:	ICMR-NIRTand 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 immune modulations caused by *M.tb* within the host. The hyper inflammation occurred due to chronic TB infection and the uptake of ATT drugs, lead to severe residual lung injury which is a common risk factor for TB recurrence 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 as a response to variation in ionic strength and the presence of a crosslinker. Functionalized nano-peptides can also act as a novel carrier to encapsulate the ATT drugs and act as a targeted nano-delivery system.

Objectives

- To develop and characterize a novel nano peptide system using carnosine as a bioactive molecule for therapeutic application
- To investigate the therapeutic potential in *in vitro* experimental infection system of pulmonary TB
- 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 over the initial intense pro-inflammatory response, immune homeostasis, and excessive inflammation that causes residual lung injury during pulmonary TB. Further, to understand the efficiency of maintaining the homeostasis of inflammation by carnosine, *in vitro* studies will be carried out using murine macrophage cell aggregates. To comprehend the biological function of the developed nanosystem, the biophysical parameters of cell recitation will be confirmed through the *in vivo* model

Study progress

The preliminary experiments are initiated to prepare and characterize the nano carnosine.

Completed studies

	Title of the project	Principal Investigator	Source of funding	Category /Pillar
BC-4	**Vitamin D concentrations in adult tuberculosis patients**	Dr N Saravanan Scientist D	ICMR Intra-mural	TB / Detect

DEPARTMENT OF HIV/AIDS

DEPARTMENT OVERVIEW AND MANDATE

The Department of HIV/AIDS plays a key role in providing high quality diagnostic services and research support for various HIV/TB and HIV clinical trials and research projects undertaken by ICMR-NIRT. The laboratory is accredited by International Agencies like NIH and WHO, and has a long record of successful participation in some of the best External Quality Assurance programs.

The Diagnostic Serology division of the Department provides routine clinical safety parameter testing services required for clinical trials and other research studies. The Molecular Diagnostic division supports the molecular diagnosis of HIV 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 and the BSL-II Virology facility supports COVID-19 testing. Besides, the department has a flow cytometry facility, sequencing laboratory, cell culture laboratory, Central TB Biorepository and a Regional HIV Biorepository.

The scientific programs of the department are organized into TB, TB/HIV and HIV research. The Department of HIV/AIDS holds the status of a National Reference Laboratory for HIV-1 drug resistance genotyping, Regional Reference Laboratory for molecular diagnosis of HIV 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 EQA program for isolation and cryopreservation of peripheral blood mononuclear cells (the first and only in country PBMC EQA program) for the RePORT India Consortium.

Studies in progress

HIVL-1:Identification of biomarkers for predicting progression from Latent Tuberculosis Infection to Active Tuberculosis disease

Principal Investigator : Dr. Luke Elizabeth Hanna, Scientist 'E'
Participating Institutes : National Institute for Research in Tuberculosis (NIRT), Byramjee Jeejeebhoy Government Medical College, Pune (BJMC), Johns Hopkins
Source of funding : ICMR Intra-mural
Study period : 2019-2022
Category : TB
Pillar : Detect

Background

Majority of *M. tuberculosis*-infected individuals remain healthy, implying that immune responses in individuals that control latent infection throughout their lifetime differ from responses in those who develop TB disease within the first years following infection. This suggests that correlates of TB progression should exist, and identification of these predictors would play a crucial role in the early identification of individuals with the highest immediate risk of progressing to active TB. This in turn could lead to timely implementation of prophylaxis and contribute in a significant way to making the aspiration of TB elimination a reality.

Objectives

- Multiplexed cytokine analysis of no induced (Nil) and induced (TB A stimulated) plasma (quantiFERO supernatant) of TB progressors and no progressors.
- microRNA profiling of non-induced ar induced plasma of TB progressors and no progressors
- Single nucleotide polymorphism (SN) analysis in TB progressors and no progressors by genotyping.

Methodology

Multiplexed cytokine analysis will be performed using the Luminex platform. miRNA expression will be profiled using Next Generation Sequencing and genetic polymorphism studies will be performed using genotypic analysis and identification of SNPs will be performed using targeted gene sequencing.

Study Progress

Circulating levels of a panel of 45 analyt comprising of inflammatory cytokine chemokines and growth factors were measur in quantiferon supernatants (from unstimulat and TB antigen tubes) of 14 progressors (hou hold contacts of TB patients who progressed TB disease during a two year follow-up perio and 20 age and sex-matched non-progresso using the Luminex Magpix Multiplex Ass system (Bio-Rad, Hercules, CA), Lumin Human Magnetic Assay kit 45 Plex (R & systems). Preliminary analysis reveal significantly differences in 20 of the analytes measured between the two stu groups. Further analysis is ongoing.

HIVL-2:Impact of malnutrition on immune responses to tuberculosis in Indian Children

Principal Investigator : Dr. Aishwarya Venkataraman,Scientist 'E'
Participating institutes : NIRT, Institute of Child Health, Stanley, KKCTH
Source of funding : DBT
Study Period : 2018-2022
Category : TB
Pillar : Treat

Background

Acute malnutrition affects 52 million children globally, of whom nearly two-thirds have moderate acute malnutrition (MAM). Malnourished children have increased susceptibility to infections like TB, probably due immunodeficiency caused by undernutrition. The present study aims to assess immune responses to *M. tuberculosis (M.tb)*in children with MAM compared to well-nourished children and to evaluate the impact of a nutrition invention on the *M.tb*-specific immune response.

Objectives

- To characterize innate and T-cell immune responses to *M.tb* in moderately malnourished and well-nourished children with TB disease.
- To characterize innate and T-cell immune responses to *M.tb* in moderately malnourished and well-nourished children with latent TB infection (LTBI).
- To assess the impact of a nutrition intervention on immune responses to *M.tb* in children with malnutrition.

Method

The study included 4 groups of HIV-uninfected children: 1) MAM children with TB disease; 2) Well-nourished children with TB disease; 3) MAM children with LTBI; 4) Well-nourished children with LTBI. A range of assays were used to compare innate, adaptive and functional immune responses to TB between the groups. The children were followed up during the 6 months of TB therapy / chemoprophylaxis. Ready-to-use supplementary food was given to MAM children for 12 weeks. Longitudinal changes in innate and adaptive immune function, monocyte: lymphocyte ratio and mycobacterial growth inhibition activity were evaluated.

Study progress:

Till date, 33 MAM children and 55 well-nourished children with latent TB infection, and 8 MAM children and 4 well-nourished children with TB have been recruited into the study. 36 children have completed 24 weeks of follow up. The study is ongoing.

HIVL-3: NIRT PBMC Cryopreservation Proficiency Testing Program

Principal Investigator	:	Dr. Luke Elizabeth Hanna, Scientist ‘E’
Participating Institutes	:	ICMR-NIRT
Source of funding	:	NIH-CRDF
Study period	:	2019-2022
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 cryopreservation of PBMC is very crucial. Since, there is no in-country PBMC PT program in India, NIRT has been implementing a country-specific PT program from 2017 for the clinical research sites participating in RePORT India Common Protocol.

Objectives:

- To assess a laboratory’s ability to provide good quality PBMC for future research
- To respond quickly and appropriately to poor performance

Methodology:

Six laboratories processing PBMC for RePORT India Consortium - CMC, MVDRC, JIPMER, BJMC, BMMRC and NIRT, are enrolled in this program.

Four quarterly surveys are rolled out each year. For each quarter, each laboratory is required to submit two aliquots of 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, thaw them and score them for viability as well as recovery. The performance scores are shared with the respective labs as well site PIs.

Study progress

The program has been successfully administering quarterly PT surveys for all the participating labs.

HIVL-4:Cohorts for HIV Resistance and Progression in Indian Children and Adults (CoHRPICA)/National HIV Cohort Program

Principal Investigator	:	Dr Luke Elizabeth Hanna,Scientist ‘E’
Participating Institutes	:	NIRT, NIE, NARI, YRG CARE, IGICH
Source of funding	:	ICMR/DBT/IAVI
Study period	:	2018-2021
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 populations.

Aim

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

Methodology

The study targets to enrol 25-30 individuals with early HIV infection from key high risk populations (MSM/TG, PWID and FSW), 1050 HIV-exposed uninfected individuals (350 in each of the above-mentioned risk category) and 250 HIV-infected adult participants (including 100 individuals without co-morbidities and 150 with/at-risk of co-morbidities like TB, CVD & diabetes) and 100 HIV-infected children, including 50 mother-child transmission pairs. NIRT will contribute 175 HIV-uninfected MSM/TG and 50 HIV-infected participants with/without comorbidities. 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

A total of 156 HIV uninfected MSM/TG participants were screened, out of which 39 were enrolled and 73 follow-up visits have been completed.

A total of 37 HIV infected adult participants were screened, out of which 35 were enrolled and 20 follow-up visits have been completed. Out of 35 enrolled participants, 24 had no comorbidity, while 8 had TB and 3 had Diabetes Mellitus respectively.

HIVL-5: Impact of HIV infection and antiretroviral therapy on biomarkers for premature onset of aging-associated disorders in HIV-infected individuals

Principal Investigator	:	Dr. A. Nusrath Unissa
Participating Institutes	:	ICMR-NIRT and YRG CARE
Source of funding	:	ICMR
Study period	:	2019-2023
Category	:	HIV

Background

Availability of antiretroviral therapy (ART) has transformed HIV infection to a chronic manageable disease. In spite of 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. The present study aims to correlate alterations in metabolite profile with risk factors for aging associated co morbidities like CVD, DM, liver and kidney diseases.

Objectives

- To identify abnormalities in immunological and biochemical parameters in HIV-infected individuals on ART.
- To correlate cellular and immunological abnormalities with biochemical markers indicative of risk for cardiovascular disease, diabetes mellitus, liver and kidney diseases.

Methodology

The study includes a sample size of 100 HIV-infected individuals on antiretroviral therapy for 2 years or more and an equal number of HIV negative healthy controls matched for age and sex. Blood samples will be collected from recruited participants for haematological and biochemical analyses. The participants will be screened for other viral co-infections like HBV, HCV, CMV and SARS-CoV-2. PBMC will be isolated and stored for flow cytometric analysis and telomere length determination.

Study progress

So far 60 participants (35 HIV-infected persons and 25 healthy volunteers) have been recruited to the study. The interim findings of the study revealed elevated levels of several biochemical parameters such as cardiac markers, liver enzymes, renal function parameters in HIV infected individuals. The study is ongoing.

HIVL-6: Construction and characterization of Infectious Molecular Clones (IMCs) of Transmitted/Founder (T/F) HIV-1 viruses

Principal Investigator	:	Dr. Luke Elizabeth Hanna,Scientist ‘E’
Participating Institutes	:	ICMR-NIRT
Source of funding	:	ICMR Intra-mural
Study period	:	2018-2022
Category	:	HIV

Background

Mucosal transmission occurs across a selective bottleneck that typically allows only a single (or few) variant(s) of the virus present in a donor to be passed on to the recipient. Understanding the unique characteristics of the unusual forms of HIV-1 (Transmitted/ founder or TF) viruses that are transmitted will help in the explicit design of effective vaccines.

Objectives

- To construct full-length infectious clones and characterize them for fitness, infectivity and replication kinetics
- To investigate the transmission of the virus across the mucosal barrier using an in vitro cell culture model.

Methodology

For generating the molecular clones, we amplified the full-length genome of HIV-1 from the plasma virus of recently infected HIV-1 positive children. The PCR products were ligated into the backbone of a cloning vector to generate full length viral clones. The clones will be analysed for presence of full-length HIV-1 genome using PCR as well as restriction digestion. Full length clones will be characterized for infectivity using TZM-bl reporter cell lines. A few representative clones from each individual will be sequenced and subjected to phylogenetic analysis for identification of T/F and CC viruses. The T/F and CC viruses will be used for further phenotypic and genotypic characterization.

