

# Disease Specific Documents for XII Plan

## *Tuberculosis*



**INDIAN COUNCIL OF MEDICAL RESEARCH**

# Disease Specific Documents for XII Plan

## Tuberculosis

**High Power Committee to Evaluate the Performance of ICMR, 2012-13**



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## ICMR Institutions working on Tuberculosis

1. National Institute for Research in Tuberculosis (NIRT), Chennai
2. National Institute for Epidemiology (NIE), Chennai
3. National JALMA Institute for Leprosy & Other Mycobacterial Diseases (NJIL&OMD), Agra
4. National AIDS Research Institute (NARI), Pune
5. Regional Medical Research Centre (RMRC), Bhubaneswar
6. Regional Medical Research Centre (RMRC), Port Blair
7. Regional Medical Research Centre for Tribals (RMRC,T), Jabalpur
8. Regional Medical Research Centre (RMRC), Belgaum
9. Desert Medical Research Centre (DMRC), Jodhpur
10. Regional Medical Research Centre (RMRC), Dibrugarh

## 1. Current situation of Disease with contribution of ICMR

Tuberculosis (TB) remains a major global health problem. It causes ill-health among millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide, after human immunodeficiency virus (HIV). The latest estimates are that there were almost 9 million new cases in 2011 and 1.4 million TB deaths (990 000 among HIV-negative people and 430 000 HIV-associated TB deaths globally). This is despite the availability of treatment that will cure most cases of TB. The risk factors for TB include undernutrition, HIV, smoking, indoor air pollution and diabetes mellitus – many of these are prevalent in India. Though prevalence and mortality have decreased globally, incidence rates are falling very slowly, at about 2% per year. Short-course regimens of first-line drugs that can cure around 90% of cases have been available since the 1980s. Many of the principles of short-course chemotherapy were established at the Tuberculosis Chemotherapy centre, later renamed as the Tuberculosis Research Centre in Chennai.

In India, there are approximately 2.0-2.3 million new cases of TB every year (26% of the global burden) and approximately 300,000 deaths. While approximately 1.4 million TB patients are treated by the national program each year, another million or so are treated in the private sector, often with unscientific and unproven regimens and undocumented outcomes. The national TB control program was reviewed in 1992 and since then, the Revised National Tuberculosis Control Programme (RNTCP) has ensured that high quality, free diagnosis and treatment are available through the network of primary health centres, district hospitals and medical colleges. The RNTCP depends on sputum smear microscopy for

diagnosis, categorization of patients and assessment of treatment progress. To provide quality assured smear microscopy services with easy access for the entire population, a network of RNTCP designated microscopy centres (DMCs) have been established. Each DMC caters to an approximate population of 1,00,000. The network of DMCs is supported by larger regional laboratories of the states (Intermediate Reference Laboratories or IRLs), which in turn are supervised by four National TB Reference Laboratories (NRLs).

Two of the ICMR institutes (NIRT and NJIL&OMD) have been functioning as NRLs and are ably assisting the RNTCP activities. NRLs not only provide training to state level staff, but also implement quality assurance and monitor the functioning of IRLs with regular on-site evaluations. NRLs perform DST for 2<sup>nd</sup> line drugs and more specialized tests like mycobacterial speciation, molecular detection of drug resistance and strain typing using spoligotyping or MIRU-VNTR. Other ICMR institutes *i.e.* RMRI, Patna, RMRCs in Bhuvaneshwar, Jabalpur, Dibrugarh and Port Blair serve as IRLs and are providing culture and DST services to their respective states. NIRT is also a WHO Supranational reference laboratory, one of two such labs in south-east Asia. NIRT has been receiving panel cultures for proficiency testing every year from the Institute of Tropical Medicine, Antwerp, Belgium and so far 18 rounds have been successfully completed with high levels of concordance. NIRT provides training for mycobacterial culture and drug susceptibility testing (DST) for international participants from Sri Lanka, Bangladesh, Indonesia and Thailand. The support for implementation of quality assured AFB microscopy is provided by sending the panel slides and assessing the performance of technicians at state level IRLs. During 2008 - 2012 the international trainees from Thailand and Sri Lanka were 29 in number consisting of 1 microbiologist, 22 lab technologists and 3 each in the cadre of Research Officer and Technical Officer. Research scholars one each from Indonesia and Bangladesh were trained in LRP assay for DST and compound screening for anti TB activity and in conventional methodologies.

During the XI plan period, the RNTCP has achieved 70% case detection and >85% cure rates and reduced mortality due to TB considerably. However, despite these efforts and a well-functioning program, TB still remains a serious threat and one of the important causes of mortality and morbidity. Further, drug resistance to the firstline anti-TB drugs poses a serious challenge and in some urban centres like Mumbai, strains resistant to multiple drugs are circulating widely. While no nationally representative drug resistance survey has been carried out (one is planned for 2013), state-level surveys have estimated that MDRTB occurs on approximately 2-2.5% of newly diagnosed patients and 11-17% of previously treated patients. Rates of isoniazid resistance are higher, at 12-20% and 30-40% respectively. XDRTB (resistance to 2<sup>nd</sup> line injectable and a fluoroquinolone) is estimated to occur in about 4% of MDRTB cases. The RNTCP has set forth an ambitious National Strategic Plan (NSP) for the period 2012-17 with the aim of Universal Access to TB diagnosis and care. Many of the operational research study findings have been used to modify policy and practice, *e.g.* testing two sputum specimen instead of three, using two weeks instead of three weeks of cough as an entry point and dropping Cat III from the regimens.

Some of the important priorities that were identified by the RNTCP in the XI<sup>th</sup> plan:

- Finding more cases and making an early diagnosis
- Making treatment more patient-friendly
- Re-engineering RNTCP systems for NRHM alignment and health systems development
- Public Private Matrix (PPM)
- Supervision, monitoring, programme operations, and research

The ICMR institutes devoted to TB research have been striving to help the RNTCP achieve these goals and address their research priorities. A multi-pronged approach is being adopted to address several aspects of TB and HIV/TB – clinical, socio-behavioral, basic, epidemiological and operational. Some of the research studies undertaken during the XI<sup>th</sup> plan have provided important leads that are being taken forward into the XII<sup>th</sup> plan.

## **2. Major Achievements of ICMR Institutes during XI plan**

### **Clinical studies**

- The focus of clinical research activities was in two areas, viz. a) efforts to shorten the duration of TB treatment and b) to evolve effective treatment and preventive regimens for the emerging threat of HIV- associated TB.
- A randomized clinical trial demonstrated for the first time that sputum positive pulmonary TB patients can be effectively treated with a 4-month regimen containing ofloxacin in addition to the other first line anti-TB drugs, thereby significantly shortening the standard duration of treatment of 6 months – this study generated a global interest in the role of the quinolone group of drugs in shortening TB treatment duration, and resulted in the emergence of newer generations of quinolones (gatifloxacin, moxifloxacin) with even more potent anti-mycobacterial activity compared to ofloxacin. (NIRT)
- Development of a patient-friendly ultra-short regimen for the treatment of patients with pulmonary TB- 5-arm randomized clinical trial is in progress in NIRT to study the efficacy and safety of 3- and 4-month regimens using moxifloxacin compared to the standard 6-month regimen. This is one of only three studies globally that is addressing this important issue. Preliminary results suggest that patients treated with the moxifloxacin regimens become sputum culture negative earlier and to a greater extent than those treated with the control regimen. This has important positive implications for the TB control programme as it helps to cut the chain of transmission of infection earlier. (NIRT)

- Studies at NIRT had shown that HIV infected persons were at a much higher risk of developing clinical TB (incidence rate 6.9/100person-years) compared to immunocompetent persons. A randomized trial comparing a 6-month two drug regimen to a 36-month INH regimen in preventing TB in HIV infected persons showed that both regimens were equally effective in preventing active TB among HIV-infected individuals in India. This finding has policy implications and has been instrumental in the National AIDS Control Organization adopting isoniazid preventive therapy in its ART clinics. (NIRT)
- A randomized clinical trial comparing the standard 6-month Category I regimen with an extended 9-month regimen showed that while the cure rates and death rates were the same in both regimens, TB recurrence was significantly less in the longer regimen. Another important finding was the high rate of acquired rifampicin resistance among patients failing treatment, highlighting the need to develop better treatment policies for this group of patients. These findings were used by the WHO in formulating its new treatment guidelines for TB/HIV, in 2010. (NIRT)
- Safety/efficacy trial of nevirapine vs efavirenz along with ATT in patients with HIV-1 and TB demonstrated that once-daily nevirapine was inferior to the efavirenz-containing regimen, with higher virological failure and death rates. Efavirenz is therefore the preferred drug for treatment of co-infected patients.
- Randomized clinical trials with Mycobacterium w immunotherapy were conducted in pulmonary TB patients to improve the therapeutic efficacy of Category I and II regimens (NJIL&OMD and NIRT). The trials were successfully completed and data analysis is ongoing.
- Pharmacokinetic studies of anti-TB and anti-HIV medicines were undertaken to address key research issues in the areas of HIV & TB such as, drug-drug interactions, significance of pharmacogenetics in HIV therapy, impact of HIV infection on the TB drug levels and studies in children. Some important findings that emerged were that Rifampicin interaction with Nevirpaine could be counteracted by increasing the dose of NVP, that Efavirenz levels were influenced more by the CYP polymorphism than rifampicin administration and that a combination of stunting, young age and CYP2B6 polymorphism could lower NVP levels in children significantly. (NIRT)

### **Socio-behavioral**

- A Pilot study of Screening for Alcohol use disorder (AUD) among TB patients - study findings have helped understand the importance, feasibility and acceptability of alcohol intervention among TB patients, and have provided the background for testing an alcohol intervention program for TB patents with AUD. (NIRT)
- Health seeking behaviour and awareness of tuberculosis among migrants - Brick kiln workers: Qualitative data findings report lack of awareness on TB among these migrants. Inaccessibility of public health care facilities and delays were reported. (NIRT)

## Diagnosis

- Diagnostic Luciferase Reporter Phage Assay had been developed and standardised by developing better constructs for performing diagnosis and drug susceptibility testing procedure for tuberculosis.
- Showed that blood agar slants may be good substitutes of LJ medium for rapid detection of *M. tuberculosis* from sputum which reduces the period of culture by 7 days.
- Developed new rapid molecular method for detection of Rifampicin, Isoniazid and Ethambutol resistance in TB with the help of indigenously developed DNA chips.
- Developed procedures for application of direct in situ hybridization and PCR on tissue specimens for early diagnosis of leprosy and TB.)
- Evaluated a tool box for diagnosis of tuberculosis based on ELISA using PGL-TB, ESAT6 and CFP 10 antigens in a multi-centric study and found not suitable because of the presence of high levels of antibody levels in healthy contacts of TB.
- Role of Interferon gamma release assay (IGRA) as an indicator of latent and active *M. tuberculosis* infection in HIV infection; it is as sensitive as tuberculin skin test for diagnosis of LTBI.
- First growth-based assay that could lead to the diagnosis of both active and dormant tubercle bacilli was developed by the use of improved luciferase reporter phage constructs.
- Search for novel Immuno-dominant antigen(s) from clinical isolates of *M.tuberculosis* revealed certain culture filtrate antigens that are recognized by majority of healthy individuals as well as patients suggesting to be good inducers of Th1 response.

## Molecular epidemiology

- Examination of possible TB transmission using molecular epidemiological tools - DNA finger printing with an IS 6110-based probe, direct repeat probe & PGRS probe. These studies have provided a better understanding of the dynamics of TB transmission between geographic regions and suggest rational measures to interrupt such transmission links.
- Study to examine the impact of HIV Infection on the Recurrence of Tuberculosis in South India showed that recurrence due to exogenous re-infection was greater in HIV infected TB patients (88%) compared to 9% in HIV uninfected patients. Among the HIV uninfected TB patients, endogenous reactivation was predominant (91%).
- Using high resolution markers in evaluating the tuberculosis control programme, it was noted that the predominant strain of *M. tuberculosis* prevalent is ST26/CASI\_Del family and not the Beijing strain.



- A study of drug resistance among the classified genotypes of south Indian strains showed that (i) Single and low copy IS6110 accounted for 66% *M.tuberculosis* (ii) majority of our strains (84%) belonged to the EAI family (iii) Multidrug resistance is more common in CAS, T and Beijing than EAI which is prevalent in South India .

### **Epidemiological/Operational Research**

- NIRT evaluated the epidemiological impact of DOTS - completed surveys demonstrated that DOTS implementation resulted in more rapid reduction in prevalence of TB compared to that in the pre-DOTS period. The reduction in TB prevalence was ~12% per year compared to ~6% in the pre-DOTS era
- NIRT provided an authentic estimation on the socio-economic burden of TB in India which is cited by National and International agencies and also specified by the Prime Minister of India while launching the program on TB. Based on these findings, WHO has projected the economic burden of TB for the country. The overall economic losses to the country due to TB are estimated to be in the range of Rs. 3 billion annually.
- Information provided to the nation on the first reliable estimate of the burden of TB (~8.5 million cases in 2000).
- Prevalence of pulmonary TB in UP districts was observed to be 35.8 per 10,000 populations. MDR cases in Kanpur urban areas was 3%, and about 2% in Agra among new smear positive cases (Cat I) of pulmonary TB.
- A study undertaken comparing > 2 weeks vs >3 weeks cough to improve the yield of smear-positive cases among outpatients was translated into the RNTCP and helped to improve case detection. It was found that 2 weeks cough was as sensitive as 3 weeks cough in the diagnosis of pulmonary TB.
- Other studies undertaken to improve case detection were (i) Feasibility and effectiveness of involving private sector in DOTS & (ii) Examination of the role of repeat sputum smear microscopy after a course of antibiotics.
- Studies to evaluate the Phenol Ammonium Sulphate sedimentation method to improve sputum microscopy showed that it compared well in terms of sensitivity and specificity with direct microscopy and was better accepted by laboratory technicians since it was safe.
- Mortality Survey in Andhra Pradesh and Orissa - Using retrospective cohort survey, the prevalence of general mortality rates was found to be similar in Andhra Pradesh and Orissa. However, TB mortality rate was higher in AP than in Orissa. The reasons for the higher mortality in AP need to be explored.
- Studies showed high prevalence of TB in tribal population and the highest prevalence was reported in Saharia primitive tribe (~1500/100,000 py)

## Basic Research

- Studies focussing on biological, immunological & molecular biological aspects of mycobacterial infections were undertaken to examine the basic pathogenic mechanism that may lead to better diagnostic tools and development of vaccines and other immune interventions for prevention and control of infection and disease (NIRT, NJIL&OMD).
- Immunogenetic studies were undertaken to study the association of certain genes (HLA & non HLA genes such as cytokine, chemokine, vitamin D receptor, mannose binding lectin, etc) with susceptibility or resistance to TB – these studies helped understand the basis of genetic susceptibility to TB and the role of these genes in the regulation of immune response to TB.
- MDR strains of *M.tuberculosis* have been observed to retain the capacity to infect through aerosol route as efficiently as sensitive strains.
- Mycobacterial cell wall does not act as a significant barrier for the accumulation of some of the fluoroquinolones of *M. tuberculosis* isolates.
- Protective efficacy and immune response was evaluated to Mw/BCG/other vaccines in animal models of TB.
- APCR-RFLP technique targeting 16S-23SrRNA gene region developed for identification of pathogenic mycobacteria patented and transferred to several labs.
- Phage constructs developed by genetic engineering could infect and detect both active and dormant bacilli. - their ability to diagnose the presence of both types of bacilli was tested in laboratory grown TB cultures and in sputum samples from patients as well.
- Standardisation and optimization of three dormant models used for simulating the growth of latent bacilli was done and the capability of the developed constructs was tested in them.

## ASSISTING THE TB CONTROL PROGRAMME

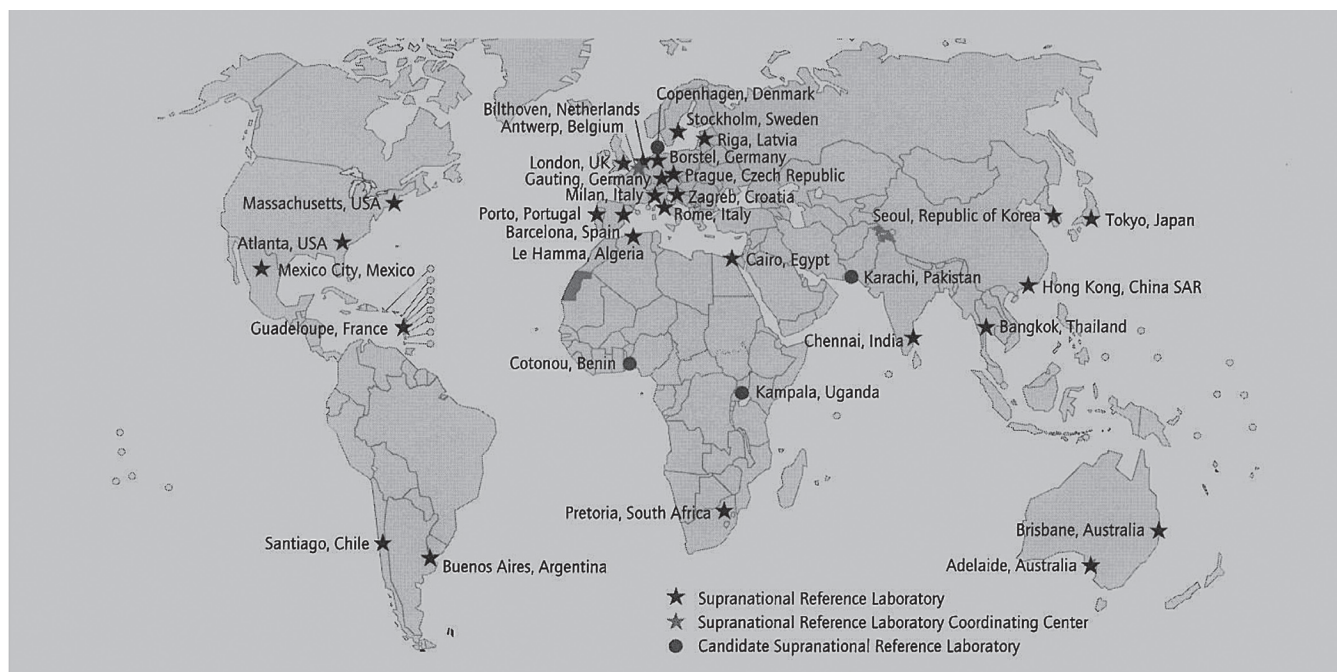
- NIRT coordinates surveys to assess the prevalence of drug resistance to anti-TB drugs and also provides quality assurance to the laboratory component of the national programme. Drug resistance surveillance has been completed in Gujarat, Madhya Pradesh, Tamil Nadu & Andhra Pradesh.
- ICMR institutes are the preferred training destination for training of personnel for the RNTCP. Experienced trainers had trained over 5000 RNTCP personnel during the last 5 years. The departments at NIRT and NJILOMD also fulfil their role as National Reference Laboratory and are supporting the National TB control programmes under RNTCP activities. As a part of the exercise, establishment and accreditation of Intermediate Reference Laboratory, training of staff in mycobacteriological techniques and periodic monitoring (external quality assurance) of performance in smear, culture and drug susceptibility testing is being routinely performed.

- ICMR laboratories have also established facilities for line probe assays (rapid drug resistance testing) and are providing this service to the respective states.
- NIRT and NJIL&OMD are among the four NRLs under RNTCP to monitor RNTCP activities in India for external quality assurance (EQA) of sputum smear microscopy and to establish and monitor intermediate reference laboratories for mycobacterial culture and drug susceptibility testing (DST) for first line drugs namely, Streptomycin, Isoniazid, Rifampicin and Ethambutol, through quality assured systems. Every year, on-site evaluation visits are being made to these states by experienced personnel to assess the situation and the report will be submitted to Central TB Division (CTD).
- NIRT and NJIL&OMD provide technical guidelines to the personnel belonging to IRLs by means of Culture and DST training and to test the isolates for second line DST for the drugs Kanamycin and Ofloxacin for XDR-TB suspects. So far, more than 600 participants from national and international sites were trained at NIRT for culture and DST. More than 1200 isolates were tested for second line DST for XDR-TB suspects. Nineteen laboratories including state IRLs, RMRCs of ICMR and private laboratories were accredited for solid culture & DST for first line drugs and accreditation for 14 laboratories are in process. NIRT is now initiating second line DST training for both solid as well as liquid for state IRLs and the detailed protocol was developed for the same in consultation with CTD.

#### **ROLE OF NIRT AS A SUPRANATIONAL REFERENCE LABORATORY (SNRL) UNDER WHO:**

As a SNRL, NIRT is receiving panel cultures for proficiency testing every year from Institute of Tropical Medicine, Antwerp, Belgium and so far 18 rounds have been successfully completed with high level of concordance. Sharing the burden of ITM, Belgium, the performance of intermediate reference laboratories is being monitored by conducting the annual panel testing of the participating national IRLs. Four rounds of panel testing had been performed from 2009 onwards and the same kind of support will be rendered to the participating laboratories in the coming years, too. NIRT provides training for mycobacterial culture and DST for international participants from Sri Lanka, Bangladesh, Indonesia and Thailand. The support for implementation of quality assured AFB microscopy is provided by sending the panel slides and assessing the performance of technicians.

During 2008 - 2012 the international trainees from Thailand and Sri Lanka were 29 in number consisting of 1 microbiologist, 22 lab technologists and 3 each in the cadre of Research Officer and Technical Officer. Research scholars one each from Indonesia and Bangladesh were trained in LRP assay for DST and compound screening for anti TB activity. They learnt conventional methodologies, as well.



(Reference laboratories under WHO)

### 3. Publications during XI Plan

NIRT, Chennai	: 342
NJIL&OMD, Agra	: 37
NARI, Pune	: 03
RMRCT, Jabalpur	: 15
RMRC, Bhubaneswar	: 04
RMRC, Dibrugarh	: 02
DMRC, Jodhpur	: 03

#### 4. List of Patents

##### NIRT, Chennai

- Dr. Vanaja Kumar – A patent related to “Sputum processing method for mycobacteria” filed through Intellectual Property Rights Unit of ICMR (Ref No P&I /IPR/TRC/137 A April 2009)
- Dr. Vanaja Kumar – Patent application filed for “Improved LRP assay for rapid detection of dormant and active tubercle bacilli from clinical samples” – (2530/DEL/2010 dated 22.10.10)
- Dr. Sujatha Narayanan – A patent related to “ A process for the preparation of primers useful for the detection of *M. tuberculosis*” in the name of Indian Council of Medical Research has been granted (Patent No. 235025).
- Dr. Vanaja Kumar – Patent applied for “ New anti-tuberculous antibiotic from marine actinomycete strain R2” – (P&I/IPR/TRC/184/June 16, 2010)

##### NJIL&OMD, Agra

1. Novel Drug Efflux Proteins of *M.tuberculosis* as Potential Therapeutic Targets (2071/DEL/2007)).
2. Probes and primers for identification of mycobacterial proteins useful as potential drug targets(Indian patent Appl No.884/DEL/2007).
3. Expression of virulence factors of *M.leprae* in host during infection by functional genomic approaches ( Indian Patent Application No. 2012/DEL/2007)
4. Primers and methods for identification of pathogenic mycobacteria (Granted no 2418/DEL/2006)

#### 5. Advocacy and Training

##### NIRT, Chennai

NIRT - Identified as a training centre by CTD to train personnel on RNTCP activities

NATIONAL : About 5000 personnel at various levels (Medical Officers, Microbiologists, Senior Treatment Supervisor, Senior TB Laboratory Supervisors, Laboratory Technicians, etc.) underwent training in RNTCP activities

INTERNATIONAL : Personnel from Thailand, Srilanka, DPR Korea, Myanmar, Bangladesh, Indonesia etc. consisting of microbiologist, lab technologists in the cadre of Research Officer and Technical Officers. Research scholars underwent training on various aspects of mycobacteriology.

Training of health workers in survey methodology: The epidemiology unit has trained health workers in survey methodology for conducting disease survey and tuberculin survey from several National Institutes including N.T.I. Bengaluru, AIIMS- New Delhi, NJIL&OMD- Agra, PGIMS- Chandigarh, MGIMS- Wardha, RMRCT- Jabalpur, New Delhi TB Centre, LRS Institute - New Delhi, & CMC, Vellore.

#### **NJIL&OMD, Agra**

- M.Sc Project Training -More than 20 M.Sc students trained in TB/HIV.
- Project/Research Assistants- Two project Assistants trained in TB in Projects.