Study progress

We generated individual-specific full-length HIV-1 clones from the plasma virus of three HIV positive children. A total of 23 full length infectious clones have been identified. The clones are being analysed for replication kinetics, tropism, co receptor usage, sensitivity/resistance to innate immune factors and broadly neutralizing antibodies, etc. The whole genome sequence data of these clones is awaited. A few representative T/F and CC clones will be used for detailed investigation of the key events/mechanisms involved in host-virus interaction, transmission across the genital mucosal surface cells and successful establishment of HIV infection.

HIVL-7: Introduction and characterization of point mutation in gag region of HIV-1 using Adenosine Deaminase acting on RNA (ADAR)

Principal Investigator	:	Dr. Luke Elizabeth Hanna,Scientist ‘E’
Participating Institutes	:	ICMR-NIRT
Source of funding	:	ICMR Intra-mural
Study period	:	2021-2024
Category	:	HIV

Background

Adenosine deaminase acting on dsRNA (ADAR) is a ubiquitously expressed enzyme that deaminates adenosine to inosine in double stranded pre-mRNA in humans. ADAR-1 has two domains, a recruiting domain which binds to the hairpin loop of guide RNA (gRNA) and a deaminating domain which deaminates the targeted adenosine to inosine. HIV uses the host machinery to translate its mRNA, and any alteration in the codon could result in the production of an incomplete/non-functional protein. The present study will focus on analyzing the gene editing efficiency of ADAR-1 using gRNA and identify a strategy to exploit its function to inhibit HIV-1 protein synthesis.

Objectives

- To construct an ADAR-1 p150 guide RNA cassette.
- To analyze the gene editing efficiency of the cassette and its ability to inhibit protein synthesis.
- 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 Gibson assembly according to the manufacturer’s protocol. The constructed clone will be confirmed by restriction digestion and sequencing using the Sanger’s method.

Study progress

This study has just been initiated. Guide RNA for HIV-1 target has been designed as a single oligonucleotide stretch. The ssOligos were annealed using TE buffer at 95°C for 2 min and gradually cooled to room temperature. The annealed oligos will be cloned with a pSilencer 2.1-U6 hygro vector and confirmed with restriction digestion and sequencing. The study is ongoing.

HIVL-8: Role of Neutrophils and Neutrophil extracellular traps in the pathogenesis of Pulmonary Tuberculosis and COVID-19 co-infection

Principal Investigator	:	Dr. Nancy Hilda J,Scienttist 'B'
Participating Institutes	:	ICMR-NIRT
Source of funding	:	ICMR Intra-mural
Study period	:	2021
Category	:	TB/COVID-19

Background

Neutrophil Extracellular Trap (NET) formation is one of the killer functions of neutrophils, where they trap the pathogen and destroy it initially. Despite this fact, at the advanced stage of infection, NETs are involved in disease pathogenesis. Even in the recent pandemic COVID-19, NETs are proven to be related to severe symptoms in patients. Since TB is anticipated to increase the susceptibility to COVID-19, it is essential to interpret the neutrophil mediated responses during pulmonary TB (PTB) and COVID-19 co- infection.

Objective

To understand neutrophil mediated responses during PTB and COVID-19 co-infection.

Methodology

Twelve millilitres of whole blood were collected from eligible participants by trained laboratory personnel. Haematological and biochemical parameters (D-Dimer, C-reactive protein, Ferritin, Lactate Dehydrogenase) will be analyzed using automated analyzers. Neutrophils isolated from peripheral whole blood will be cultured overnight with PMA/Ionomycin overnight in 5% CO_2 incubator. Cell culture supernatants will be collected and stored at -80^{O}C for analysing cytokines. Complement proteins (C3a, C5a and C5b-9 complex) and NET markers will be estimated using commercial ELISAs from the plasma samples.

Study progress with Interim Findings :

Recruitment has begun and 30 PTB patients have been recruited so far. In the PTB-COVID co-infected category 7 participants have been recruited. The CBC results and biochemical test results of CRP, D-Dimer, Ferritin and lactate dehydrogenase are available. Neutrophils were isolated from the peripheral blood of participants and cultured with PMA overnight. Cell culture supernatants have been stored at -80^{0}C for cytokine and complement assays. Serum has also been stored for quantification of MPO-DNA complexes, Cit-H3 and cell free DNA.

HIVL-9: Molecular and immune profiling in adults affected with COVID-19 disease

Principal Investigator	:	Dr. N. Sudhakar , Scinetist 'B'
Participating Institutes	:	ICMR-NIRT, Government Corona Hospital, Guindy
Source of funding	:	ICMR Intra-mural
Study period	:	2020-2021
Category	:	COVID-19

Background

Corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic that has affected more than 180 million individuals worldwide. Angiotension converting enzyme 2 (ACE2) receptor serves as the entry receptor for SARS-CoV-2 into 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 the serine protease TMPRSS2 and FURIN that are readily expressed in lung tissue. The proposed study aims to analyze levels of ACE-2 and TMPRSS-2 gene expression in SARS-CoV-2 infected individuals and correlate it with cytokine production and disease severity.

Objectives

- To analyze expression of ACE-2 and TMPRSS-2 genes in nasal epithelial cells and peripheral blood mononuclear cells (PBMC) and correlate it with circulating levels of ACE2 in SARS-CoV-2infected individuals.
- To investigate the extent of immune dysregulation in infected individuals by measuring circulating levels of cytokines and chemokines in plasma.

Methodology

The study includes 120 SARS-CoV-2 infected individuals with mild/moderate/severe disease as well as 40 healthy controls. COVID-19 testing will be performed using diagnostic real time RT-PCR. Viral load will be estimated from nasal swab using quantitative real time RT-PCR. Expression of ACE-2 and TMPRSS-2 genes in epithelial cells from nasal swabs and PBMC were performed using quantitative real time RT-PCR. Immune dysregulation will be analyzed by measuring a panel of inflammatory cytokines and chemokines using the Luminex Multiplex assay. Transcriptomic analysis will be performed in a subset of 20 individuals using RNAseq analysis.

Study Progress

The study has recruited 88 mild, 26 moderate and 6 severe COVID-19 cases. Twelve millilitres of blood and nasal swab sample were collected from study participants. Blood components including plasma/serum and PBMCs were separated and stored appropriately. Viral RNA was extracted from nasal swab and total RNA was extracted from PBMC and analyzed for *ACE-2* and *TMPRSS-2* gene expression. Preliminary analysis has revealed a distinct difference in the levels of expression of *ACE-2* gene in the nasal swabs of mild versus moderate/severe COVID-19 cases. The study is ongoing.

HIVL-10:Development and validation of a diagnostic kit for early detection of Human Papilloma Virus (HPV) infection in cervical cancer

Principal Investigator	:	Dr. N. Sudhakar
Participating Institutes	:	ICMR-NIRT, IOG - Egmore
Source of funding	:	DST Scheme for Young Scientists and Technologists (SYST) under SEED funding
Study period	:	2019-2021
Category	:	HPV

Background

Cervical cancer is caused by Human Papilloma Virus (HPV) infection. There are more than 100 HPV genotypes present and they are classified into high-risk and low-risk types. Currently available Methodology for early detection of HPV involve conventional PCR and Real-time PCR based techniques which require sophisticated equipment and laboratory expertise, making it difficult to implement in low resource settings. This project aims to develop a detection kit for HPV based on Loop-Mediated Isothermal Amplification (LAMP) that uses isothermal temperature for amplification of target gene.

Objectives

- To design primers for detection of HPV infection using Loop Mediated Isothermal Amplification (LAMP) technique
- To validate the LAMP assay in HPV positive cervical cancer cell lines (SiHa, CasKi) and a HPV negative cervical cancer cell line (C33A)
- To detect HPV infection in cervical cancer tissue samples using LAMP technique (n=100) vs. PCR based method (n=100).

Methodology

LAMP primers targeting the L1 region of the HPV genome were designed using Primer Explorer software https://primerexplorer.jp/e/. The designed primers were validated in genomic DNA isolated from HPV positive cervical cancer cell lines Caski and SiHa. Eighty five cervical cancer tissue biopsy samples were collected from Institute of Obstetrics and Gynecology (IOG), Egmore, Chennai. Genomic DNA was extracted from cervical cancer tissue samples using the QIAamp DNA mini kit (Qiagen Inc). HPV testing was done using traditional PCR with GP5+ GP6+ primers specific for HPV-L1 region. LAMP assay was performed in genomic DNA isolated from 60 cervical cancer tissue samples.

Study Progress:

Out of eighty five cervical tissue biopsy samples tested, 70 were amplified with GP5+ GP6+ primers and 41 of 60 samples (68.3%) were amplified in LAMP assay with our designed set of primers. HPV high-risk genotypes HPV16/18 were detected in 76 of 85 (89%) cervical tissue samples. The study is ongoing.

Completed studies

S.No.	Title of the project	Principal Investigator	Source of funding	Category /Pillar
HIVL-11	Role of complement in pulmonary tuberculosis	Dr. Nancy Hilda, Scientist B	ICMR-Intramural	TB/Detect
HIVL-12	Molecular Dynamics Simulation and Structural Analysis of HIV-1 Antisense Protein (ASP)	Dr. Luke Elizabeth Hanna Scientist “E”	NIL	HIV
HIVL-13	Non-Invasive, Rapid, Specific and Sensitive Electrochemical Biosensor for Detection of COVID-19 infection	Dr. Murugan Veerapandian Scientist, CSIR-CECRI, Co-Principal Investigators : Dr. N. Sudhakar – NIRT, Dr. K. Anand Babu, Research Scientist, Dr.A.P.J. Abdul Kalam Centre, Chennai	DBT	COVID-19

DEPARTMENT OF STATISTICS

DEPARTMENT OVERVIEW AND MANDATES

The Department of Statistics is extending its consistent statistical support in various stages of medical research and undertakes major roles in study planning, sample selection, data management, interpretation and reporting. The department staff contribute as collaborative scientists, providing expertise in statistical Methodology for different research studies dine in ICMR-NIRT. The staff members also pursue their individual research projects and activities and participate in curriculum development for courses/trainings. Our department has expertise in linear, nonlinear, and longitudinal modelling; clinical trial and experimental design; survival analysis; categorical data analysis; causal inference; TB, HIV and Cancer disease modelling; computational biology and bioinformatics; machine learning algorithms and data mining; GIS based spatial modelling and Bayesian methodology. The mission of the department is to advance the discipline by training students in methodological research and its application, conducting collaborative interdisciplinary research in the fields of public health and medicine, and by contributing to the academic, research and professional committees.

Our current research focus areas are survival analysis for high-dimensional data, machine learning Methodology and data mining, latent variable modelling, longitudinal data analysis, categorical data analysis, GIS based spatial modelling and Bayesian analysis.

Studies in progress

S-1:Development of a Database of Clinical Study X-rays at ICMR-NIRT, Chennai

Principal Investigator	:	Dr.C.Ponnuraja, Scientist 'E'
Participating Institutes	:	ICMR-NIRT
Source of funding	:	ICMR Intra-mural
Study period	:	2019 - 2020
Category	:	TB
Pillar	:	Build

Background

NIRT has been conducting clinical trials to define better treatment for various forms of TB during the last several decades. This involves laborious manual documentation of X-rays and follow-up of patients up to five years. An efficient electronic image capturing (EIC) through a clinical trial management system (CTMS) is essential to create a database of X-rays as an e-storage. The radiograph film digitization is a process to maintain electronic records in permanent archives which could be useful for future research.

Objective

The objective is to convert the existing hard copies of X-rays into DICOM images as an Electronic Data Capture (EDC) system and to provide for architecting a solution to enable the interfacing of different applications for developing a repository.

Methodology

The image quality is maintained since film fading is prevented. To maintain metadata as digital data for a longer period of time, physical archive storage will be used. All images will be documented electronically and stored in a database. All authorized local norms and international standards are met by these electronic records. The picture life cycle entity's durability is ensured by the lifespan of the x-ray data. This database is simple to use, accessable, and can be managed in conjunction with clinical trial data.