#### **DMRC, JODHPUR**

- Imparted training to 28 M. Sc. Microbiology students on 'Rapid culture and drug sensitivity of *Mycobacterium tuberculosis* '

#### **RMRC, JABALPUR**

##### **TB:**

- Technicians in microscopy, culture and DST-12
- Attendants in washing, sterilization, sputum collection and transportation-10
- Field staff in planning, census taking, data collection, sputum collection, transportation and report preparation - 20
- SRF in microscopy, culture, DST, field survey planning, monitoring and report preparation - 2
- Statistician in data verification, supervision for data entry, data analysis and report preparation – 2
- Data entry operator & verifier in data entry & verification - 4

##### **HIV:**

- Medical officers in testing, quality assurance & biosafety for HIV & CD4 tests- 40
- Laboratory technicians in testing, biosafety & quality assurance in HIV lab. – 361
- Staff nurses – testing of HIV in emergency & biosafety - 46

#### **RMRC, DIBRUGARH**

- One Scientist and one Laboratory Technician of the Centre have been trained in TB Work

**DMRC, JODHPUR**

- Trained two project staff- One SRF and one Field Investigator on sensitivity of *M. tuberculosis* to pyrazinamide.

**6. Capacity Building:****NIRT, Chennai**

- Ph.D. - 35 Ph.D. Scholars
- MPS - 1 scholar
- M.Sc. - 1 scholar

**NJILOMD, Agra**

- Ph.D Scholar- Five Ph.D. Scholars in TB.

**RMRC, Dibrugarh**

- Ph.D – Two Students

**Table 1: Status of Completed Research Studies undertaken during XI Plan**

Sr. No.	Thematic Area and Title of the Study	Objectives	Completed with outcome of the study	If off-shoot, Refer to XII plan study	Institution		
<b>Basic Studies</b>							
1	<p><b>Immunogenetic Studies in Tuberculosis</b></p> <p>(i) Regulatory role of Human Leucocyte Antigen DR (HLA-DR), Mannose binding lectin (MBL), vitamin D receptor (VDR) and Cytokine gene variants on immune functions in pulmonary TB</p>	<p>To understand the regulatory role played by host genetics (HLA-DR, MBL, VDR and Cytokine gene variants) on the Immunity to TB</p>	<p>Studies revealed the association of HLA-DR2, functional mutant homozygotes of Mannose binding lectin (MBL) (non-HLA) and vitamin D receptor (VDR) gene (non-HLA) variants with susceptibility to TB.</p> <ul style="list-style-type: none"> <li>◆ HLA-DRB1 alleles regulated perforin positive cells, macrophage phagocytosis and Th1 and Th2 cytokine response to <i>M. tuberculosis</i> antigens.</li> <li>◆ The variant genotypes of MBL gene regulated the MBL production, as well as macrophage phagocytosis.</li> <li>◆ VDR genotypes regulated the vitamin D3 modulated immune functions in pulmonary TB.</li> <li>◆ Cytokine +1188 polymorphism of IL-12B gene could regulate IL-12p40 production and may play a major role on acquired immunity to TB.</li> </ul>	<p>Other non HLA gene polymorphisms will be examined for susceptibility to TB</p>	NIRT, Chennai		



	(ii) Role of Chemokine, DC-SIGN and Toll-like receptor gene variants on immunity to TB	<ol style="list-style-type: none"> <li>1. To find out whether Chemokine, DC-SIGN and Toll-like receptor genes are associated with susceptibility or resistance to TB.</li> <li>2. To understand the regulatory role of these gene variants on immunity to TB.</li> </ol>	<p>TLR gene polymorphisms are not associated with susceptibility to TB. T allele of TIRAP 975C/T polymorphism may be associated with susceptibility to pulmonary TB.</p> <p>◆ The SDF G/A genotype of In2+5887 and G/G genotype of 3'UTR +12197 polymorphisms may be associated with susceptibility to pulmonary TB among females.</p> <p>The CCL5 gene haplotype A-C-C and the diplotype G/A-T /C may be associated with resistance to pulmonary TB.</p>	<ol style="list-style-type: none"> <li>1. Other chemokine and DC-SIGN gene polymorphisms to be studied.</li> <li>2. Regulatory role of these gene variants on immunity to TB - to be studied.</li> </ol>	NIRT, Chennai		
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	(iii) Immunomodulatory effect of Vitamin D3 on innate and adaptive immunity in pulmonary TB	To understand the immunomodulatory effect on immunity to TB	<ul style="list-style-type: none"> <li>◆ Vitamin D<sub>3</sub> exerts differential effects on cytokine production in TB with a prominent suppressive effect on IL-12 and IFN-<math>\gamma</math>.</li> <li>◆ Vitamin D<sub>3</sub> enhances Cathelicidin (an antimicrobial peptide associated with innate immunity) in pulmonary TB patients.</li> <li>◆ Vitamin D<sub>3</sub> suppresses intracellular expression of IFN-<math>\gamma</math> and TNF-<math>\alpha</math> in pulmonary TB and this might have a role in reducing inflammation at the site of infection.</li> <li>◆ Vitamin D<sub>3</sub> may down regulate the IP-10 and MIG chemokines at the site of infection and may act as a potential anti-inflammatory agent.</li> </ul>	Vitamin D levels and response to anti-TB treatment will be studied in patients enrolled in clinical trials	NIRT, Chennai		
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2	<p><b>Immunogenetic Studies in HIV and HIV-TB</b> Human Leucocyte Antigen (HLA) and non-HLA gene polymorphism studies in HIV and HIV-TB patients (ICMR Task Force Project)</p>	<p>To find out the HLA and non-HLA genes associated with susceptibility or resistance to HIV and HIV-TB</p>	<ul style="list-style-type: none"> <li>◆ HLA-A11 may be associated with resistance to HIV infection and HIV with active TB while HLA-B40 and HLA-DR2 may be associated with susceptibility to HIV and HIV associated TB.</li> <li>◆ The subtype HLA-A*1101 is associated with resistance while HLA-B*4006 with susceptibility to HIV and development of TB in HIV patients.</li> <li>◆ HLA-DRB1*1501 subtype might be associated with susceptibility to HIV-1 infection whereas HLA-DRB1*1502 may be associated with susceptibility to pulmonary TB in HIV patients.</li> <li>◆ Higher MBL levels and diplotypes (YA/YA) of MBL genes may predispose HIV infected patients to TB infection.</li> </ul>		<p>NIRT, Chennai</p>		
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3	<p><b>Pathogenesis of HIV/TB co-infection</b></p> <p>(i) Influence of active TB on chemokine and chemokine receptor expression in HIV-infected persons</p> <p>(ii) Incomplete immunological recovery following six months of anti-tuberculosis treatment in HIV infected individuals.</p>	<p>To examine the influence of TB co infection in HIV-infected individuals with respect to chemokine and chemokine receptor expression.</p> <p>To examine whether successful anti-TB treatment brought about a significant decline in the heightened levels of immune activation seen in HIV patients with active TB, and improve prognosis.</p>	<p>The study has been completed. Findings revealed elevated levels of beta-chemokines in HIV-positive individuals dually infected with <i>M. tuberculosis</i>. Persistently elevated chemokines may provide a suitable condition for continuous replication of HIV and <i>M. tuberculosis</i>. This in turn may contribute at least in part to the observed persistently elevated plasma HIV viremia in co infected patients despite anti-TB treatment.</p> <p>The findings revealed that although ATT was effective in clearing <i>M. tuberculosis</i> infection, a high proportion of HIV infected TB patients continued to have levels well above the normal range, indicating that underlying immune activation persists despite successful TB treatment alone. This suggests that in co infected individuals ATT needs to be supplemented with ART as well.</p>	<p>No</p> <p>No</p>	<p>NIRT, Chennai</p> <p>NIRT, Chennai</p>		
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4	<p><b>HIV and Hepatitis B/Hepatitis C co infection</b> Effect of anti-tuberculosis drugs on liver function in HIV patients with Hepatitis B or Hepatitis C co infection</p>	<p>To determine the prevalence of Hepatitis B and C virus co infection in HIV infected patients in Tamil Nadu and to investigate the effect of TB drugs on their liver function.</p>	<p>The prevalence of hepatitis B and C co infections was fairly high in the largely heterosexually infected population studied. This observation encourages the use of more careful screening for these viruses in HIV positive persons in this region. Findings also revealed that ATT as well as TB preventive therapy can be safely employed in HIV and hepatitis co infected patients, if baseline liver function tests are within normal limits.</p>	No	NIRT, Chennai		
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5	<b>Immune response in tuberculous pleuritis</b>	To understand the host immune response (Th1/Th2 paradigm) at the site of infection in TB pleuritis (TP)	<p>This study was completed with the following outcome. Compartmentalization of enhanced Th1 cells, cytokines, chemokines and its receptors established their role in robust Th1 immune response at the site of infection. Further in vitro studies on correlates of protective immune response showed a shift towards TH0/TH2 type.</p> <p>The better sensitivity and equal specificity of IP-10 assay compared with IFN-<math>\gamma</math> suggest that IP-10 is a potential diagnostic marker for evaluating TP.</p> <p>First time, we reported the ability of non-phagocytic cells (pleural mesothelial cells -PMC) to uptake and internalize <i>M. tuberculosis</i>. To survive within the hostile environment of PMC, the engulfed bacilli adopted defense strategies of latency and expressed the stress response proteins.</p>	No	NIRT, Chennai		
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6	<b>Role of soluble Toll like receptor 2 (sTLR 2) in mycobacterial diseases</b>	To compare soluble toll-like receptor levels between TB patients and household contacts/ healthy controls	After estimating sTLR2 in 175 active pulmonary TB patients, 123 household contacts and 44 healthy controls, a lower level of sTLR 2 was observed in TB patients than their household contacts and healthy controls ( $P < 0.05$ ). Three polypeptides, 51, 29 and 7 kDa were detected and were found to significantly effect the TLR2 mediated NFkB activation.	No	NIRT, Chennai
7	<b>Gene regulation of mycobacteria</b>	To understand the role of HSP 10 protein gene in regulation of <i>M.tuberculosis</i>	We have shown that <i>M. tuberculosis groE</i> promoter controls the expression of the bicistronic <i>groESL1</i> operon and shows differential regulation under stress conditions.		NIRT, Chennai
8	<b>Modulation of immune response and apoptosis by the most prevalent clinical strains of <i>M.tuberculosis</i> and its antigens</b>	To study the modulation of immune response and apoptosis by most prevalent clinical strains of <i>M.tuberculosis</i> and its antigens	This study was completed with the following outcome. The sonicate antigens from the most prevalent strains of <i>M. tuberculosis</i> harboring single copy of IS6110 showed differential protein expression and had potential to induce T-cell activation in normal PPD positive population. A correlation between phagocytosis and apoptosis indicated a differential mode of infection by clinical strains and their adaptation to different survival strategies that may lead to immune suppression and pathogenesis of the disease.	No	NIRT, Chennai

9	<p><b>Immunoproteomic Studies in Tuberculosis.</b></p> <p>(i) Identification of immunodiagnostic B-cell antigens from the secretory proteome of <i>M. tuberculosis</i></p> <p>(ii) Immunoproteomically identified <i>M. tuberculosis</i> T-cell antigens involved in protective immunity</p>	<p><i>M. tuberculosis</i> can code for at least 4000 proteins, of which hardly 100 have been characterized. A complementary approach is to study the proteomics, which will reveal the functional information, since proteins are the workhorses of cellular metabolism, ultimately.</p> <p>The aim of the project was to identify and characterize immunodiagnostic antigens of <i>M. tuberculosis</i>, in order to develop early and rapid diagnostic assays.</p> <p>The aim of the project was to identify to antigens specifically recognized only by healthy household contacts and not by TB, so that they can differentiate between infection and disease and also be useful as candidates for protective immunity.</p>	<p>About 500 antigenic fractions were resolved using preparatory 2-D electrophoresis. The individual fractions are being screened by ELISA for their sensitivity and specificity.</p> <p>Sixteen antigens have been identified to be specifically recognized only by healthy household contacts and may be useful in differentiation / protective immunity. Additionally, Rv0009, Rv2204c and Rv0753 also have been added. The short listed antigens have been over-expressed in <i>E. coli</i>.</p>	<p>The off-shoot will be continued up to 2014. The short listed fractions will be further analysed by MALDI-TOF/TOF to identify single and combination of antigens for early diagnosis of TB.</p> <p>The off-shoot will be continued up to 2014. The immunological characterization of the expressed antigens will be done in vitro in various control and disease groups, by measuring activities of the immune parameters.</p>	NIRT, Chennai
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<p>(iii) Search for novel immuno-dominant antigen(s) from clinical isolates of <i>M.tuberculosis</i></p>	<p>Greater lympho-proliferation as well as cytokine IFN-<math>\gamma</math> production was noted with clinical isolates as compared to laboratory strains. Screening of T cell response to CFPs of <i>M tb</i> has identified Rv2588c, Rv2557, Rv1357c, Rv1038c, Rv2096c and Rv3358 hypothetical CFPs antigens recognized by majority of healthy individuals as well as patients suggesting to be good inducers of Th1 response. This can be further explored to develop diagnostic reagent or recombinant vaccine after confirming in a statistically calculated sample size.</p>	<p>Completed</p>		<p>NJIL&amp;OMD, Agra</p>
<p>(iv) Role of Interferon gamma release assay (IGRA) as an indicator of latent and active <i>M. tuberculosis</i> infection in HIV infection.</p>	<p>The aim of the project was to assess the usefulness of <i>in vitro</i> assays of cellular immunity such as the Interferon <math>\gamma</math> (IFN-<math>\gamma</math>) release assay (IGRA), in response to selected antigens of <i>M. tuberculosis</i>, and analyze whether it will be a better and more useful indicator of latent and active <i>M. tuberculosis</i> infection than TST, in the HIV infected individuals.</p>	<p>QFT-IT was more sensitive than TST in detecting active TB cases among HIV negative subjects. QFT-IT positivity was very low in children with low risk for TB infection, while it increased over age among adults.</p>	<p>As an off-shoot of the observation that IGRA is specific in childhood, it has been proposed to test this assay in Childhood TB for its sensitivity and specificity.</p>	

	(v) Dormancy associated antigens of <i>M. tuberculosis</i>	The aim of the project was to identify and characterize the mycobacterial antigens associated with the slowly replicating, post-logarithmic phase growth of <i>M. tuberculosis</i> , the so-called "dormant" phase. In addition to the laboratory strain, clinical isolates have also been studied.	The dormancy associated antigens which are newly expressed/overexpressed/underexpressed mycobacterial antigens in <i>M. tuberculosis</i> and 2 clinical isolates, under oxygen sufficient and oxygen-deficient conditions have been identified.	Identification of differentially expressed antigens is completed. Further characterization of these antigens using MALDI-TOF/TOF etc will spill over in the 12th plan period.	
10	Development of rapid methods for TB diagnosis using luciferase reported phages	To develop and evaluate rapid methods for TB diagnosis and drug susceptibility testing of <i>M. tuberculosis</i>	Standardisation of assay protocol and ideal phage combinations completed; Lyophilisation of phages completed;	Kit development in collaboration with private partner initiated (Advertisements placed in ICMR website; Partner identification in process)	NIRT, Chennai
<b>Clinical Research</b>					
1	Randomized clinical trial of 4-month thrice-weekly Gatifloxacin and Moxifloxacin containing regimens to shorten treatment in sputum positive pulmonary TB	To study the safety and efficacy of gatifloxacin and moxifloxacin in the treatment of pulmonary TB	While an earlier clinical trial of NIRT had shown good efficacy of a daily 4-month regimen containing ofloxacin in the treatment of sputum positive pulmonary TB, this clinical trial which compared two 4-month regimens using gatifloxacin or moxifloxacin given thrice-weekly, with a standard 6-month regimen was terminated midway due to unacceptably high relapse rates in the test regimens. The manuscript has been submitted for publication.		NIRT, Chennai

2	Efficacy of short-course chemotherapy for TB in HIV-infected patients – 9 month intermittent regimen vs 6-month thrice-weekly regimen	To assess the efficacy of short course intermittent regimens for the treatment of HIV associated TB.	Both regimens had similar cure and death rates, but a significantly lower bacteriological recurrence rate was observed in the 9-month intermittent regimen. High incidence of acquired rifampicin resistance was observed.	The off shoot of this study is comparing daily versus thrice-weekly treatment in HIV co-infected TB patients to see if outcomes can be improved	NIRT, Chennai
3	Randomized clinical trial to test safety and efficacy of nevirapine vs efavirenz along with ATT in patients with HIV-1 and TB	To evaluate the safety and efficacy of two different once-daily anti retroviral treatment regimens along with anti-TB treatment in patients with HIV – 1 & TB.	The trial showed that once-daily nevirapine was inferior to the efavirenz-containing regimen, with higher virological failure and death rates.		NIRT, Chennai
4	Pharmacogenetic studies in HIV therapy	To study the impact of certain gene polymorphisms on plasma nevirapine and efavirenz	We reported for the first time that a G to T shift at 516 of the <i>CYP2B6</i> gene significantly influenced plasma efavirenz & nevirapine levels in an ethnic south Indian HIV+ve cohort; TT genotypes had elevated drug levels than GG/GT genotypes. The T allele frequency was 0.44, the highest reported world-wide.	Further studies will examine the impact of dose reduction of EFV among patients with TT genotype	NIRT, Chennai
5	Pharmacokinetics of nevirapine and efavirenz in HIV+ children	To study the pharmacokinetics of nevirapine and efavirenz in HIV-infected children and factors influencing drug levels	The study showed that a combination of factors, such as, young age, stunting and <i>CYP2B6</i> GG/GT genotype could potentially result in sub-therapeutic nevirapine concentration. The study suggested that ART dosing recommendations for children should be reviewed in the light of these findings.		NIRT, Chennai

6	Diagnosis of pulmonary infections in HIV positive patients	To study the role of induced sputum as a non-invasive tool for diagnosis of pulmonary infections in HIV + patients	Novel sequences submitted to Gen Bank. 2 novel mutations submitted to GenBank (accession nos. JX101868 and JX101869 for the Dihydropteroate synthase gene of <i>Pneumocystis jiroveci</i> isolates.	No	NIRT, Chennai
<b>Socio-Behavioral Research</b>					
1	Alcohol use disorders among TB patients	To screen for Alcohol use disorder (AUD) among TB patients	The study findings have helped understand the importance, feasibility and acceptability of alcohol intervention among TB patients, and have provided the background for testing an alcohol intervention program for TB patients with AUD. The study findings have helped develop intervention IEC material-Flip Charts and Posters on TB and Alcohol which can be used for health providers working for RNTCP.	A randomized clinical trial will be performed to test the efficacy of the developed behavioural intervention	NIRT, Chennai
2	Addressing psychosocial needs and HIV risks in Indian MSM	To understand the behavioural risk factors among men who have sex with men.	This study has provided the background for designing a large multi centric intervention study. Mental health interventions to be included in all HIV prevention intervention programmes.		NIRT, Chennai

3	Community-Based approach to designing an AIDS program for HIV positive mothers in India	To explore the perceptions and needs of mothers living with HIV to gain greater insights into the challenges they face in relation to their health seeking behaviour, and issues related to stigma, disclosure and discrimination.	Mothers living with HIV face numerous challenges which are not addressed. The findings emphasized the need for psychosocial intervention for mothers living with HIV to enable them cope with their illness and ensure a better quality of life for themselves and their families.		NIRT, Chennai
4	Sociological studies on tuberculosis patients		Status of knowledge of TB patients was evaluated	Not Applicable	DMRC, Jodhpur
<b>Epidemiological/Operational Research</b>					
1	Survey of the prevalence of anti-tubercular drug resistance & evaluation of risk factors for TB ; and status of HIV/AIDS in the tea garden workers of Assam (2010-2012)	To investigate the MTB drug resistance pattern and prevalence of HIV/AIDS among tea garden workers in Assam	The door to door surveys, covering 33,082 persons living in 12 randomly selected tea gardens of Dibrugarh district revealed 64 AFB positive, thus, giving overall point prevalence rate of MTB of about 2 per 1000 population. The prevalence rate varied from 0.41 / 1000 to 5.02 /1000 in different tea gardens. Prevalence of MDR was found 2%. The presence of a positive family history of TB increased the risk of TB. Lower BMI significantly increased the risk of TB Among the 1,086 blood samples tested only 1 was positive	No immediate future plans in XII <sup>th</sup> Plan	RMRC, Dibrugarh

2	Prevalence and molecular diagnosis of human pulmonary paragonimiasis in NE region (is a differential diagnosis for pulmonary TB)	To determine the disease burden due to paragonimiasis and to study the etiological agent of human pulmonary paragonimiasis using molecular methods in NE India	This study recorded 1.9% community prevalence of paragonimiasis, highest being in Arunachal Pradesh (3.7%) followed by Meghalaya (1.8 %) and Assam (1.1%). In this study, 4 types of lung flukes-3 belonging to Westermani complex ( <i>P. westermani</i> genotype 1, <i>P. westermani</i> genotype 2, <i>P. siamensis</i> like) and <i>P. heterotremus</i> were detected. Near complete mitochondrial genome sequencing of <i>P. westermani</i> genotype 1 was accomplished	“Development of an ELISA based diagnostic kit for detection of paragonimiasis” (during XII <sup>th</sup> Plan)	RMRC, Dibrugarh
3	Assessing the Epidemiological impact of DOTS	To assess the impact of RNTCP on the incidence and prevalence of TB disease.	Completed surveys demonstrated that DOTS implementation resulted in more rapid reduction in prevalence of TB (12% per year) compared to that in the pre-DOTS period (~6% per year).		NIRT, Chennai
4	Mortality Survey in Andhra Pradesh and Orissa	To collect baseline TB mortality data in the states of Andhra and Orissa.	Using retrospective cohort survey, the prevalence of general mortality rates was found to be similar in Andhra Pradesh and Orissa. However, TB mortality rate was higher in AP than in Orissa.		NIRT, Chennai

5	Molecular Epidemiology	<p>To study the impact of HIV Infection on the Recurrence of TB in South India.</p> <p>To study the drug resistance patterns among the classified genotypes of south Indian strains</p>	<p>The recurrence due to exogenous re-infection was greater in HIV infected TB patients (88%) compared to 9% in HIV uninfected patients. Among the HIV uninfected TB patients' endogenous reactivation was predominant (91%)</p> <p>Single and low copy IS6110 accounted for 66% of <i>M.tuberculosis</i> strains. The majority of our strains belonged to the EAI (84%) MDR is more common in CAS, T and Beijing than EAI which is prevalent in South India</p>	<p>Extensive genotyping of <i>M.tuberculosis</i> strains is being planned in both HIV-infected and uninfected TB patients.</p> <p>No</p>	NIRT, Chennai
6	Study of the drug sensitivity profile and molecular characterization of <i>M. tuberculosis</i> strains isolated in Assam (2004-2008)	To understand the transmission of TB using DNA fingerprinting techniques in select populations of north-east India; and to establish microbiological & molecular biological techniques for diagnosis and determination of drug resistance in north-east India	A total of 490 sputum samples were collected from TB suspected patients attending RNTCP from Assam, Meghalaya, Arunachal Pradesh and Nagaland. 15 strains, 2 from Dibrugarh, 5 from Manipur and remaining from Shillong were MDR. Spoligotyping results revealed 6/10 were unique to NE region, were related to Beijing and CAS clades.	"Genetic diversity and drug resistance pattern of <i>M. tuberculosis</i> in NE India" will be studied during the 12 <sup>th</sup> Plan period	RMRC, Dibrugarh

7	Prevalence of Pulmonary TB in Jabalpur district of MP as a sentinel site of Central TB division	To estimate the prevalence of bacillary TB in Jabalpur District of Madhya Pradesh	The study indicates that the TB situation in the study area is similar to other areas of the country. Findings communicated to health authorities and the Central TB division		RMRCT Jabalpur
8	Prevalence of Pulmonary TB in primitive tribes of MP	1. To estimate the prevalence of pulmonary TB in tribal population of MP 2. To estimate the prevalence of TB infection in tribal population of MP	Other than "Saharia" primitive tribe, TB prevalence was similar to National average among tribal and non-tribal populations.	Follow-up studies are being planned to undertake interventions to reduce TB in the Saharia tribe.	RMRCT Jabalpur
<b>Translational Research/Technology Developed</b>					
1	Towards developing vaccine	To clone and create knock out mutants of lipoprotein gene LPQS and test its vaccine potential	LPQS gene of <i>M. tuberculosis</i> coding for a lipoprotein has been cloned, overexpressed, and characterized. A deletion mutant also has been created. Both in THP1 cells and in guinea pigs the LPQS knockout is attenuated and holds promise as a vaccine candidate.	No	NIRT, Chennai
2	Sensitivity and specificity of combination testing algorithms for HIV among TB patients	Serial testing of blood samples using different rapid tests	Algorithms developed can reduce time of testing of HIV among TB patients, ideal for use in settings like TB clinics or Primary Health Centres.		NIRT, Chennai