Study Progress

We have arranged hard copies of x-ray and are scanning them with x-ray-digitizer which was purchased recently. The project has supported by sharing 1500 images (1000 normal and 500 abnormal) for Artificial Intelligent projects as per the MoU of NIRT-IPR.

S-2: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
Study period	:	2020 - 2022
Category	:	TB
Pillar	:	Treat

Background

Health Related Quality of Life (HRQoL) is a multidimensional concept that is evaluated by number of 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, we are planning 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

Objectives
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 continuation phase, and after three month of completion of anti TB treatment) using BSEM.

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

Study Progress
The study was initiated in November 2020. A total of 103 TB patients at the initiation of anti-TB treatment, 59 TB patients at the end of intensive phase of treatment and 19 TB patients at the end continuous phase of treatment were interviewed. The study is on-going.

S-3:ICMR-IPR Project of AI tool for Survey X-rays: Phase-I X-rays Annotation at NIRT, Chennai

Principal Investigator	:	Dr.C.Ponnuraja, Scientist 'E'
Participating Institutes	:	ICMR-NIRT
Source of funding	:	IPR
Study period	:	2021 - 2022
Category	:	TB
Pillar	:	Detect

Background
It is vital to have an efficient tool to diagnose TB in a peripheral health sector level and remote area. Still, finding a user-friendly, fast, quick, and robust method for TB diagnosis utilizing chest x-rays is difficult. The ICMR-NIRT has compiled vast collections of x-rays from numerous clinical trials and related investigations over the course of several decades. The data sources of NIRT would be utilized for the development of the AI tool for X-rays. The objective is to annotate all images related to the ongoing project "Development of a Database of Clinical Study X-rays at NIRT, Chennai". As per the requirement of the NIRT-IPR MoU of the "Development of Artificial Intelligence Tool for Screening/detection of Pulmonary TB using Chest X-rays", the required images may be annotated for the AI project.

X-Ray Images:
It is required to share 5000 chest-rays from NIRT for Phase 1, which includes 4000 abnormal chest x-ray and 1000 normal x-rays. As per MoU, we have collected 5000 chest x-ray images, 1000 are normal and 4000 are abnormal in DICOM format. Since the annotation software of IPR, can accommodate only JPEG images and all 5000 images have been converted into JPEG format.

X-Ray Annotation:
X-ray Annotation is planned be done by an Expert in reading the chest x-ray images.

DEPARTMENT OF EPIDEMIOLOGY

E-1: National Survey for state-wise prevalence of microbiologically confirmed pulmonary tuberculosis in India

Principal Investigator	:	Dr.Sriram Selvaraju, Scientist 'D'
Participating Institutes	:	ICMR-NIRT,
Source of funding	:	Central TB Division through DHR-ICMR
Study period	:	2018-2021
Category	:	TB
Pillar	:	Monitoring

Background: Monitoring progress by estimating TB disease burden in the community has been a challenge. Nationwide Survey during 1955-1958 and a number of surveys in geographically defined areas conducted earlier confirmed that TB disease was highly prevalent throughout the country. Noticeably, TB nationwide survey was never repeated after 1956. It is important to conduct a nationwide TB prevalence survey, if we really want to closely monitor the progress towards TB control with the aim to 'End TB' as per Sustainable Development Goals (SDGs).

Objectives

To estimate the point prevalence of microbiologically confirmed pulmonary TB among persons aged ≥15 years in India at National level and for 20 states / state groups.

Method

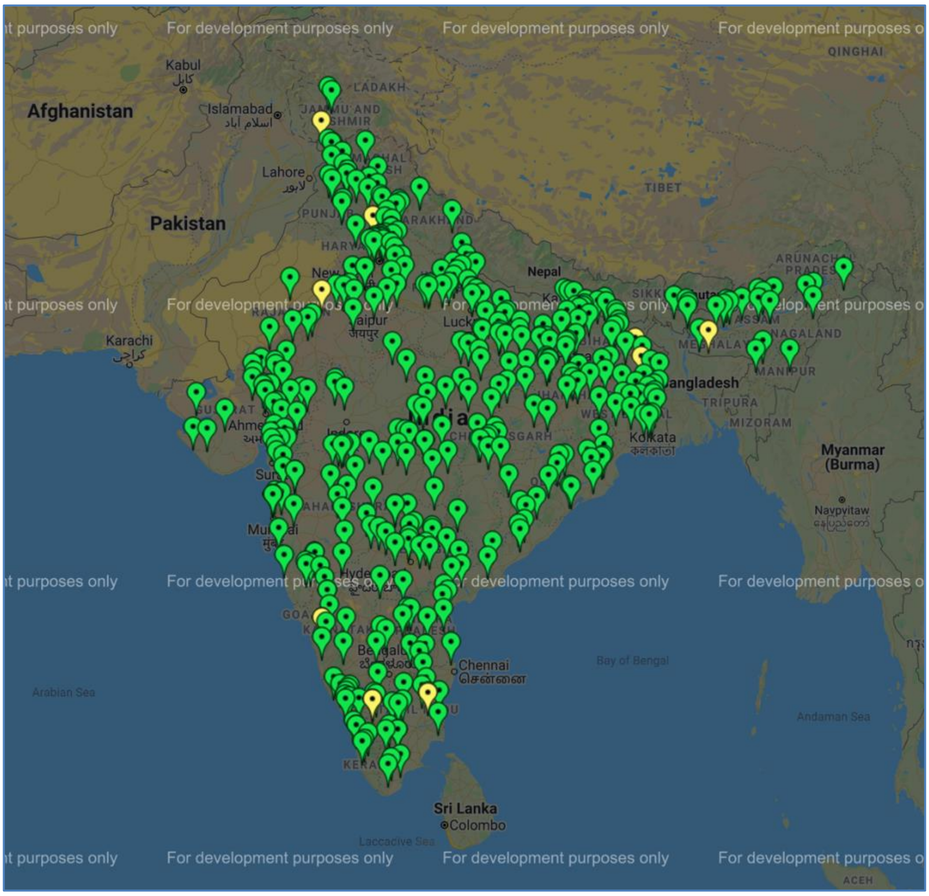
Cross sectional survey among individuals aged ≥15 years in the selected village / urban census enumeration block. A total of 625 clusters will be surveyed in the country using 23 teams. Each cluster will have a sample size of 800. Eligible participants after obtaining consent will be interviewed at the 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 with CBNAAT at the survey site itself and the second specimen will be subjected to 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 by the CPMU

Study progress

The survey was inaugurated in September 2019 by Honourable Health and Family Welfare Minister in New Delhi. As of June 2021, 21 teams are operational, and 362 clusters

have been covered and 21 ongoing. 4, 19,339 participants were enumerated of which 3, 04,972 participants were eligible, 272403 participants were interviewed and 2,68,546chest x-rays were taken and 899 TB patients were identified. The study is expected to be completed by October 2021.

Fig 5: Coverage of the National TB Prevalence Survey clusters in India,2019-2021



E-2: District wise prevalence of microbiologically confirmed pulmonary tuberculosis in Tamil Nadu

Principal Investigator : Dr. G. Prathiksha, Scientist B
Participating Institutes : State TB Cell, Tamil Nadu
Source of funding : National Health Mission, Tamil Nadu
Study period : 2020-2021
Category : TB
Pillar : Detect

Background

India is conducting a National level TB prevalence survey to estimate the prevalence of microbiologically confirmed pulmonary TB at the National and 20 state/state group level. Controlling TB at the district level if the TB prevalence estimates are available at the district level it would be useful monitoring the districts based on the local TB epidemiology. With this background, NIRT in partnership with the Tamil Nadu government planned to estimate the district level TB burden to monitor the effectiveness of TB control activities in various districts of Tamil Nadu.

Objectives

Primary objective

To estimate the point prevalence of microbiologically confirmed pulmonary TB among persons aged ≥15 years in all districts of Tamil Nadu.

Secondary objectives

- To explore the health seeking behaviour of survey participants who are symptomatic and currently on TB treatment
- To determine the proportion of those currently on TB treatment who were notified to the NTEP surveillance system

- To estimate the expenditure incurred by survey participants who are currently on TB treatment

Method

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 in 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

Progress

The study was initiated in Chennai in February 2021. As of March 2021, one team was operational and 2 clusters have been covered. sites. 2839 participants were screened of which 1605 participants were eligible, 1050 participants were interviewed and1021 chest x-rays were taken and 1 case of TB was identified. The survey is ongoing.

E-3: 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 B
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 index TBcases. 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 STIs for contact tracing. The use of such slips in the context of TB case finding is novel and it will be a practical and cost effective way to screen TB contacts especially, the community contacts which is difficult to be captured in the programme setting otherwise.

Objectives

To evaluate the effectiveness of the information slip method in improving the contact tracing and 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,patients who are willing will be offered small information slips to take to their household and close contacts These slips will contain messages 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 centres 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

Thestudy was initiated in October 2020.As of March 2021, a total of 232 participants were recruited. Proportion of contacts screened in the intervention and control arm was 17% (n=68) and 1.63% (n=11) respectively. No of contacts diagnosed in the intervention and control arm was 0 and 1 respectively. The study is ongoing.

Completed studies

S.No.	Title of the project	Principal Investigator	Source of funding	Category
E-4	Prevalence of SARS-CoV-2 infection in India: Findings from the national sero-survey, May-June 2020	Dr.Sriram Selvaraju, Scientist ‘D’	ICMR Intra-mural	COVID-19
E-5	SARS-CoV-2 antibody seroprevalence in India, August–September, 2020: findings from the second nationwide household sero-survey	Dr.Sriram Selvaraju, Scientist ‘D’	ICMR Intra-mural	COVID-19
E-6	SARS-CoV-2 sero-prevalence among the general population and healthcare workers in India, December 2020–January 2021	Dr.Sriram Selvaraju, Scientist ‘D’	ICMR Intra-mural	COVID-19
E-7	Prevalence of IgG antibodies against SARS-CoV-2 among the general population and healthcare workers in India, June–July 2021	Dr.Sriram Selvaraju, Scientist ‘D’	ICMR Intra-mural	COVID-19
E-8	Sero-survey for SARS-CoV-2 infection in Greater Chennai Corporation, July, 2020	Dr.Sriram Selvaraju, Scientist ‘D’	Greater Chennai Corporation	COVID-19
E-9	Second Sero-survey for SARS-CoV-2 infection in Greater Chennai Corporation, October, 2020	Dr.Sriram Selvaraju, Scientist ‘D’	Greater Chennai Corporation	COVID-19
E-10	Population-based sero-survey for SARS-CoV-2 infection transmission in Greater Chennai Corporation, Tamil Nadu – Fourth round, June-July 2021	Dr.Sriram Selvaraju, Scientist ‘D’	Greater Chennai Corporation	COVID-19

Statistics division of Epidemiology (Epid Stats)

The division is involved in the quality control of TB prevalence survey data collection process in the field and data management at NIRT. The activities include monthly meetings to assess the work of the field team to achieve the target in the stipulated period of the study period, assigning chest x-rays for the assessment by Doctors (X-ray readers - 1 and 2), co-ordinating the sputum and culture results from bacteriology department, co-ordinating with the field, laboratory and EDP team for data clarification, corrections and validation. Server base online real time data management and performance of high-quality statistical analysis provide solutions to issues in TB prevention, spread, and treatment.

The following activities were undertaken by the Division.

1. Introduced personal digital assistant (PDA) for online and off line server-based data collection in prevalence survey. PDA technology, has reduced the cost and labor as improved information quality, reduced data collection error, provided effective quality data management.
2. “Redcap” was licensed and used till date for 35 more research studies which includes COVID19 Vaccine trial.
3. Successfully introduced Global Positioning System (GPS) to locate the patients in TB prevalence survey.
4. Auto plagiarism software has been procured and distributed to all scientist in NIRT to ensure quality in research publication.
5. Projects status management software was created and introduced to monitor all projects in NIRT.
6. Introduced advanced GIS software to co-ordinate base spatial analysis.
7. Enhanced data analysis capacity by procuring advance software like SPSS, STATA, Arc GIS, MATLAP and TREEAGE. Training sessions have been conducting to all statistician in NIRT and other Institutes.
8. Efforts to digitalise for paperless work at NIRT is been done.

DEPARTMENT OF HEALTH ECONOMICS

DEPARTMENT OVERVIEW AND MANDATES

Health economics is increasingly recognized in public health and health research settings. And 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 on 4th July 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 health economics evidence through cost-effectiveness studies 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.

Studies in progress

HE-1: Establishment of Regional Resource Centre for Health Technology Assessment in India (HTA-In)

Principal Investigator	:	Dr. M Muniyandi
Source of funding	:	DHR, MoHFW, New Delhi
Study period	:	2018-2026

Background

Ministry of Health and Family Welfare (MoHFW), Department of Health Research (DHR) had set up a system for the evaluation of appropriateness and cost-effectiveness of the available and new health technologies in India as part of the research governance mandate of the DHR. The purpose of HTA-In is to design and institutionalize HTA that embodies modern 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.

Objectives

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

Activities of ICMR-NIRT

- 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.
- To promote the introduction and assessment of new and existing health technologies in the Health system and will provide support for the adoption of health technologies.
- This resource centre will undertake HTA in terms of medical effectiveness, cost-effectiveness, appropriateness, efficacy, safety, psychological, social, ethical, organizational, and economic aspects.
- To build capacity in the country towards Health Technology Assessment.
- To support evaluation of health technologies for industry through DHR for products that may enter the public health domain.

Progress

We have been working closely with the Government of Tamil Nadu and the Government of India for this project. 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 have been completed and approved by the Technical Advisory Committee of DHR, New Delhi. Based on the study findings the policy brief has been submitted to DHR. In addition, we have conducted a systematic review and meta-analysis workshop towards capacity building.

HE-2: 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'
Source of funding	:	Liverpool School of Tropical Medicine, UK
Study period	:	2018-2022
Category	:	TB
Pillar	:	Treat

Background

Multidrug-resistant TB (MDR-TB) remains a major challenge for global TB control efforts. The STREAM II trial is assessing favourable efficacy outcomes of regimens for the treatment of MDR-TB. The health economics component of the STREAM II trial in India is aiming to assess the impact of the study regimens.

Objectives

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

Methodology

A societal perspective will be taken, so that health systems and patient costs are included. Patients randomised to the control arm will receive usual clinical care under NTEP. Patients allocated to the study regimen will be treated at facilities that will have trained staff. An economic evaluation comparing two study regimen and control regimen is planned. The participants of this study will be patients with MDR-TB and their caregivers. Data related to the health system and patient costs will be collected. . For the health system, we will estimate costs based on the quantities of resources consumed in the system for delivering different treatment regimens and the prices of those resources. Details of costs patients incur throughout the treatment period and how such expenses affects the lives and livelihoods of patients of different socio-economic status will be collected. Data for health-related quality of life (HRQoL) will be collected using the EQ5D-5L tool. The main health economics-related outcomes will be mean incremental costs incurred by patients, the incremental cost to the health system of the study regimen compared with the control regimen.

Study Progress

We have collected information from a total of49 patients enrolled in the main STEAM trail. Data collection on basic information on socio-economic status has been completed for all patients. Data collection on cost information during treatment period is completed while the data collection on cost for follow-up is in progress. Data collection on health status and quality of life of patients during follow-up is in progress.

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

Principal Investigator	:	Dr. N Karikalan, Scientist 'B'
Source of funding	:	IMPRESS Scheme of Indian Council of Social Science Research, New Delhi
Study period	:	2019-2021
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 like TB. 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 is used for data collection.

Study Progress

The study was initiated in December 2019 and 80 baseline interviews among eligible TB patients has been completed.

HE-4: 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 'B'
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

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

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 2021and data collection is in progress. A total of 40 patients and 10 care-giver shave been interviewed

HE-5: Economic evaluation of implementing a decentralized dengue screening intervention under National Vector Borne Disease Control Programme in Tamil Nadu, South India

Principal Investigator	:	Dr. M Muniyandi, Scientist ‘D’
Source of funding	:	DHR, MoHFW, New Delhi
Study period	:	2019-2021
Category	:	Dengue

Background

Tamil Nadu is one of the largest states in India, which reported a high burden of dengue infection. One of the major hindrances in the control and management of dengue infection is the lack of timely and point-of-care diagnosis. The complex clinical presentation of dengue symptoms and lack of effective screening and diagnosis results in delayed diagnosis and leads to rapid disease progression and mortality. Dengue screening and diagnosis are done at Tertiary Health Care (THC) facilities in Tamil Nadu. Currently, the Government of Tamil Nadu has adopted a decentralized dengue screening strategy at Primary Health Care (PHC) settings using the blood platelet counter. Under this strategy, diagnosing dengue at an earlier stage is prioritized which could help in the reduction of dengue morbidity and mortality. The objective of this study is to find out the cost-effectiveness of a decentralized screening strategy for dengue at PHC facilities in comparison to the current practice at THC facilities

Objectives

- To estimate the quality-adjusted life years (QALYs) gained as a result of screening dengue suspects at primary health care facilities by monitoring platelet levels.
- To estimate the incremental cost incurred as a result of screening dengue suspects at primary health care facilities by monitoring platelet levels.
- To estimate the incremental cost-effectiveness ratio (ICER) as a result of screening dengue suspects at primary health care facilities by monitoring platelet levels.

Methodology

This economic evaluation was conducted from a societal perspective with reference to the year 2019. The present model compared the proposed strategy in which dengue screening will be performed at the PHC level with the current screening strategy used for dengue diagnosis under the national vector-borne disease control programme (NVBDCP) at THC level. A single episode of dengue infection with a lifetime horizon and a global discount rate of 3% is considered for the effectiveness and cost estimation. The outcomes of the model are expressed in terms of quality-adjusted life-years (QALYs) gained, life-years gained and overall cost incurred per patient in both, intervention and comparator scenarios. The model also compared the incremental cost with incremental QALYs to obtain incremental cost-effectiveness ratio (ICER). Further ICER was compared with a threshold of one-time Gross Domestic Product (GDP) per capita of India to determine its cost-effectiveness. We also calculated net monetary benefit (NMB) and the additional budget required for implementing hematology analyzers for screening dengue suspects at the PHC level.

Study progress

The proposed strategy was found to be cost-saving and the ICER was estimated to be -41197. PSA showed that the proposed strategy had a 0.84 probability of being an economically dominant strategy. The total health system cost for the cohort estimated in the proposed and current strategy were₹1910131 and ₹1696177 respectively. It contributes 17.45% and 14.67% to the total cost estimation in the proposed and current strategy. The patient out-of-pocket expenditure and productivity loss were less in the proposed strategy when compared to the current strategy (₹9030056 vs ₹9859103). The productivity loss due to premature death contributes higher to the total cost in the proposed and current strategy (81.57% and 83.87%). The ICER value calculated using discounted life years and QALYs gained was -41197.10 and -2383.58 respectively. The incremental cost-effectiveness plane plotted indicates that the proposed dengue screening strategy is more effective and less expensive compared with the current strategy.

ELECTRONIC DATA PROCESSING

Electronic Data Processing

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

Ongoing activities

Data conversion:

The Electronic Data Processing division has archived datasets of major research projects undertaken by the Epidemiology Unit since 1968. Most of them were data captured using the IBM 80-column punched card. The division is now in the process of converting all these available old databases to the latest database formats.

IT services

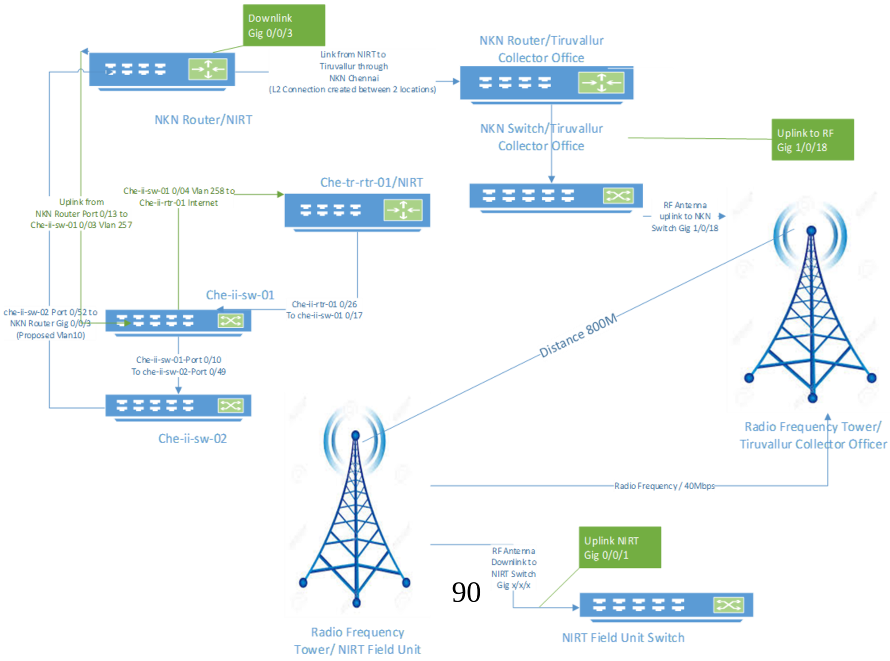
Maintenance of IT Equipment.

- Maintaining IT Equipment through Annual Maintenance Contract (AMC) and Warranty Service calls.
- The EDP registers IT equipment breakdown calls from the various departmental end-users and provides necessary services.
- One resident AMC engineer is available at EDP for providing immediate service to desktops and printer breakdown calls which are under AMC.
- ICER-NIH IT Support Service Engineers maintain the Network Setup which provides Internet and Intranet LAN facility.
- The EDP takes responsibility for providing/changing spares including Wires/Cables, Keyboard/Mouse, Cartridges for Printers, UPS, etc., for IT equipment.

Internet facility at NIRT-Tiruvallur Unit

NIC and BSNL based new NKN connection through Radiofrequency (RF) has been provided to NIRT-Tiruvallur unit. The work was initiated in 2015 with ICER (NIH) project fund and completed in August 2020. Cloud-Based Networking Switches have been installed in the Tiruvallur field unit and the Internet Service was enabled through NKN. NIRT- Thiruvallure is now a fully **Wi-Fi enabled campus.** Its internet facility is similar to that of NIRT Chennai. It is a major achievement from this department.

Fig 6:Network facility at NIRT-Tiruvallur by Radio Frequency (RF)



New servers had been created for research studies which are all in production.

- SMS Server for Data Centre and Freezers alerts
- Redcap application Server for NIRT & ICER
- Redcap Database Server for NIRT & ICER
- Active Server for National Prevalence Study
- Active Server for Tamil Nadu Prevalence Study
- DataMart Application Server for NIRT & ICER
- DataMart Database Server for NIRT & ICER
- The Eduroam provides access to the NIRT services for NIRT scientists when they travel to other eduroam enabled campuses, within or outside the country.