**Table 2: Important and Essential Activities which need to be continued in XII<sup>th</sup> Plan (ongoing studies)**

Sr. No.	Thematic area and title of the study	Work done in XI <sup>th</sup> Plan/ Justification for continuation	Time frame	Deliverable outcome with public impact	Institution
<b>Basic Research</b>					
1	Role of Chemokine, DC-SIGN and Toll-like receptor gene variants on immunity to TB.	Other Chemokine and DC-SIGN gene polymorphisms to be studied. Regulatory role of these gene variants on immunity to TB to be studied.	2013-14	These studies will be useful to understand the genetic susceptibility to TB in the south Indian population.	NIRT, Chennai
2	TLR-2 polymorphism in patients with mycobacterial diseases	Analyzed TLR 9. SNPs (T1237C) showed 62.24% Heterozygous and 37.76% wild type. In TB cases. Analyzed four polymorphisms in two biologically plausible candidate genes (TLR2 -196 to -174 del, G2408A (Arg753Gln) and TLR9 (T-1237C and G2848A) for TB and leprosy susceptibility (TLR2 and TLR9). Marginally significant association with allele frequency at TLR9 G2848A, but this was not significant when adjusted for age and sex.	2007-12	Completing this year	NJIL&OMD, Agra

3	Role of Nucleotide Binding Oligomerization Domain (NOD2) in Mycobacterial Disaeses	NOD 2 variants (Arg702Trp and 3020insC) were found to be monomorphic(wild), and 7 subjects were heterozygous for Gly908Arg SNP in 263 patients with TB, 260 patients with leprosy and 270 healthy controls residing in nothern Indian states suggesting the minimal role of these variants in susceptibility/resistance to TB and leprosy in this population.	2007 - 2012	Will throw light on genetic factors involved in leprosy & TB	NJIL&OMD, Agra
4	Analysis of SNPs in <i>TLRs</i> , <i>TIRAP</i> , <i>MCP 1</i> , <i>MiRNAs</i> in tuberculosis and investigating the possible role of these molecules in immunopathogenesis of the disease	Analyzed 285 TB cases and 164 Controls for mcp1 -2518A/G SNP. Heterozygous genotypesA/G was found to be in 42% Controls and 30% Cases. Out of 207 TB cases and 84 controls analyzed for mcp1 -363G/C SNP, homozygous mutant CC genotypes was foundto be in 13% cases and 7% controls. Out of 173 TB cases and 128 controls analyzed for TLR1 A743G genotype,heterozygous genotype AG was found to be in 48% Cases and 61% of controls. Out of 174 TB cases and 120 healthy controls analyzed for TLR6 C745T SNP, TT genotype was absent and CT was distributed in equal percentage between TB Cases and Controls.	2008-2014		NJIL&OMD, Agra

5	DNA fingerprinting of <i>M. tuberculosis</i> isolates from defined population/ regions using IS 6110 probe	Analysis of strains from different states of the country show that 2-10% of the strains has low copy numbers and can be missed if only this probe is used for detection of TB cases	2012-14	<p>It has been suggested to use this method in defined ethnic groups of the country and will be done during the early 12<sup>th</sup> plan period. While this IS-6110 based RFLP technique has the limitation of low or no copy numbers in a section of Indian isolates, overall the information obtained is easily comparable at international level. It has been proved to be an important tool for tracing outbreaks and relapses in different communities. Other molecular markers of fingerprinting like RAPD, Ribotyping, and Spoligotyping will be applied specially where low copy no of <i>M. tuberculosis</i> isolates observed and these markers will be used as complementary tools. Correlation of the results of this typing with drug susceptibility profile and contact status as well as disease profile will also be recorded and the information generated will serve as baseline data for the country.</p>	NJIL&OMD, Agra
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6	Study of cell wall components of tubercle bacilli in different metabolic states.	Cell wall components isolated	2013-14	Mycobacterial cell wall components such as mAGP (mycolyl - Arabino Galacton Peptidoglycan) complex, MAMEs (Mycolic Acid Methyl Esters), Peptidoglycan and Arabino galactan will be characterized. This may have implications for diagnosis.	NIRT, Chennai
7	Taxonomical studies on mycobacteria using HPLC techniques	Mycobacterial strains both <i>M. tuberculosis</i> and MOTT from clinical samples isolated	2012-14	Will help in understanding of geographic distribution of TB and non-tuberculous mycobacteria in our region	NIRT, Chennai
8	Innate immune responses in TB	To study the role of dendritic cells (DC) and neutrophils in innate immunity of TB It was observed that prevalent clinical strains of <i>M. tuberculosis</i> interfere with migration, maturation and the intricate functions of DC to evade the immune recognition for its intracellular persistence. It was demonstrated that KG-1 derived DC can be used as an <i>in vitro</i> infection model for studying <i>M. tuberculosis</i> - DC interaction. Clinical strains also inhibited the early activation of neutrophils and compromised the killing mechanisms for their own survival.	2012-14	Further studies on functional role of neutrophils and signaling cascades of apoptosis are planned in both normals and TB patients. This will be carried over in 12 <sup>th</sup> plan period	NIRT, Chennai

9	Culture & sensitivity studies on <i>M. tuberculosis</i> using blood agar slants for reduction of time in diagnosis of TB	Results of study showed direct drug sensitivity testing of <i>M. tuberculosis</i> using supplemented media in seven days.	2012-14	Our method needs to be standardized and validated to make it useful for all patients of pulmonary TB. RNTCP presently carries out sensitivity testing for only suspects of MDR TB in re-treatment category, thus most new TB cases with MDR remain undetected and continue to transmit TB in community 2. DMRC has been directed to help RNTCP in culture and sensitivity testing of <i>M. tuberculosis</i> from sputum samples of patients of Jodhpur division. This service component is also included in the study.	DMRC, Jodhpur
10	Gene Regulation Of mycobacteria	The regulation of acetamidase gene of <i>M. smegmatis</i> , the first inducible gene of mycobacteria has been partially unraveled. It is a very complex process.	2007-2014	Mycobacteria vary in their pathogenecity by adopting different gene regulatory mechanisms. This has implications for treatment.	NIRT, Chennai

11	Functional Genomics of <i>M. tuberculosis</i> with reference serine threonine kinases	<p>Protein kinase PknI is one of 11 functional serine/threonine protein kinases in <i>M. tuberculosis</i>. Specialized transduction was performed to create null mutant in the PknI gene. The resulting mutant was used to determine the role of PknI in <i>M. tuberculosis</i> growth and infectivity. We have shown that PknI plays a role in sensing the host macrophage's environment and translating it to slow the growth of <i>M. tuberculosis</i> within the infected host.</p> <p>The regulatory effect of serine threonine protein kinase, PknL, from <i>M. tuberculosis</i> strain H37Rv was investigated under nutrient deprived conditions that simulate circumstances leading to latency. In vitro growth kinetics experiments revealed that clone expressing active PknL had a significant growth advantage under nutrient limiting conditions. PknL has a role in regulating glutamine metabolism in mycobacteria. Furthermore, a role for PknL in cell wall biogenesis/cell division was shown by scanning electron microscopy.</p>	2007 -2014	Understanding the role of the functions of the genes of <i>M. tuberculosis</i> can throw light on the pathogenesis of the disease and thereby help in finding out newer drug targets and vaccine	NIRT, Chennai
12	Pharmacoproteomic effect of fluoroquinolones as well as aminoglycoside resistance in <i>Mycobacterium tuberculosis</i> isolates using proteomic approaches	Establishment of relationship with hypothetical proteins observed during the study with drug resistance is being undertaken	2012-13	Will be completed within 1 year of XII <sup>th</sup> plan period	NJIL&OMD, Agra

13	Open Source Drug Discovery on tuberculosis	Some of the well characterized MDR strains genotyped. Workshop on OSDD of CSIR organized for University students at Agra	2012-17	Will continue in XII <sup>th</sup> plan.	NJIL&OMD, Agra
14	Molecular and ultrastructure characterization in mycobacteria	pH and temperature differences alter the biofilm formation of mycobacteria and water and air channels demonstrated in them ultrastructurally	2012-13	Will be completed in the first year of 12 <sup>th</sup> plan period.	NJIL&OMD, Agra
<b>Clinical Research</b>					
1	Randomised clinical trial to study the efficacy and tolerability of 3- and 4-month regimens containing moxifloxacin in the treatment of patients with sputum smear and culture positive pulmonary TB	Preliminary results suggest that patients treated with the moxifloxacin regimens become sputum culture negative earlier and to a greater extent than those treated with the control regimen. This has important positive implications for the TB control programme.	2012-17	Subject recruitment will continue in the Plan XII period. Results will help to develop an efficacious regimen that can be used for a shorter TB treatment duration .	NIRT, Chennai
2	A randomized controlled clinical trial comparing daily vs. intermittent 6-month short course chemotherapy in patients with HIV and TB	Recruitment of patients to the trial is in progress. This study provides a unique opportunity to compare various aspects of TB outcome in HIV-pulmonary TB such as sputum conversion, immune reconstitution inflammatory syndrome, emergence of acquired rifampicin resistance, radiological improvement and toxicity profile.	2012-16	This study will provide important information to the TB & AIDS control programmes regarding the periodicity (daily or intermittent) of treatment of TB in HIV-infected patients.	NIRT, Chennai

Socio-Behavioural Research					
1	HIV Prevention via mobile phones among male sex workers.	The study is done in phases and has been planned for 2 years. The first phase of the study has been completed. The intervention manual has been developed and will be tested through a RCT. The study is in progress.	2012-14	This study is being done to develop an HIV risk reduction counselling intervention for MSWs mobile phone technology as a medium to promote long term behavioral changes.	NIRT, Chennai
2	A community based approach in designing a model TB sensitization programme for Self Help Groups (SHG's) - A study from Tamil Nadu, Tiruvallur District, Tamil Nadu	The situational analysis, geographical and social mapping is complete. Formative research on acceptability and feasibility of involving SHGs has been done and the TB intervention finalized using a community based approach. The study is in progress.	2012-14	This study will help to develop a test model for TB sensitization programme for SHGs. They are a powerful task force in all states. The study findings would throw light on how SHGs could be effectively involved in the TB programme.	NIRT, Chennai



3	Health seeking behavior and awareness of TB among migrants – Brick kiln workers – A study from Tiruvallur District, Tamil Nadu	The qualitative findings have highlighted the challenges that migrants and health providers face in relation to awareness of TB, care and management of chest symptomatics as well as barriers in TB management.	2009-12 ( study will be completed in 1 <sup>st</sup> year of XII plan period)	This study on migrant brick kiln workers will help to understand the health seeking behavior patterns of chest symptomatics and their awareness of TB. The findings would help evolve strategies to facilitate early diagnosis and treatment for TB among migrants. Will be completed in 1 <sup>st</sup> year of XII plan.	NIRT, Chennai
4	Pharmacokinetics of anti-TB drugs in children	This study is undertaken for the first time in children receiving ATT in the RNTCP. The study findings with respect to children with TB showed that age, nutritional status & isoniazid acetylase status significantly influenced the PK of first line anti-TB drugs. The study has provided some evidence to the programme that the existing doses may have to be increased. While recruitment of children with TB has been completed, that with TB & HIV co-infections is in progress.	2009 - 2013	This study will provide information to the TB control programme on the adequacy of existing drug doses in children with TB and TB/HIV	NIRT, Chennai

Epidemiological/Operational Research					
1	Prevalence of pulmonary tuberculosis and annual risk among the Nicobarese of car Nicobar and control of TB among the tribes	Observations indicate that the prevalence and Annual Risk of Infection has doubled among the Nicobarese in comparison to the mainland India.	2012 -2015	The study carried out among Nicobarese of Car Nicobar in 1986 by the DHS, A&N Administration and National TB Institute, Bangalore had shown prevalence of sputum positive TB of 4.1 per 1000 and the annual risk of TB infection as 1.3%. In spite of intensification of TB Control Programme after 1986, the study undertaken by the Centre in 2001 showed that the prevalence has increased to 7.3 per 1000 and the ARTI to 2.4%. RNTCP was introduced in 2005 and is operational in Car Nicobar for the last 8 years. The impact of RNTCP in controlling the high prevalence risk of TB among the Nicobarese has not been evaluated. The State TB Control Programme Office has also requested RMRC to evaluate the impact of the programme in terms of TB. Therefore, comprehensive studies to assess the current situation among the Nicobarese is warranted. The proposed activity has public health significance in the context of the ongoing TB control programme.	RMRC, Port Blair