IT Support services

- User Accounts have been created with email access to 15 NIRT users,160 Project Usersand75 User Account have been extended.
- Bio-thermic Phase III has been completed in Main Lab Building, ICER, and Clinic Facility to monitor freezers, incubators, humidity, nitrogen Gas(-180) 24x7 This facility is now available for NIRT-TB Vaccine Trial in Chennai, Madurai & Tiruvallur.
- New Core Switch to enable 1Gig Speed Data transfer in Internal Network was installed at the NIRT Data Centre.
- New Video Conference Facility had been built in Tiruvallur Site & SPT Conference Room, Chennai.
- New Network Connections have been created in Canteen, Main Lab & Clinic Buildings
- The following servers have migrated to NIRT Domain
    - ✓ Application Servers
    - ✓ Federated and Access Management Server
- New servers have been created for research studies based on requirement which are all in production.
    - ✓ Temperature Monitoring Server
    - ✓ Physical Application, Database & Image open-mind Server for National TB Prevalence Study
    - ✓ Storage Upgrade for Physical Servers for National TB Prevalence Study

- Services provided by ICER IT Support Team
    - ✓ Warranty support for Desktops and network printer
    - ✓ Structured and Managed Network Support to NIRT Chennai, Madurai & Tiruvallur site
    - ✓ 24/7 monitoring support to the Data Centre, Network, Application and internet Services and infrastructure support

- COVID19 data entry lab was set up at NIRT
- Digital display board at ICMR-NIRT was installed during the lockdown period to disseminate TB and COVID-19 awareness to the public.
- During the lockdown due to the COVID19 pandemic, IT support was offered to run the office online.
- Projects Management Software was introduced.
- Maintenance of “Bacteriology Laboratory Automation Software”

REDCap

Redcap is a secure web based application for building and managing online surveys and databases. It is specifically geared to support online or offline data capture for research studies and operations. NIRT had obtained a license under the REDCap consortium which became functional in August 2018. Currently, the NIRT REDCap has 278 active users. There are 55 projects out of which, 27 are in production mode, 17 under development, and 11 projects are archived. Mobile apps were used for data collection by 15 projects.

Data Mart for NIRT

Data Mart Project had been initiated for creating a Central Data Ware House of all completed NIRT epidemiological and clinical studies with the support of NIH-OCICB/NIAID.

The role of EDP in this collaborative work is to prepare the raw data sets and also the ETL (Extraction, Transformation, and Loading) programming based on CDISC specifications.

Supportive role to NIRT administration's egovernance:

The division delivers supportive role to the NIRT Administration towards its electronic-based administrative services like ***e-Procurement*** and ***e-Marketing***, which are internet-based avenues provided by the Central Government.

E-Office is a digital workplace solution, provided by the National Informatics Centre, to achieve a simplified, responsive, effective, and transparent working of all government offices. EDP has been facilitating the effective utilization of this digital solution at NIRT for all its permanent employees. The Leave Management module has effectively been utilizing by all of the NIRT employees in which the EDP serves as a hub for troubleshooting and facilitating activities for e-Office within NIRT. The paperless movement of communications is being implemented by the e-File module to trace the files movements within NIRT. The file management system and leave management system are now active in NIRT. EDP has been providing the necessary training by demand basis at NIRT and other ICMR institutes to make this feature of e-Office functional.

Studies in progress

EDP-1: Development of a quantitative tool to assess barriers and facilitators for completion of TB treatment

Principal Investigator	:	Mrs. Basilea Watson, Scientist C Mr. T. Kannan, Technical Officer 'A'
Participating Institutes	:	ICMR-NIRT,
Study Collaborators	:	State TB Officer, Tamilnadu
Source of funding	:	ICMR Intra-mural
Study period	:	2021 - 2023
Category	:	TB
Pillar	:	Treat

Background

TB is preventable if people can access health care for prompt diagnosis and treatment. However, diagnosis and treatment barriers are inevitable and pave way for TB disease transmission. Thus, identifying the factors that correlate with different types of barriers can support TB control programs and assist health care providers to improve diagnosis and treatment efforts. The patient-centric ascertainment of barriers and facilitators is crucial in influencing the completion of TB diagnostic and treatment process. A standardized quantitative tool that determines the barriers and facilitators will help to effectively deal with a TB patient.

Objectives

The study is aimed to develop a patient-specific quantitative questionnaire to identify barriers and facilitators for patients with symptoms of TB to complete the diagnostic and treatment process in an urban Indian setting.

Methodology

The study will be carried out using a mixed-Methodology design involving qualitative and quantitative Methodology. The qualitative component will involve focus groups discussions (FGDs) and in-depth interviews (IDIs) with TB patients who have completed TB treatment to understand the barriers and facilitators that they had experienced.

Separate focus groups will also be conducted with TB patients who failed to achieve successful treatment completion. The qualitative component data will be used to develop a quantitative tool, which will be subjected to an iterative process using cognitive interviews, expert panels, and modifications based on their input. The reliability and validity of the tool will be established.

Study progress

The study has been initiated and 12 FGDs and 13 IDIs have been completed.

EDP-2: Application of Multiple Imputation approaches to the prevalence estimation in large-scale tuberculosis prevalence surveys

Principal Investigator	:	Mrs. Basilea Watson, Scientist C
Participating Institutes	:	ICMR-NIRT,
Source of funding	:	ICMR Intra-mural
Study period	:	2021 - 2022
Category	:	TB
Pillar	:	Build

Background

Population-based surveys of the prevalence of pulmonary TB disease in adults can be used to measure the burden of disease caused by TB and to measure trends in disease burden when repeat surveys are performed. The most crucial characteristic of analysis of TB prevalence survey designs is that they take into account the clustering of individuals: if this is not done, the calculated 95% confidence interval (CI) for true pulmonary TB prevalence will have less than the nominal 95% coverage due to underestimation of the standard error of the prevalence estimate. Adjustment for missing data is important in a TB prevalence survey. The analysis of the TB prevalence surveys using analytical Methodology adjusted for clustering and correcting for missing data will provide a robust estimate which uses the collected data to the maximum without any compromise on data wastage due to incomplete data records.

Objective

The study is aimed to obtain a robust and standard estimate of TB prevalence using best-practice Methodology for the analysis of TB prevalence surveys, including analyses at the individual level adjusted for clustering and correction for biases using multiple imputation Methodology.

Methodology

This is a secondary analysis of existing data using five recommended logistic regression models, all of which accounting for the cluster sample survey design and three of which attempt to correct for the bias due to missing data.

Study progress

The secondary data is being collated and the study is ongoing.

INTERNATIONAL CENTER FOR EXCELLENCE IN RESEARCH

DEPARTMENT OVERVIEW AND MANDATES

To develop a sustained research program in areas of high infectious disease burden through partnerships with scientists and physicians in US and India. To partner with in-country scientists to address major endemic diseases and foster research in areas such as helminth infections, HIV, COVID-19, and TB. To train local scientists so that they are prepared to tackle emerging and re-emerging infectious diseases in the future. The focus of research is to understand the pathogenesis and host immune responses in TB, LTB, helminthic infections, COVID-19, co-morbidity which includes diabetes mellites and co-infections namely helminths and HIV.

Studies in progress

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

Principal Investigator	:	Dr. Subash Babu, Scientific Director
Participating Institutes	:	NIH-NIAID
Source of funding	:	NIRT-ICER
Study period	:	2021-2026
Category	:	TB
Pillar	:	Detect

Background:

Approximately 2 billion people worldwide are infected with *Mycobacterium tuberculosis*, with 90% of individuals having a latent infection (LTBI). Among the various risk factors that are known to play a role in promoting active TB, HIV is the most well studied and described. However, 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

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

Methodology

During the study phase, a complete medical history will be taken. The study phase will involve an additional 30-ml blood draw. Blood will be used for laboratory evaluations like Haematology, IGRA, Biochemistry evaluations, screening for helminth infections. Blood collected in the study phase will be used for Tempus or PAXgene tube blood collection for DNA and RNA isolation, Peripheral blood mononuclear cell (PBMC) isolation samples will be used for cellular responses, proteomics, Transcriptomics and Metabolomics, immune signatures of PBMCs, and memory CD4+ and CD8+ T cells. Stool samples will be used for helminth screening and urine samples will be used for proteomics, Transcriptomics, and Metabolomics studiFor primary objective n=5000 and for secondary objective n=300 and 50 for each group.

Study progress

The recruitment phase of the project is underway. We have recruited 114 samples so far.

ICER-2: 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
Study period	:	2021-2026
Category	:	TB
Pillar	:	Detect and Prevent

Background

About 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. The World Health Organization (WHO) and the Indian government have an ambitious goal to eliminate TB. To accomplish this, new TB research is needed, including the development of rapid, sensitive, low-cost diagnostics; identification of biomarkers to assess TB treatment response and risk of developing the disease, and a deeper understanding of TB immunology and pathogenesis to inform vaccine development.

Objectives

- Evaluate novel diagnostics and biomarkers of diverse states of *Mycobacterium tuberculosis (M.tb)* infection.
- Identify markers of treatment response.
- Identify markers of lung injury associated with unfavourable TB treatment outcomes
- Examine mechanisms of protection against TB in exposed persons.
- Identify immunologic markers of persons at highest risk of progress of latent TB infection to TB.

Methodology

We will compare blood RNA and plasma cytokine biomarkers that assess inflammation, indirectly reflect bacterial burden and show promise for predicting cure. Candidate Methodology 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 Methodology in parallel allows comparison of accuracy and potential for advancement to a point-of-care (POC) diagnostic test. Cases of microbiologically confirmed treatment failure (positive sputum culture at month 5 and/or 6) and recurrence within 12 months after the end of treatment (EOT) 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

The recruitment phase is underway. Sample recruitment yet to be initiated.

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	:	NIRT-ICER
Study period	:	2020-2021
Category	:	COVID-19

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is spreading rapidly throughout the world. A large epidemic in India poses a major threat to the public health system. There is a poor understanding of why some individuals infected with SARS-CoV-2 are asymptomatic while others develop severe hyper inflammation, 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.

Methodology

The study population is–with or without SARS-CoV-2 and helminth infection-.Blood will be assessed for SARS-CoV-2 antibodies and experimental studies, including transcriptomics. The stool will be used for the diagnosis of parasitic infections and for microbiome 16S sequencing and transcriptomics. Stool DNA extraction for qPCR diagnostics to detect hookworms, Ascaris, Strongyloides, and Trichuris and for 16S sequencing for the microbiome. Fecal occult blood and fecal calprotectin testing. PBMCs will be assessed by multiparameter (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

The recruitment phase is underway..We have collected 300 samples sofar.

ICER-4: Role of neutralizing antibodies and inflammatory biomarkers in children with Pediatric Inflammatory Multisystem Syndrome - Temporally Associated with SARS-CoV-2 (PIMS-TS)

Principal Investigator	:	Dr. Subash Babu, Scientific Director Dr. Aishwarya, Scientist E
Participating Institutes	:	ICH, KKCTH, and Mehta children Hospital
Source of funding	:	ICER
Study period	:	2020-2021
Category	:	COVID-19

Background

The COVID-19 disease caused by SARS-CoV2 coronavirus has affected more than 10 million people globally with the WHO declaring it as a public health emergency of international concern (PHEIC). Although the disease affects people of all ages, children, in general, appear to have mild or moderate disease, the reasons for which are not fully understood. Likewise, the effect of neutralising antibodies in relation to the clinical manifestations in COVID 19 has not been well studied. Neutralizing antibodies play important role in virus clearance and have been considered as a key immune product for protection or treatment against viral diseases.

In addition, plasma and serum cytokines and chemokines are known to play an important role in the pathogenesis of COVID 19 in adults, although their role in children is not well explored. Finally, the association of tissue repair factors and vascular and endothelial growth factors, as well as matrix metalloproteinases and their tissue inhibitors with SARS-CoV2 infection/COVID 19 disease is poorly understood.

Objectives

- To estimate the levels of anti-SARS-CoV-2 neutralizing antibodies, in COVID 19 positive children with symptoms and compare it with that seen in asymptomatic children.
- To compare the levels of various inflammatory cytokines and chemokines as well as other biomarkers in COVID 19 positive children with symptoms and compare them with COVID 19 asymptomatic children.

Methodology

All Children presenting to Kanchi Kamakoti CHILD Trust hospital (KKCTH) in Chennai will be screened for COVID 19 (RT-PCR and/or IgM & IgG), following caregiver informed consent. Stored serum or plasma samples after serological analysis will be used to measure levels of neutralizing antibodies as well as cytokines, chemokines, and other biomarkers.

SARS-CoV-2 IgG and IgM antibody titter assay kits will be employed for estimating the titer of nCov-2019 specific IgG and IgM antibodies, Screening for neutralizing antibodies against SARS CoV-2, estimation of IL-1 beta, IL-6, IL-2, IL-7, IL-10, IL-18, TNF-α, INF-γ, TGF-β, G-CSF, IP-10, MIG, MCP-1, MIP-1α, sIL-2R, CCL1, CCL2, CCL3, CCL4, CCL11, CXCL1, CXCL2, CXCL9, CXCL10, CXCL11 using Human Magnetic Luminex Assay.

Study progress

A total of 245children have been recruited for the study. We observed that PIMS-TS is a distinct and unique immunopathogenic paediatric illness related to SARS-CoV-2 presenting with cytokine storm different from acute COVID-19 infection and other hyperinflammatory conditions. Severe disease in both MIS-C and acute COVID-19 was associated with elevated levels of MMPs. MMP levels exhibited a significant correlation with laboratory parameters including lymphocyte counts, CRP, D-dimer, Ferritin, and Sodium levels. MMPs are biomarkers of MIS-C as well as severe disease in MIS-C and acute COVID-19 in children.

ICER-5: Humoral and cellular immune response among recovered COVID-19 patients: A cross-sectional study, Tiruvallur district and Chennai, Tamil Nadu, India, 2020

Principal Investigator	:	Dr S Subash Babu, Scientific Director
Participating Institutes	:	National Institute of Epidemiology
Source of funding	:	NIRT-ICER; ICER-NIE
Study period	:	2020-2021
Category	:	COVID-19

Background

Higher plasma levels of pro-inflammatory cytokines along with decreased lymphocyte counts and pneumonia in severe COVID-19 patients suggest the involvement of the host immune system in the disease pathogenesis. Information on the kinetics and characterisation of SARS-CoV-2-specific T cells is limited. COVID-19 patients showed the presence of SARS-CoV-2 Spike surface glycoprotein (S), membrane (M), and nucleoprotein (NP)-specific T cells. SARS-CoV-2-specific CD4+ and CD8+ T cells start appearing in COVID-19 patients in the first two weeks post-onset of symptoms. CD4+ and CD8+ T cells were detected in 100% and 70% of convalescent COVID-19 patients.

T cell responses were focused not only on a spike but also on M, N, and other ORFs. SARS-CoV-2 specific T cells response was also observed in 20-50% of the unexposed individuals and this cross response may be induced due to other circulating seasonal human coronaviruses.

Objectives

- Estimate the proportion of patients recovered from SARS-CoV-2 infection positive for IgG antibodies by duration since RT-PCR confirmation
- Estimate the proportionof patients recovered from SARS-CoV-2 infection having neutralizing antibodies against SARS-CoV-2 by duration since RT-PCR confirmation

- Estimate the proportion of COVID-19 recovered patients having SARS-CoV-2 specific T cells by duration since RT-PCR confirmation
- Characterize adaptive immune response to SARS-CoV-2 infection among RT-PCR confirmed patients
- Describe adaptive immune response to SARS-CoV-2 infection among recovered COVID-19 patients by clinical severity of the illness

Methodology

We measured the immune response among recovered patients at the following days since RT-PCR confirmation: Days 15-30, 31-45, 46-60, 61-75, 76-90, and more than 90. The sera will be tested for the presence of IgG antibodies against SARS-CoV-2. The surrogate virus neutralization test (sVNT) test, which detects neutralizing antibodies (Nabs). PBMCs were isolated from study groups to elucidate the mechanism of this SARS-CoV-2/COVID-19 antigen-specific immune responses. PBMC cells from study participants were 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. Measurement of cytokines, chemokines, and other immune parameters will be measured.

Study progress

We examined the absolute counts of monocytes, the frequency of monocyte subsets, and the plasma levels of monocyte activation markers in seven groups of COVID-19 individuals, classified based on days since RT-PCR confirmation of SARS-CoV-2 infection. We measured the frequency of monocyte subsets and the plasma levels of monocyte activation markers using flow cytometry and ELISA. Our data show that the absolute counts of total monocytes and the frequencies of intermediate and non-classical monocytes increase from Days 15-30 to Days 61-90 and plateau thereafter. In contrast, the frequency of classical monocytes decreases from Days 15-30 till Days 121-150. The plasma levels of sCD14, CRP, sCD163 and sTissue Factor (sTF) - all decrease from Days 15-30 till Days 151-180. COVID-19 patients with severe disease exhibit higher levels of monocyte counts and frequencies, higher frequencies of classical monocytes and lower frequencies of intermediate and non-classical monocytes, and elevated plasma levels of sCD14, CRP, sCD163, and sTF in comparison to those with mild disease. Thus, our study provides evidence of dynamic alterations in monocyte counts, subset frequencies, and activation status in acute and convalescent COVID-19 individuals.

ICER-6: Impact of COVID-19 on clinical manifestations, diagnosis, treatment outcome and immune response for pulmonary tuberculosis. Acronym: ABRICOT - “Associative BRICS Research in COVID-19 and Tuberculosis”

Principal Investigator	:	Dr. Anuradha. R, Scientist Dr. S. Subash Babu, Scientific Director
Participating Institutes	:	Madras Medical College, Oswaldo Cruz Foundation (FIOCRUZ)/ National Institute of Infectious Disease Evandro Chagas (INI)/Clinical Research Laboratory on Mycobacteria (LAPCLIN-TB), Brazil, University of the Witwatersrand, Johannesburg, South Africa.
Source of funding	:	DBT, BRICS-CRDF-Global
Study period	:	2020-2021
Category	:	TB and COVID-19

Background: The link between TB and COVID-19 is likely to be bi-directional. The temporary immunosuppression induced by tuberculosis may increase the susceptibility of patients to COVID-19, and COVID may, in turn, also increase susceptibility to TB. In 2025, an additional 1.4 million TB deaths could occur as a direct consequence of the COVID-19 pandemic. The COVID-19 disease rate was high in patients with active TB. TB and SARS-CoV-2 are both infectious diseases that primarily attack the alveolar region of the lungs and share common symptom patterns. Coinfection most probably exacerbates inflammation through heightened secretion of cytokines and accelerates the development of the severe acute respiratory syndrome and also worsens the TB disease and its outcome. Hence, we propose that understanding mechanisms of immune regulation during SARS-CoV-2 disease may lead to the development of better therapeutic strategies and the results of our fundamental studies may inform future plans for clinical interventional studies. The main fundamental research component of this study might identify clinical parameters and treatment Methodology and to understand the immunological mechanism for the severity in coinfected SARS-CoV-2 and TB patients.

Objectives :

- To analyse the baseline differences in immune cell populations in active TB patients with or without SARS-CoV-2 (present or prior asymptomatic) disease.
- To compare the immune responses of active TB patients with (present or prior asymptomatic) or without SARS-CoV-2 after the intensive phase of anti-TB therapy (ATT) and after the completion of ATT.
- To compare the proteomic profiles in SARS-CoV-2 positive (present or prior asymptomatic) and negative TB patients on presentation, after the intensive phase of ATT, and after the completion of ATT.
- To establish a partnership among researchers in Brazil, India, and South Africa to facilitate recruitment of well-defined groups of patients with pulmonary TB who are infected or not infected with SARS-CoV-2, and persons with COVID-19 without TB.

Methodology:

Whole blood will be used both for ex vivo phenotyping, PBMC isolation and proteomics. PBMC will be collected and will be used to determine the T cell immune responses in terms of different subsets will be examined by flow cytometry. Whole blood will be used both for ex vivo phenotyping and in vitro cell culture. Plasma samples from these individuals will be measured by Luminex to determine levels of circulating cytokines and chemokines.

Study progress with Interim Findings : Study to be initiated.

Completed studies

S.No.	Title of the project	Principal Investigator	Source of funding	Category /Pillar
ICER-7	Effect of diabetes on the immune responses in tuberculosis	Dr. S. Subash Babu, Scientific Director Dr. Syed Hissar Scientist 'D'	Department of Biotechnology and NIAID	TB /Detect
ICER-8	Impact of immune changes of pregnancy on tuberculosis	Dr. Luke Elizabeth Hanna Scientist 'E' Dr.S. Subash Babu, Scientific Director	Indo-US VAP Initiative	TB/Detect

CONTRIBUTION TO NATIONAL PROGRAMMES

NTEP ACTIVITIES IN NATIONAL REFERENCE LABORATORY, NIRT, CHENNAI (2020-21)

Contact person	**:**	**Dr Padmapriyadarsini C and Dr. S Siva Kumar**
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) closely monitors five states (Andhra Pradesh, Gujarat, Kerala, Tamil Nadu, Telangana) and five Union territories (Andaman & Nicobar, Puducherry, Lakshadweep, Daman & Diu and Dadra & Nagar Haveli) in India for NTEP activities. NRL Microbiologists visit assigned states at least once a year for onsite evaluation (OSE) for monitoring human resources, BSL facilities, EQA activities of smear microscopy, culture, and DST by both phenotypic and genotypic Methodology as per the NTEP protocol. During OSE visit, NRL microbiologist provides technical support for establishing quality-assured smear microscopy, C&DST services, including facility design for the introduction of newer diagnostic tools (liquid culture and molecular tests) for the rapid diagnosis of MDR/XDR TB. NRL also undertakes yearly proficiency testing of IRL and Culture and Drug susceptibility testing labs as part of the certification process under NTEP. Seven IRLs, 12 C & DST labs have been certified and 8 C& DST labs certification is in progress for diagnosis of DR-TB patients from the aforementioned states. During 2020-2021, the Institute conducted the 12th round of proficiency testing for 19 labs including three NRLs in India, with a panel of 20 cultures for susceptibility testing for both first and second-line anti-TB drugs by genotypic and phenotypic Methodology. Based on the proficiency results, five IRLs received the first certification for PZA and Linezolid from CTD.   The retesting process has been completed for two C & DST laboratories for certification by both Liquid and LPA. A pre-assessment visit has been conducted for three C&DST labs (PSG Medical college Coimbatore, GCMC medical college, Coimbatore, and KAPV medical college, Trichy) as part of the certification process. Three Laboratories. As part of PMDT activities, the Institute is supporting 6 districts of Tamil Nadu for diagnosis of DR-TB patients by both first & second line DST in NTEP settings. A total of 5475 samples were received for DR-TB diagnosis and 975 samples were received for follow-up cultures from six districts of Tamil Nadu.

As part of NRL EQA activities, On-Site Evaluation (OSE) of sputum microscopy and C&DST have been conducted by NRL Microbiologists for two states (Gujarat, Tamil Nadu) and one UT (Puducherry) for on-site evaluation of sputum microscopy, and 220 panel slides were used to assess the proficiency of 44 laboratory personnel for smear microscopy. The training on C & DST was provided (campus, on-site) for 12 laboratory personnel of C& DST labs.

HIV Laboratory testing services to the National AIDS Control Program (NACO)

Principal Investigator	:	Dr. Luke Elizabeth Hanna
Source of funding	:	National AIDS Control Program, NACO

Background:

During the reporting year, the HIV lab continued its support to the National AIDS Control Organisation’s Early Infant Diagnosis (EID) Program. The program aims to screen HIV exposed infants aged between 6 weeks to 18 months for HIV-1 positivity. Under this program, dried blood spot (DBS) samples collected in different districts of Tamilnadu, Kerala, Pondicherry, Andhra Pradesh, Orissa and Telangana were sent to this Laboratory for HIV-1 testing by DNA PCR assay. Further, samples were also sent to this laboratory for HIV-1 Viral load testing (VL) for Virological Monitoring of Patients with HIV-1 on first and second line ART.