2	Operational Research studies to support RNTCP activities	Studies done so far have fetched more than 125 publications; many of these have been translated into policy.	Continuing Operational research is required to support and further strengthen the RNTCP	Several key research issues are being addressed.	NIRT, Chennai
3	Using spoligotyping as a secondary marker for typing of <i>M. tuberculosis</i> from defined populations )	Largest cluster belonged to ST26/CAS1_Del, followed by ST288/CAS2, ST1401/CAS1_del.,ST50/H3 followed by EA strains. ST1/Beijing was detected in about 2% of the strains and this was not associated with MDR profile in patients.	2012-16	To be continued in the XII <sup>th</sup> plan with extramural funding in Bhopal Gas Disaster victims and patients from Sahariya tribe combined with MIRU and other typing methods. Spacer oligonucleotide typing (Spoligotyping) has become a popular molecular method used to differentiate <i>M.tuberculosis</i> complex isolates. This method is based on the analysis of polymorphism in the <i>M.tuberculosis</i> complex direct repeat (DR) chromosomal region consisting of identical 36 bp DRs alternating with 35 to 41 bp unique spacer sequence. In order to determine the usefulness of this technique in strains from our population, we are using this well standardized system from a commercial source to identify the genotypic differences among <i>M. tuberculosis</i> strains from various settings.	NJIL&OMD, Agra

4	Follow up of cases of tuberculosis treated with DOTS and DOTS + MIP immunotherapy at MRHRU, Ghatampur	Ongoing; Training of ASHA and health workers help in better completion of treatment, follow-up of patients and identification of complications in the community. Analysis ongoing of benefits of MIP + DOTS in Cat II patients; blind codes still there for CAT I patients	2012-14	Will continue in XII <sup>th</sup> plan period	NJIL&OMD, Agra
<b>Translational Research</b>					
1	Towards vaccine development:	To develop epitope based recombinant BCG vaccine with powerful immunodominant epitopes, 10 epitopes were selected from well defined antigens and grafted to cpn10 based epitope delivery system are cloned and evaluated for immune response in mice and protective immunity in guineapigs Recombinant BCG based epitope vaccine with immunodominant epitopes elicit TH1 type of immune response and protective immunity in guinea pigs .	2012-15	Since the recombinant BCG constructs and Deleted LPQS clones show promise as vaccine candidates. These two projects would be continued into the XII <sup>th</sup> plan budget .	NIRT, Chennai
<b>Program Support</b>					
1	National reference laboratory for TB	Laboratory support to Intermediate Reference Labs in states and training as per RNTCP requirements	ongoing	Accreditation of more private and Government medical colleges in the region for RNTCP laboratory support. To be continued in next plan period	NJIL&OMD, Agra NIRT, Chennai
2	Mycobacterial repository	Providing well characterized strains to researchers all over the country	ongoing	To continue in XII <sup>th</sup> plan period	NJIL & OMD, Agra

Table 3. New proposed Research activities to be undertaken in 12<sup>th</sup> Plan

Sr. No.	Thematic area and Title of the study	Off-shoot/ De novo/ New study	Justification	Time frame	Deliverables	Institution/ Centre
<b>Basic Research</b>						
1	Pharmacokinetics of rifabutin during lopinavir/ritonavir co-administration	New study	HIV-infected TB patients receiving a ritonavir-based ART regimen. The dose rifabutin is reduced by 50% those receiving concomitant ritonavir. In the absence of PK data to support this reduction, PK studies are required to decide the appropriate dose of rifabutin to be used during concomitant administration of ritonavir.	2013-2014	This study information will be useful to the National AIDS Control programme to decide the dose of rifabutin.	NIRT, Chennai
2	Pharmacokinetics of moxifloxacin in pulmonary TB patients	New study	This study will be complementary to the clinical trial and will help determine optimal dosage of moxifloxacin Indian subjects.	2013 - 2014	This study will help to understand the clinical significance of the PK interaction between moxifloxacin & rifampicin.	NIRT, Chennai
3	Novel subunit vaccine targets for TB	De novo idea	This is nationally relevant since vaccine efficacy of three new antigens will be tested	The project will extend up to Dec 2015 to complete the objectives.	Possible vaccine candidates	NIRT, Chennai

4	Cloning and expression of Rv2675c, Rv1177 and Rv3503c	Off shoot of a completed study on bioinformatics analysis of T-cell proteomics	The antigens will be studied for drug targets	This project will be completed by December 2015.	Possible drug targets	NIRT, Chennai
5	Vitamin D receptor gene polymorphisms and treatment outcome in pulmonary TB	Off shoot	This is an offshoot of our earlier study on HLA and Non-HLA gene polymorphism on HIV and HIV-TB. (ICMR Task Force Project). The study revealed an association of various HLA and non-HLA genes with susceptibility or resistance to HIV and HIV-TB.	2013- 2015	Vitamin D receptor gene variants have been associated with sputum conversion during anti-TB treatment. The study will explore the role of Vitamin D receptor gene polymorphisms (host genetic factors) on anti-TB treatment.	NIRT, Chennai
6	Cytokine gene polymorphisms in HIV-1 infection	Off shoot	The genetic basis of susceptibility to HIV-1 infection will be studied.	2014-16	The study will explore whether cytokine genes are associated with susceptibility or resistance to HIV-1 infection.	NIRT, Chennai

7	Studies on bacteriophage lysis gene: biology and its large scale production	Off-shoot of an earlier program. Bacteriophage genomes have been sequenced and lysis gene identified. The project has the potential for a new breakthrough as it aims at developing a novel, bio-friendly alternative to antibiotics for controlling normal flora while raising liquid cultures from processed sputum samples for rapid detection of MTB.	Nationally relevant as this can be adopted in the program as an alternative to antibiotics in liquid systems used for TB diagnosis such as MGIT, DLRP assay etc	2013-15		NIRT, Chennai
8	Innate Immune responses with neutrophils	Innate immune responses by DC were completed during XI <sup>th</sup> plan period. Innate Immune responses with neutrophils is not complete. It is planned to study functional assays and signalling pathways by infected neutrophils to understand the complete Innate immunity in TB. This will be done in XII <sup>th</sup> plan period.	The outcome may not have direct public impact but will definitely enhance our knowledge in understanding innate immunity against tuberculosis.	2012-2015	This basic study will help to understand important functions of neutrophils, its capability to kill <i>M. tuberculosis</i> and generate proper innate immune responses to protect from TB.	NIRT, Chennai

9	Estimation of prevalence of pulmonary TB and annual risk of infection, control of TB and support to Revised National TB control programme (RNTCP) to act as IRL for RNTCP	Among the Nicobarese, who constitute over 90% of the tribal communities, the TB situation in terms of prevalence and Annual Risk of Infection has doubled in comparison to the mainland India. Therefore, the present study has public health significance.	There is no systematic study conducted to generate information on prevalence of Pulmonary TB. Moreover, the annual risk of infection has not been estimated in other population groups of Andaman & Nicobar Islands. RNTCP was introduced in 2005 and the DOTS Plus strategy in 2012. The Centre provides laboratory support for DOTS Plus to the State TB Control Office under RNTCP Programme. Therefore the study would help to generate such valuable information for the control of TB. This would also serve as base line data for impact assessment of RNTCP in the islands	2014 –2016	ART I and TB prevalence rates among Nicobarese tribe.	RMRC, Port Blair
<b>Clinical Research</b>						
1	Clinical trials for shortening treatment of TB using newer drug molecules.	New	Finding shorter and more patient – friendly regimens for drug sensitive and drug resistant TB is a priority. As and when new drug candidates become available, NIRT will undertake trials to test new regimens.			NIRT, Chennai NJIL&OMD, Agra RMRIs, Patna
2	Phase I and II trials for new TB Vaccines.	New	TB vaccines are critical for control of the disease. NIRT will undertake phase I, II and III trials of new vaccine candidates as they become available. A GSK fusino protein vaccine candidate is available for phase II trial.	2013-15	Efficacy of new vaccine	NIRT, Chennai



3	Randomized clinical trials using newer regimens for treatment and prevention of TB in HIV-infected persons.	Treatment of TB in HIV-infected persons is important to reduce mortality. NIRT will undertake clinical trials of new drug combinations for prevention and treatment of TB in HIV.	New drug molecules like TMC – 207, PA 824 and Delamanid are now available and will be tested in clinical trials.	2012-17	New treatment regimen for HIV/ TB	NIRT, Chennai
4	STREAM Study – Investigating efficacy of new study of Regimens effective against MDR-TB.	De novo	Multi-country trial to test the efficacy of a 9-month regimen for treatment of MDRTB. NIRT will participate in this trial.	2013-15	Shorter treatment regimen for MDR TB	NIRT, Chennai
5	Studies on extra pulmonary TB and smear negative TB comprising diagnosis and management.	Off shoot	Efficacy of shorter TB regimens will be studied in various forms of extrapulmonary TB.	2012-17	Shorter regimen for EPTB	NIRT, Chennai NJIL&OMD, Agra RMRIs, Patna
6	Alternate regimens for HIV-TB and neurocognitive studies	New	Neurocognitive changes in HIV affect quality of life. Studies will be conducted to reduce the occurrence of such complications. For example, dose optimization studies.	2013-14	Safer antiretroviral regimens	NIRT, Chennai

7	Pharmacokinetics of first-line anti-TB drugs in TB patients receiving treatment according to RNTCP guidelines	New study	Data is lacking in Indian TB patients regarding the pharmacokinetics of anti-TB drugs. In order to achieve optimal TB treatment outcomes, it is essential to study whether adequate blood levels are being achieved with the dosages currently used in the RNTCP.	2013 – 2015	This study will help to understand (i) PK & adequacy of drugs in patients treated with CAT I & CAT II regimens, (ii) relationship between drug levels & TB treatment outcomes (iii) influence of factors such as, diabetes, gene polymorphisms, disease severity, age etc on drug levels.	NIRT, Chennai
8	Assessment of the utility of mass vitamin D supplementation to effectively reduce the incidence of TB in vitamin D deficient population.	New study	Incidence of TB in healthy contacts of open cases is very high in those with Vitamin D deficiency. Vitamin D supplementation may therefore prevent TB in healthy contacts of open cases in Vit D deficient population.	2012-17		DMRC, Jodhpur
9	Study of current rate of irregular treatment, defaulters and drop out in the treatment of TB and its causes and remedial steps.	Off shoot study		2012-17		DMRC, Jodhpur

10	<i>Research in HIV-TB co infections: (New) Studies in New diagnostics management and prevention:</i>	Off shoot	Prevalence on MDR / XDR TB among HIV infected individuals in India. Evaluation of newer diagnostics including biomarkers.	2013-16		NIRT, Pune
<b>Socio Behavioral Research</b>						
1	A study on psychosocial issues facing MDR TB and to evolve intervention strategies to promote drug adherence and quality of life.	New	MDR TB poses new challenges for TB control especially with regard to non adherence for TB treatment. The proposed study would explore a feasible and acceptable intervention that would help enhance treatment adherence.	2013-14	Better intervention for patients with MDRTB	NIRT, Chennai
2	Estimation of the TB burden, feasibility and acceptability of suitable interventions to promote TB case finding – A multicentre study among primitive tribal groups.	This study would involve RMRI's of ICMR working with tribals as well as Government, NGOs and medical colleges. The study aims to estimate the prevalence of TB, identify health seeking behavior patterns, barriers to TB care, review the functioning of the RNTCP in these areas and evolve interventions to promote TB case finding.	The findings would help in understanding the prevalence of TB among PTGs as well as provide information on barriers to TB care and evolve effective interventions to promote early diagnosis and treatment of TB	2013-15	Better intervention for TB in Tribal population.	NIRT, Chennai NJIL&OMD, Agra RMRI's, Patna