Objectives:

- To detect HIV infection in children born to HIV-infected women very early so as to link the reactive infants to appropriate care, support and treatment facilities as quickly as possible.
- To monitor the viral load in HIV-infected persons on antiretroviral therapy as an indicator of prognosis and as an aid in assessing viral response to antiretroviral treatment as measured by changes in HIV-1 RNA levels

Methodology:

Dried blood spots collected for early infant diagnosis are tested using the total HIV-1 nucleic acid assay. Plasma samples sent for HIV-1 viral load testing will be tested for circulating HIV-1 viral RNA using a real time quantitative PCR test. Both tests are performed on the fully automated Abbott m2000sp/Abbott m2000rt Instrument.

Table 6: Summary of HIV-1 DNA PCR testing and viral load testing services provided for the NACO HIV Programme during the period Apr 2020-March 2021

		Testing Discipline										
		HIV-1 DNA PCR TESTING (NACO EID Programme)						**HIV-1 Viral load testing services**				
		Sample Details			**Result Details**			**Sample Details**		**Result Details**		
S.No.	Month/Year	Samples Received	Samples tested	Screening Detected	Screening Not Detected	Confirmatory Detected	Not Detected	Samples Received	Samples tested	Target not Detected	1000 Copies/ml	>1000 Copies/ml
1	Apr-20	28	20	0	20	0	0	51	45	26	9	10
2	May-20	44	-	-	-	-	-	50	35	24	1	10
3	Jun-20	68	-	-	-	-	-	122	119	86	17	16
4	Jul-20	139	196	5	190	0	0	178	208	152	27	29
5	Aug-20	263	176	7	165	4	0	282	78	62	7	9
6	Sep-20	288	264	11	246	5	1	804	898	806	29	63
7	Oct-20	158	88	3	79	6	0	983	583	491	49	43
8	Nov-20	170	44	1	42	0	0	655	384	305	24	14
9	Dec-20	276	712	13	689	5	0	293	0	0	0	0
10	Jan-21	377	220	5	160	5	1	157	74	66	5	3
11	Feb-21	221	352	12	309	6	2	131	728	547	62	30
12	Mar-21	166	280	9	129	10	3	180	546	418	63	50
	Total	**2198**	**2352**	**66**	**2029**	**41**	**7**	**3886**	**3698**	**2983**	**293**	**277**

Other major activities:

COVID response:

NIRT responded to the COVID-19 pandemic by pitching in its services and support in several fronts including COVID testing, COVID seroprevalence surveys, SARS-CoV-2 genomic surveillance, vaccine trials and basic research. NIRT also served as one of the four Central Depots for COVID reagents for ICMR.

Regional Reference Lab for the National AIDS Control Organization:

The Regional Reference Lab which is a part of the HIV/AIDS Department has continued to provide support for NACO’s early infant diagnosis (EID) program. Infants’ blood samples in the form of dried blood spots were received from various districts of Tamilnadu, Kerala, Pondicherry, Andhra Pradesh, Orissa and Telangana for HIV-1 testing by DNA PCR assay to this Laboratory. A total of 2352 DBS samples were tested during the previous year for the different states. In addition, samples were also referred for HIV-1 Viral load testing (VL) services for Virological Monitoring of HIV-infected individuals on first and second line ART. A total of 3698 samples were tested for HIV-1 viral load for this activity.

Contribution to Patient care/Clinical trials:

The Serology Division of the HIV/AIDS Department provides laboratory support for all ongoing clinical trials and other research studies in HIV and TB. The services include diagnostic serology for HIV, HBV, HCV, syphilis and HSV-2, complete blood count (CBC) and estimation of CD4/CD8 cell count. The Molecular Division provides services like HIV-1 DNA PCR, HIV-1 viral load, HIV-1 drug resistance testing, DNA sequencing for pharmacogenomics and COVID RNA PCR. The labs store a large number of biological samples collected as part of the ongoing NIRT research studies and clinical trials.

LIBRARY & INFORMATION

ICMR-NIRT Library

(Librarian : Dr. R. Rathinasabapati)

A hybrid library, moving towards an electronic integrated platform.The information resources available to NIRT scientists supports their research activities. The quality of metadata is easier to find the books and other library materials. In this context, we migrated our catalog into Open Source software Koha and made it available on a cloud platform as an Online Public Access Catalog. Our NIRT Library management system builds the following core Library services.

SERVICES

Value-**A**dded **S**ervices (VAS)

- Access to electronic resources through **Digital Library** Portal *(since 2001)*
    - It has been updated with hyperlinks to
        - Institutional Repository
        - IRINS *(Indian Research Information Network System),*
        - iThenticate *(plagiarism software)* Database
        - NIH Library
        - recent Open Access Resources
        - Science Citation Index
        - Web of Science *(ICMR e-Consortium Database)*
        - Journal Impact Factor-2018 list_by Clarivate Analytics *(a Web of Science Group)*
- **Automation**: Electronic Check-in and Check-out services since 2002
- NIRT Library took initiative for NIRT to became 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 provide an opportunity to create the scholarly network.

I. <u>**S**elective **D**issemination of **I**nformation</u> (**SDI**)

- e-Publications
- Information Resources/Journal Articles Published (*Tuberculosis, COVID-19, HIV*)
- Digital Document Delivery Service *(DDDS)*
- Literature search
- Reference Assistance (Face-to-face, Telephone, E-Mail)
- Resource Sharing (ICMR; NIH; NML)

II. <u>**C**urrent **A**wareness **S**ervice</u> (**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)* - 15 Nos. Published
- **HIV Monitor***(Fortnightly)*- 15 Nos. Published
- **News Bulletin***(Weekly)* - 52 Issues Published

TRANSLATIONAL VALUE OF RESEARCH PROJECTS : 2020-2021

The research activities of ICMR-NIRT focus towards achieving the goal to end the tuberculosis (TB) epidemic by 2025.TB elimination requiresintensified efforts to translate research findings to clinical use.Our focus is in the direction of stimulating outcome-oriented research invalidating theinnovativeand indigenous new TB diagnostics, improving the treatment outcome by newinterventions/optimising existing treatment strategies, prevention of TB and in strengthening health-seeking behaviour for TB services.

Translational value of the research projects

TB diagnosis

Validation of indigenous new TB diagnostics kit:

Truenat MTB is an indigenous, rapid, point-of-care test developed by Molbio Diagnostics for the diagnosis of TB. ICMR-NIRT conducted a multicentric validation study of this kit for MTB diagnosis and RIF resistance in two phases. With the encouraging results, the validation study was further extended to check its feasibilityinvolving 100 Designated Microscopy centers (DMC) in 10 States across India. The feasibility of Truenat as the point of care test was evaluated in a pilot study at Gujarat with the testing of samples in mobile vans. In addition, validation of Truenat testing in paediatric population was carried out as a multicentric study. In 2019, a global validation study of Truenat coordinated by FIND/ICMR was conducted both in National and International sites. With the key findings of this study, in May 2020, WHO endorsed Truenat assays for the detection of MTB and rifampicin resistance. Department of Bacteriology played a vital role in the development and validation of the Truenat Kit and the WHO endorsement of Truenat as Point of Care (POC) test.

TB treatment and prevention

- **T**he 4-month moxifloxacin containing daily regimen (2RHZEM daily / 2 RHM daily) with the favourable response of 92% at the end of treatment and 4.1% TB recurrence is worth exploring for its implementing in TB program settings.
- Faster sputum culture conversion, Relapse free cure with similar adverse events as compared to conventional dose, suggests 25mg/kg/day Rifampicin containing regimen can be successfully implemented in treating pulmonary TB patients.
- The results of the Standardised and shortened regimen for MDR-TB (STREAM study stage 2) will provide evidence for a fully oral regimen containing Bedaquiline in the treatment of MDR-TB.
- The results of the BEAT trial with the fully-oral regimen has immense translational value in the implementation of the regimen in the treatment of pre-XDR and XDR-TB.
- The *in-silico* interaction profiles of novel phytochemicals namely Gardenin-A, Swertiamarin, Glycyrrhizin, Alizarin, Mangiferin, Laccaic acid and Aloe-emodin with crucial functional protein domains of *mycobacterium tuberculosis* revealed that these compounds display better binding affinity than the classical anti-TB drugs. If these compounds are experimentally validated, they could be developed as multi-target specific alternative drug candidates.
- Evaluation of 99DOTS Technology-based adherence tools had shown its better acceptance levels among health care providers and varied acceptance levels among

the patient population, thereby providing evidence on the implementation scopes of this technology

- The TB vaccine trial with VPM1002 and Immuvac will generate evidence for adoption of the vaccines in the prevention of TB among household contacts of smear positive PTB patient.
- Our study suggested that helminth infection has the ability to down modulate the protective immune mechanism in the LTBI individuals and these down-modulated effects are at least partially reversed following anti-helmintic treatment. This suggests that individuals withLTBI should be screened for helminth infection and nutrition assessment. The treatment for heminthic infection and nutritional deficiency would prevent the progression of latent TB to the development of active TB.
- The findings from the study on prevalence of TB among tribal populations in India and the barriers related to their health-seeking behaviour for TB services could strengthen the TB elimination efforts in tribal populations by evolving new intervention strategies.

Nation- Wide Tb Prevalence Survey

- The nation wide TB prevalence survey coorindated by ICMR-NIRT will provide reliable estimate of TB prevalence in the country In addition the magnitude of TB infection will be revelaed and the information on health seeking behaviour of the people will also be available. The findngs from this study are important to plan appropriate TB elimination efforts at national and sub national levels.

COVID-19

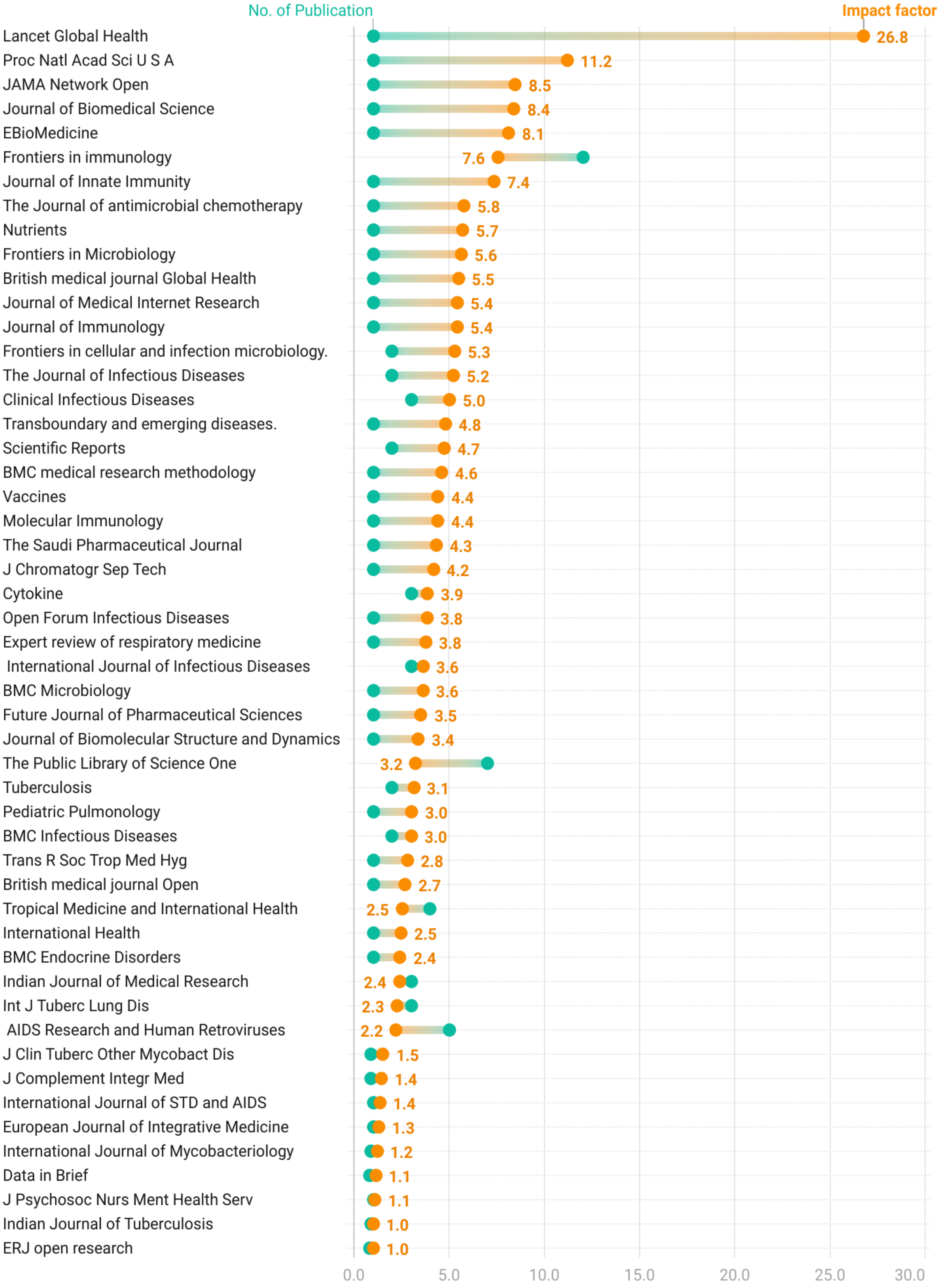
- The findings from the effectiveness of BCG vaccine in reducing morbidity and mortality in elderly individuals in COVID-19 hotspots in India will provide evidence for the implementation of BCG vaccine.
- Prediction and risk score towards handling COVID-19 confirmed patients with a risk score formulation has implications in devising strategies for future pandemics and epidemics.
- The studies on COVID related stigma and mental health status in India will provide crucial guidance on addressing them through appropriate interventions.