3	Prevalence of TB and barriers to TB management in prisons	New study	TB transmission in prisons can be problematic. However little is known on the prevalence of TB in prisons, factors that influence TB transmission and interventions that are required for TB diagnosis and management among prisoners. This study aims at finding out TB prevalence in prisons, the barriers for TB management and feasible TB interventions.	2013-15	The findings would provide information on TB transmission dynamics in prisons as well as help evolve effective interventions for TB management and care.	NIRT, Chennai
<b>Epidemiological/Operational Research</b>						
1	Feasibility study looking at isoniazid as preventive therapy for TB in HIV infected individuals		Previous studies have shown the effectiveness of isoniazid preventive therapy. We will now undertake implementation research to study its feasibility and effectiveness in ART centres under program settings	2012-14	If found feasible NACO will scale up this intervention at ART centres across India.	NIRT, Chennai
2	Estimating the burden of TB and co-infections and their impact on endemic communities.	New study	Studies examining the impact of co-infections such as HIV, filariasis on the risk of TB disease progression will be undertaken	2013-15		NIRT, Chennai
3	Prevalence of PTB in selected settings of different parts of India	Disease prevalence surveys are being undertaken every 5 years or so and will continue, in order to determine the burden of TB		2013-14	Prevalence rate of TB established	NIRT, Chennai NJIL&OMD, Agra RMRI, Patna
4	Prevalence of pulmonary TB among tribal population of Chhattisgarh	New study	National Relevance	2014-15	Intervention to reduce TB prevalence in Tribal area.	RMRCT Jabalpur

5	Study of pulmonary TB and its risk factors in Saharia: a primitive tribe in Gwalior district of Madhya Pradesh	Initiated: Oct 2012	No information on tuberculosis situation among Saharia primitive tribe of Gwalior district of Madhya Pradesh, is available and this study has been undertaken to assess the TB situation and risk factors for TB among them.	2013	Intervention to reduce TB prevalence in Tribal area.	RMRCT Jabalpur
6	Drug resistance survey for TB in Saharia tribe of Guna & Gwalior districts	Initiated: Aug 2011	In view of the high prevalence of TB among Saharia tribe, this study is undertaken to assess the drug susceptibility pattern particularly MDR/XDR TB among them.	2013	Intervention to reduce TB prevalence in Tribal area.	RMRCT Jabalpur
7	IEC intervention to improve KAP related to TB and its impact on risk factors and TB disease burden amongst Saharia - a primitive tribe of Madhya Pradesh.	Initiated: Oct 2012	Based on the findings of earlier study conducted among Saharia tribe, this study has been undertaken to design and implement an evidence based IEC programme in this primitive tribal group.	2015	Intervention to reduce TB prevalence in Tribal area.	RMRCT Jabalpur
8	Multi-centric cohort study of recurrence of TB among newly diagnosed sputum positive pulmonary TB patients treated under RNTCP	New study	Though the reported cure rate under RNTCP is high, there is little information on the predictors of poor treatment outcomes and on the proportion of patients who develop recurrent TB. With this in view, it is proposed to conduct a multi-centric study to study the recurrence of TB among newly diagnosed pulmonary TB patients who have successfully completed treatment and to distinguish if this recurrence is due to endogenous reactivation or re-infection and to assess risk factors for unfavourable outcomes to treatment.	2013-2016	Information on risk factors for TB recurrence in India.	RMRCT, Jabalpur NIRT, Chennai & Other Centres

9	Integrated Intensive Tuberculosis Case Finding Strategy (IITCFS) to reach out the vulnerable segment of the tribal population of Madhya Pradesh: An experimental model	New study	The current policy under RNTCP is passive case finding and the programme expects patients to come to the health facilities for diagnosis. However, there is a need to promote intensified case finding strategies for the specific high risk groups who have limited access to health services and / or are less likely to seek care on their own. This study aims at developing integrated intensive case finding (IICF) model to reach out the vulnerable segment of the tribal population of Madhya Pradesh.	2013-15		RMRCT, Jabalpur
10	Epidemiology of TB amongst primitive tribal groups (PTGs) of India	New study	Primitive Tribal Groups constitute the most vulnerable population among various tribal groups. The information on TB situation amongst most of these tribal groups is hardly available. Studies carried out by the centre amongst the primitive tribes of Madhya Pradesh show wide variation in TB situation amongst them. This study aims at assessing the TB situation amongst the primitive tribal groups in the country and their health seeking behaviour especially in light of the ongoing RNTCP in these areas. The findings of the study would enable the Govt. in making necessary modifications in the TB control strategies amongst the PTGs in the country.	2013-16		RMRCT, Jabalpur

Translational Research						
1	Newer TB drug development	Ongoing	Novel antibiotic; preclinical and animal studies are being done. Transitmycin, a novel compound from marine <i>Streptomyces</i> sp. was found to have high activity against TB and HIV. Characterization and structure identification completed. In vivo efficacy studies, production scale up and Preclinical trials required.	2012-16	In vitro animal and human studies with new molecule against TB and HIV	NIRT, Chennai
Programme Support						
1	Experimental animal National Guinea pig facility for intranasal TB infection	National facility with drug testing and vaccine testing animal facility with experiments done for over 30 groups till now	Will continue			NJIL&OMD, Agra

**Table 4. Status of Major Projects Funded by Other Funding Agencies:**

Sr. No.	Thematic Area and Title of the Study	Objectives	Completed/ Ongoing with outcome of the study	Justification for continuation	Time Frame	Institution	Source of Funding
1	Heterogeneity profiling of field strains from Tamilnadu , Kerala & Gujarat .	To understand the genetic variability of field strains of <i>M.tuberculosis</i> in three different regions.	(i) The polymorphism created by different loci and the discriminatory power of MIRU varies among strains of diverse geographical origin. Change in transcription level due to these repeat elements may also play a role in virulence of <i>M.tuberculosis</i> . (ii) The regional differences in distribution of spoligotypes and IS6110 RFLP pattern may be linked to the different ethnic subpopulations in North (Gujarat) versus South (Tamil Nadu and Kerala), and their respective migration histories. Such analysis clearly indicates the prevalence of historical versus recently imported “modern” C lones of TB in regions of India.	Completed	2007-10	NIRT, Chennai	DBT



2	Bioprocessing Lichens for antimycobacterial compounds	To undertake bioprocessing studies of Lichens to check for antimycobacterial activity.	Ongoing	One of the Lichens has antimycobacterial activity. It is further pursued.	2012-15	NIRT, Chennai	DBT
3	Nevirapine versus Efavirenz based highly active antiretroviral therapy regimens in antiretroviral naïve patients with HIV and Tuberculosis infection in India	To compare Nevirapine versus Efavirenz based HAART regimens in HIV TB patients	Ongoing	---	April 2007 to July 2013	NARI, Pune	NACO
4	Trial of once – daily Nevirapine versus Efavirenz – based HAART in HIV Co-infected TB patients	To study safety efficacy of 2 different ART regimens in HIV/TB	Completed		2006-09	NIRT, Chennai	NACO
5	Pharmacokinetics of anti-tuberculosis drugs in children: impact of age, nutritional status and HIV infection.	To study factors affecting blood levels of anti TB drugs in children.	Completed		2009-11	NIRT, Chennai	ICMR Extramural (Task force on Pediatric HIV)
6	Anaemia and nutrition among children with perinatally acquired HIV infection in South India.	To study prevalence and risk factors for anemia in HIV-infected children	Completed		2009-11	NIRT, Chennai	ICMR Extramural (Task force on Pediatric HIV)
7	Genetic basis for HIV-1 transmission, resistance and disease progression: Polymorphism in MHC, chemokine/cytokine and their receptor genes	To study HLA & non HLA polymorphism in HIV dis. prognosis	completed		2007-9	NIRT, Chennai	DBT
8	HIV associated Lipodystrophy Syndrome in Children: Role of nutrition, ART & Genes	To study risk factors for lipodystrophy in HIV + children on HAART	Ongoing	Intake into the study is continuing and following will be for 2 years	2010-13	NIRT, Chennai	NIH (NIAID)

9	Predictors and Immunologic Characterization of Tuberculosis-associated Immune Reconstitution Inflammatory Syndrome in a Prospective Clinical Trial Cohort	To study risk factors for IRIS in HIV/TB patients	Completed		2009-11	NIRT, Chennai	NIH (NIAID)
10	Addressing Psychosocial Needs and HIV Risks in Indian MSM.	To find out psychological issues faced by MSM	Completed		2009-11	NIRT, Chennai	NIH
11	A Randomized Controlled Clinical Trial Comparing Daily vs. Intermittent 6- month Short Course Chemotherapy in Reducing Failures & Emergence of Acquired Rifampicin Resistance (ARR) in Patients with HIV and Pulmonary Tuberculosis.	To compare the efficacy of 3 different anti TB regimens in the treatment of HIV/TB	Ongoing	Intake to the trial is continuing ( 180 of the 440 total sample has been enrolled)	2008-13	NIRT, Chennai	USAID
12	Study to evaluate the effect of Physician's advice in quitting smoking in HIV and TB patients in South India- A pilot study	To compare two different intervention in smoking cessation among TB patients	Completed		2009-11	NIRT, Chennai	US National Health
13	Prevalence of Pulmonary Tuberculosis in Jabalpur district of MP	To estimate the prevalence of bacillary tuberculosis in Jabalpur District of Madhya Pradesh	Completed The results indicate that the TB situation in the study area is not different from other areas of the country.	--	2009-2011	RMRCT, Jabalpur	WHO, with financial assistance from USAID under Model DOTS Project and ICMR

14	Prevalence of Pulmonary Tuberculosis in tribal population of Madhya Pradesh	<p>1. To estimate the prevalence of pulmonary tuberculosis in tribal population of MP</p> <p>2. To estimate the prevalence of tuberculosis infection in tribal population of MP</p>	<p>Completed</p> <p>The findings suggest that the TB situation amongst the tribal population of MP is not that different from the situation among non-tribal population in the country except among Saharia "primitive" tribal community where TB disease remains a major public health problem.</p>	--	2006-2008	RMRCT, Jabalpur	WHO, with financial assistance from USAID under Model DOTS Project
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## EXTRAMURAL RESEARCH

### Achievements

The projects completed during XI<sup>th</sup> plan period have significantly contributed to advancement in TB research in India. Some of the Indo-foreign collaborative projects have resulted in the technology transfer. A wide range of sophisticated techniques and assay systems have been developed. Some of the major achievements are given below:

- Technology transfer : MIRU-VNTR typing, Spoligotyping techniques have been successfully transferred and established in India and have led to the understanding the basic problem of genetic diversity of *M. tuberculosis* in India. MIRU-VNTR typing when combined with other genetic markers has provided useful information about lineage of Indian isolates of *M. Tuberculosis*. This typing system appears to be useful for detecting the source of re-infection in tuberculosis case with & without HIV co-infection. These techniques will now be used in comparing the diversity of North & South Indian isolates specially in relation to understand the impact of TB control programme on transmission.
- PCR-Restriction Analysis (PRA) technique has been developed and is a reliable and simple method for direct identification clinically important mycobacterial to the species level. The technique is highly specific directly from clinical samples.
- A novel set of primers ITS PCR was found to be most sensitive diagnostic tool in comparison to smear, solid & liquid cultures. The ITS primers were further standardized for use with out novel & patented esate-6 PCR primers with highest possible sensitivity & specificity for the diagnosis of pulmonary as well as extra pulmonary tuberculosis.
- Various studies using molecular diagnostic techniques have resulted in generation of the important epidemiological data on the prevalence of *M.TB* in Kashmir valley, Jaipur and Agra.

### Total Publications

- A total of 26 publications have been published and another 13 have been submitted to various peer reviewed journals.