Validation of COVID 19 diagnostics kit:

1. The developed electrochemical biosensor is highly sensitive and specific and can identify the SARS CoV-2 specific peptides and provide test results in <45 minutes. Hence this will be a useful tool for rapid detection of SARS CoV-2 infection. Further, this can be developed into handy device for use as a point of care (PoC) test.
2. Developed infectious molecular clones of HIV-1 transmitted/founder (T/F) viruses which will serve as valuable tools for the design and testing of vaccine candidates and preventive tools such as broadly neutralizing antibodies.
3. Identified elite neutralizers from a cohort of HIV – infected individuals whose samples will serve as valuable sources for isolation of broadly neutralizing monoclonal antibodies that can be developed into therapeutic / prophylactic tools for HIV.

APPENDICES

SUMMARY OF PUBLICATIONS & IMPACT FACTOR FOR ICMR - NIRT 2020 - 2021



A total of 93 research articles published in 51 journals with an impact factor of 1 to 26.8.

LIST OF PUBLICATIONS :2020

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Awards/Honours

Young Investigator Award by American Society of Tropical Medicine and Hygiene Annual Meeting, November 15-19, 2020.Gokul Raj. K. ICER

Workshop(s)/Symposium/Other Events

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

Staff List

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

List of students who have registered (full -time) for their Ph.D. Programme with University of Madras

Sl.No.	Name of the Candidate	Source of Funding	Supervisor/ Guide	Name of the Department
1.	Mr. AnandSonowane	Construction and characterization of infectious molecular clones of HIV – transmitted founder (T/F) viruses	Dr. Luke Elizabeth Hanna	Department of HIV/AIDS
2.	Mr. Deepak Selvam	Generation of Stable Lactobacillus strains for enhancement of plasmid stability and muscosal adhesion	Dr. Luke Elizabeth Hanna	Department of HIV/AIDS
3.	Ms. Evangeline Ann Daniel	Identification of biomarkers for predicting progression from latent TB infection to active TB disease.	Dr. Luke Elizabeth Hanna	Department of HIV/AIDS
4.	Mr. Balakumar S	Pre-mRNA editing of HIV-1 using Adenosine deaminase acting on double stranded RNA (ADAR)	Dr. Luke Elizabeth Hanna	Department of HIV/AIDS
5.	Ms. Sandhya V	Isolation and characterization of broadly neutralizing monoclonal antibodies from HIV-1 elite neutralizers	Dr. Luke Elizabeth Hanna	Department of HIV/AIDS
6.	Mr. Kadar Moideen A	Exploration of Immunological Biomakers for Pulmonary Tuberculosis	Dr. B. Ramalingam	Department of Immunology
7.	Ms.Pavithra S.	Molecular analysis of monocyte subsets in humans infected with M.tb	Dr. B. Ramalingam	Department of Immunology
8.	Ms.J.S.V. Soundarya	Attenuated Mycobacteria based vaccine against tuberculosis with a novel strategy for T cell priming	Dr.K.R. Uma Devi	Department of Immunology
9.	Mr.P.Venkatesan	CRISPR mediated platform for diagnosis and rapid detection of drug resistance pattern in Tuberculosis	Dr.K.R. Uma Devi	Department of Immunology
10.	Mr.KrishnaMoorthi P	Immunomodulation of autophagy by VitaminD3 in Macrophages infected with M.tuberculosis	Dr.K.R. Uma Devi	Department of Immunology

11.	Ms.R.Ananthi	Study on mutations associated with pyrazinamide resistance in M.tuberculosis	Dr.P.Kannan	Department of Immunology
12.	Mr. Shaik FayazAhamed	Machin Learning Approach for survival Data-FT_UOM	Dr. Ponnu Raja	Department of Statistics

List of students who have registered (full -time) for their Ph.D. programme with The TamilnNaduDr. M.G.R. Medical University

Sl.No.	Name of the Candidate	Title of the Ph.D. thesis	Supervisor/ Guide	Name of the Department
1.	Mary Rebecca	Pharmacokinetic drug-drug interaction between first line anti –TB and anti – diabetic drugs	Dr.A.K.Hemanth Kumar	Department of Clinical Pharmacology

Staffs (Part -time) registered for their Ph.D. programme with University of Madras, Chennai

Sl.No.	Name of the Candidate	Title of the Ph.D. thesis	Supervisor/ Guide	Name of the Department
1.	Mr. Kannan T	An evaluation of predictive statistical data mining techniques	Dr. K. Rajendran	Department of Epid stats
2.	Mrs. B. Angayarkanni	Novel Anti mycrobacterial agents from Indian traditional system	Dr. Azger Dustachkeer	Department of Bacteriology
3.	Mrs. B. Mahizhaveni	Isolatiion stabilization and encapsulation of mycrobacterium tuberculosis	Dr. Azger Dustachkeer	Department of Bacteriology
4.	Mr. Michel Premkumar	Rapid Diagnosis and drug suspectibility testing of mycrobacterium tuberculosis	Dr.S.Sivakumar	Department of Bacteriology
5.	Mr. A. Radhakrishnan	Evaluation of essential oils, volatile chemicals and repurposing of drug of anti-tuberculosis activity	Dr. Azger Dustachkeer	Department of Bacteriology
6.	Mr.P. Palaniyandi	Spatial survival models PT-UOM DR PR	Dr. Ponnu Raja	Department of Statistics

Staffs (Part -time) registered for their Ph.D. Programme with Meenakshi University of higher education and Research (deemed to be University) , Chennai

Sl.No.	Name of the Candidate	Title of the Ph.D. thesis	Supervisor/ Guide	Name of the Department
1.	V.Sudha	Bioavailability of fixed dose combination of first line anti-TB drugs in patients with Pulmonary Tuberculosis	Dr.A.K.Hemanth Kumar	Department of Clinical Pharmacology

Candidate (Part -time) registered for their Ph.D. Programme with University of Madras Chennai

Sl.No.	Name of the Candidate	Title of the Ph.D. thesis	Supervisor/ Guide
1.	Mr. N. Selvam	Frailty Models in Survival Analysis-PT-UOM	Dr. Ponnu Raja

List of Post-Doctoral fellows

Sl.No.	Name of the Candidate	Funding Agency	Title of the PDF Research Work	Supervisor/ Guide
1.	Dr. Sam Ebenezer Post Doctoral Fellow	ICMR	Study on the strain specific modulation of uberculosis granulomatous reaction using in Nitro 3D granulome model	Dr. Azger Dustachkeer
2.	Dr. N. Usha Rani ICMR-Research Associate	ICMR	Development and Characterization of a Novel Nanopeptide system for Therapeutic applicatiuon in Residual Lung Injury caused by pulmonary tuberculosis	Dr. N. Saravanan
3.	Dr. K. Gokul Raj DBT Research Associate-III	DBT	Effect of pre-diabetes on immune responses in latent and active tuberculosis	Dr.SubashBabu

List of staffs/students who have obtained their Ph.D. degree (Full Time) from University of Madras

Sl. No.	Name of the Candidate	Title of the Ph.D. thesis	Supervisor/ Guide	Name of the Department
1.	Sivasankaran M.P	Evaluation Of Mucosal Immune Responses To HIV And HIV Exposed Uninfected Women	Dr. Luke Elizabeth Hanna	Department of HIV/AIDS
2.	VidhyaVijayan K.K	Characterisation of viral and host factors responsible for clinical differences seen in HIV 1 & 2 infection	Dr. Luke Elizabeth Hanna	Department of HIV/AIDS

List of staffs/students who have submitted their Thesis and waiting for their Ph.D. degree from the University of Madras (Full Time)

Sl. No.	Name of the Candidate	Title of the Ph.D. thesis	Supervisor/ Guide	Name of the Department
1.	Hemalatha.B	Inflammation And Aging In Long Term Treated HIV – 1 Infected Individuals	Dr. Luke Elizabeth Hanna	Department of HIV/AIDS
2.	Ms. GunapatiBhargavi	Functional characterization of oxidoreductases of M.tb	Dr.P.Kannan	Department of Immunology

List of students who have registered (full -time) for their Ph.D. programme with University of Madras

Sl. No.	Name of the Candidate	Source of Funding	Title of the Ph.D. thesis	Supervisor/ Guide
1.	Ms. GunapatiBhargavi	INSPIRE Fellow	Functional characterization of oxidoreductases of M.tb	Dr.P.Kannan
2.	Mr.KadarMoideen A.	ICER	Immune responses to TB coincident with diabetes	Dr.B.Mahalingam
3.	Ms.Pavithra S.	INSPIRE Fellow	Molecular analysis of monocyte subsets in humans infected with M.tb	Dr.B.Mahalingam
4.	Mr.S.Deepak	ICMR	Development of lactobacillus strains for the purpose of enhanced DNA stability,mucosaladhesion and delivery of therapeutic proteins	Dr.LukeE.hanna

5.	Mr.Anand B Sonawane	UGC	Molecular mechanisms of HIV pathogenesis in target cells	Dr.LukeE.hanna
6.	Ms.J.S.V. Soundarya	ICMR	Attenuated Mycobacteria based vaccine against tuberculosis with a novel strategy for T cell priming	Dr.K.R. Uma Devi
7.	Mr.P.Venkatesan	Lady Tata	CRISPR mediated platform for diagnosis and rapid detection of drug resistance pattern in Tuberculosis	Dr.K.R. Uma Devi
8.	Mr.KrishnaMoorthi P	ICMR	Immunomodulation of autophagy by VitaminD_3 in Macrophages infected with M.tuberculosis	Dr.K.R. Uma Devi
9.	Ms.R.Ananthi	ICMR	Study on mutations associated with pyrazinamide resistance in M.tuberculosis	Dr.P.Kannan
10.	Ms.Evangeline Ann Daniel	INSPIRE Fellow	Identification of biomarkers for predicting TB disease progression and treatment response	Dr.LukeE.Hanna

OBITUARY

Sl. No	Name of the staff	Designation	Date of Death
1	Mr. S. Sriramachandran	Ex- Senior Technician	19.04.2021
2	Mr. B. Vijayakumar	Ex-Senior Technician II	21.04.2021
3	Mr. V. Partheeban	Ex-Senior Technician III	24.05.2021
4	Mr. D. Sukumar	Ex-Upper Division Clerk	11.06.2021

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