## EXTRAMURAL STUDIES

**Table 1: Status of Completed Extramural Research Studies undertaken during XI Plan**

Sr. No.	Thematic Area and Title of the Study	Objectives	Completed with outcome of the study	If off-shoot, Refer to XII plan study	Institution
<b>Basic Sciences</b>					
1	The stringent response in Mycobacteria: a new target for therapy of tuberculosis	The project aimed to determine complete structure of Rel protein involved in synthesizing ppGpp under dormancy to elicit stringent response in mycobacteria.	The study is completed The discovery of a novel (p)ppGpp synthetase in <i>M. Smegmatis</i> possessing an RNae H domain, brings out a new aspect of stringent response, connecting it to essential metabolic pathways of DNA replication and transcription.	This new link will provide novel target for drug development against tuberculosis.	Indian Institute of Science, Bangalore
2	High resolution Molecular markers as tools for evaluation of Tuberculosis control programs in 2 Indian regions	The study aimed at finding out population based molecular epidemiology of tuberculosis transmission in a South Indian model DOTS area	The study is completed <ul style="list-style-type: none"> <li>• The study resulted in technology transfer of MIRU-VNTR typing, Spoligotyping techniques in India</li> <li>• MIRU-VNTR typing provided useful information about lineage of Indian isolates of <i>M. tuberculosis</i>.</li> <li>• Useful for detecting the source of re-infection in tuberculosis case with &amp; without HIV co-infection.</li> <li>• Can be used in comparing the diversity of North &amp; South Indian isolates specially in relation to understand the impact of TB control programme on transmission.</li> </ul>	This technique is useful for detecting the source of re-infection in tuberculosis case with & without HIV co-infection	NJIL&OMD, Agra
3	Molecular characterization of ethambutol resistant <i>Mycobacterium tuberculosis</i> -implication in molecular diagnosis	The study aimed at isolating the ethambutol resistant <i>M. tuberculosis</i> and perform molecular characterization & study of polymorphism in ethambutol resistant clinical isolates for the genes involved in resistance.	The study is completed <ul style="list-style-type: none"> <li>• Generated the data on mutations in genes involved in resistance to ethambutol in <i>M. tuberculosis</i> clinical isolates of Indian origin.</li> </ul>	Will help in the preparation of the new regime in the anti-tubercular prevention/control and treatment.	Sanjay Gandhi postgraduate Institute of Medical Science, Lucknow

4	<i>Mycobacterium tuberculosis</i> and human dendritic cells: Deciphering molecular interactions of novel cell wall	The study aimed to characterize phenotype of human dendritic cell during maturation in the presence of cell wall associated antigens of <i>M. tuberculosis</i> and to investigate the effect of these antigens on cytokine & chemokine secretion of human dendritic cells	The study is completed The results showed that synergistic stimulation of TLR2 and NOD receptors renders enhanced refractoriness to TGF- $\beta$ - or CTLA-4-mediated impairment of human DC maturation	Can be a useful target for developing the mechanism for containment of mycobacterial infections,	Indian Institute of Science, Bangalore
5	Rapid identification of Mycobacteria to the species level by PCR restriction analysis in clinical samples	<ul style="list-style-type: none"> <li>To use PCR restriction analysis for rapid identification of <i>M. tuberculosis</i> &amp; other Mycobacterial isolates</li> <li>To search for novel restriction enzymes using Bioinformatics to aid in developing an indigenous assay, for rapid identification of <i>M. tuberculosis</i> infection.</li> </ul>	The study is completed PCR-Restriction Analysis (PRA) proved to be a highly specific, reliable, rapid and simple method for direct identification clinically important mycobacterial to the species level directly from clinical samples.	Follow up study will be helpful in validating the usefulness of this technique.	VP Chest Institute University of Delhi
6	Longitudinal Study of TB patients & their healthy PPD positive house hold contacts for determining the immunological signature of the diseased state	The study aimed to determine the immunological parameters to distinguish TB patients from their healthy PPD+ contacts and identify the immunological markers that changes in the TB patient as a result of treatment leading to resolution of the clinical symptoms.	The study is completed The study shows higher CD8 T cells producing IFN $\gamma$ and production of pro inflammatory cytokines IFN $\gamma$ and IL-17 in household contacts of TB patients who are exposed to <i>M. tuberculosis</i> but are disease free, suggesting role of these immune parameter in protection. <i>M. tb</i> antigen increased IFN $\gamma$ and IL-10 production in patients which suggests that ratio of these cytokines could have role in the outcome of infection.	---	NJIL&OMD, Agra

7	Serum Leptin, Nutritional status & inflammatory markers in Chronic Obstructive Pulmonary Disease. Relationship with dyspnea & severity of disease.	The study aimed to study serum leptin, inflammatory markers (CRP and tumor necrosis factor alpha) and nutritional status (biochemically and anthropometrically) in patients with chronic obstructive pulmonary disease (COPD).	The study is completed The study suggested that as the severity of COPD increase the level of inflammatory markers in serum rise and nutritional status deteriorates. This affects the overall health of the individual and systemic inflammation contributes to more extra pulmonary problems. This information may help in the management of COPD patients especially those with malnutrition.	----	AIIMS, New Delhi
8	Molecular identification of potential drug targets in <i>Mycobacterium tuberculosis</i>	The study aimed to understand the role of polyphosphate in mycobacterial physiology, the role of eukaryotic like serine/threonine kinases (STRKs) on cell division of Mycobacteria	The study is completed Two putative peptide operons have been identified in the genome of <i>M. tuberculosis</i> as new drug targets to control infection.	-----	Deptt of Chemistry, Bose Institute, Kolkata
9	Potent role of pro-memory cytokines in the protection & generation & sustenance of memory responses in animals immunized with vaccine prepared from macrophages infected with live <i>M. tuberculosis</i>	The study aimed to understand the role of pro-memory cytokines in the protection of memory responses in <i>M.tb</i> infected vaccine immunized animals.	The study is completed Animals (mince and guinea pigs) vaccinated with vaccine prepared from macrophages infected with live <i>M. tuberculosis</i> (both syngeneic & xenogenic vaccines) showed better T cell memory response. These responses can be enhanced by the use of proinflammatory cytokines while efficacy of the current BCG vaccine can be improved by utilizing pro-memory cytokines	----	Institute of Microbial Technology, Chandigarh

10.	Rapid & accurate diagnosis of tuberculosis using a novel set of primers	The study aimed to use a novel set of primers <i>i.e</i> ITS PCR for diagnosis of pulmonary tuberculosis well as extra pulmonary tuberculosis.	The study is completed The ITS PCR was found to be most sensitive diagnostic tool in comparison to smear, solid & liquid cultures. The ITS primers were standardized for use with out novel & patented esate-6 PCR primers with highest possible sensitivity & specify for the diagnosis of pulmonary as well as EPTB.	---	AIIMS, New Delhi
11	Structure function relationship in a circularly permuted gtpase from <i>M. tuberculosis</i> for the development of novel anti-bacterial drug targets.	The study aims at characterizing the potential of a circularly permuted GTPase from <i>M. tuberculosis</i> as an anti-bacterial drug target using biochemistry, X-ray crystallography, NMR and drug screening.	The study is completed YjeQ protein was recognized as an important drug target due to its role in ribosome biogenesis to find new drug targets for <i>M. tuberculosis</i> to develop newer anti- microbial.	---	IIT, Kanpur
13	Insight into the Pathogenetic Mechanisms in Anti-tubercular Drugs (ATD) Induced Hepatotoxicity	The study aimed to see the mode of action of hepatotoxicity by Isoniazid (INH) with emphasis on cellular oxidative stress and its effect on mitochondrial permeability transition (MPT) in the initiation & progression of liver injury	The study is completed. The study indicated that hydrazine is more toxic than INH & CYP2E1 contributes to AT drug induced hepatic steatosis and injury in murine model & long term treatment of INH-RMP casuses increased hepatic collagenesis.	----	Postgraduate Institute of Medical Education & Research, Chandigarh
14	Biochemical evaluation of iron deprivation in <i>M.tb</i> with specific reference to iron-regulated envelope proteins and to action of anti-Myco bacterial drugs.	The study aimed at cloning & characterization of an iron-regulated envelope protein Irep-28, a major cell wall associated protein expressed upon iron deprivation and assess the effect of iron deprivation on the action of two first line anti-Myco bacterial drugs, namely isonicatonic acid hydrazide (INH) & Pyrazinamide (PZA).	The study is completed The overall achievement in this project was the demonstration of the specific interaction of HupB, an iron-regulated protein with the ferric siderophores mycobactin and carboxymycobactin. This will help to understand what are the genes that are affected by the deletion of hupB gene.	-----	University of Hyderabad



Epidemiological/Operational Studies					
1	Molecular epidemiology of tuberculosis in slum area of Agra	The study aimed to generate epidemiological data by isolation & identification of <i>M.tb</i> strains from cases of pulmonary tuberculosis in slum area of Agra region and their molecular characterization of Isolates by RELP using IS6110 probe, RAPD using 986FP primers and MIRU-VNTR. The study also aimed at determine the primary drug resistance in these cases and to evaluate utility of molecular typing if any in contact tracing specially drug resistance.	The study is completed The results showed the potential of IS6110 based RFLP fro strain characterization of <i>M. tuberculosis</i> in Agra, to understand the molecular epidemiology of tuberculosis in this Agra.	-----	S.N. Medical College, Agra
2	Determination sensitivity profile & molecular typing of Mycobacterium tuberculosis from Kashmir Valley	The study aimed to study the sensitivity pattern of <i>M. tuberculosis</i> in Kashmir Valley and to identify molecular types of <i>M. tuberculosis</i> in Kashmir Valley.	The study is completed This study generated data on molecular epidemiology of m.tb from Kashmir Valley. This information will be useful in monitoring the impact of DOTS in this part of country	----	Sher-i-Kashmir Institute of Medical Sciences, Srinagar

3	Molecular epidemiology of tuberculosis in Slum areas of Jaipur city	The study aimed at isolation & identification of <i>M. Tb</i> strains in pulmonary tb cases from slum areas of Jaipur city and do molecular characterization using molecular techniques and to evaluate utility of MGIT, a rapid automated culture system in enhancing the scope of molecular typing & contact tracing.	The study is completed The results showed that 7.32% of <i>M. TB</i> isolates were multi drug resistant (MDR) 9.4% were poly resistant. The study documented that the RFLP using IS 6110 is most discriminatory and IS 6110 genotype can be compared internationally but is not being applicable for all Indian strains as also observed in 9.8% of study isolates. RAPD is a simple rapid method which takes few hours but is not reproducible and has low discriminatory power		S.M.S Medical College, Jabalpur
4	Genotyping of <i>M. tuberculosis</i> isolates from South Delhi area and determining their Transmission Dynamics in the household contacts and the community using Molecular methods	The study aimed to detect open cases of pulmonary tuberculosis in TB endemic areas of South Delhi and detect latent tuberculosis among close contacts of these open index cases and to <i>Genotype</i> the <i>M.Tb</i> to strain level by using spoligotyping and IS6110 RELP from the culture & trace the routes of transmission of infection from "Index cases" to close contacts.	The study is completed <ul style="list-style-type: none"> <li>• Genotyping of 491 <i>M. tuberculosis</i> strains isolated from 408 index PTB patients &amp; their 83 showed great diversity among <i>M.TB</i> isolates.</li> <li>• Most predominant clades were, CAS with 46.71%, followed by EAI with 12.55%, Beijing with 7.41%, T clade 6.17%.</li> <li>• Predominance of these suggests their comparative high transmission ability &amp; adaptability in Delhi population.</li> </ul>	----	AIIMS, New Delhi

**Table 2: Important and Essential Extramural Activities which need to be continued in XII<sup>th</sup> Plan (ongoing studies)**

Sr. No.	Thematic area and title of the study	Work done in XI <sup>th</sup> Plan/ Justification for continuation	Time frame	Deliverable outcome with public impact	Institution
<b>Basic Research</b>					
1	Study of variability in the degree of systemic inflammation in patients with chronic obstructive pulmonary disease due to tobacco and non tobacco related causes	The study aims to compare the systemic inflammatory response, mutational status, & quality of life between patients with stable COPD due to tobacco & non- tobacco causes and with patients without COPD.	3 Years	The results so far have indicated that presence of COPD is associated with increased systemic inflammatory response, muscle wasting, lower exercise capacity & poorer QOL. The etiological agent of COPD, however does not seem to be an important factor in affecting the affecting the above parameters.	AIIMS, New Delhi
2	Investigative workup of smear negative cases of tuberculosis (tb) in HIV patients and antibiogram of mycobacterial isolates	The study aims to evolve alternate diagnostic methods in the diagnosis of Tuberculosis among HIV patients and the role of faeces culture in HIV patients who present with symptoms of enteropathy. The study also aims to find out the drug resistance of Mycobacterial isolates from HIV +ve patients & compare it with the isolates from HIV-ve patients.	3 Years	The results so far have indicated that culture of specimens for mycobacteria is more sensitive in detecting more TB cases in HIV reactive patients. Antibiotic susceptibility tests showed that HIV does not in any way influence the drug susceptibility pattern.	J.S.S. Medical College And Hospital Shivarathrishwara Nagar
3	Evaluation of the role of supplementation of vitamin d3 chenodeoxycholic acid and retinoic acid on pulmonary tuberculosis in mice model: a step towards host based strategy to combat tuberculosis.	The study aims to evaluate role of supplementation of vitamin d3 chenodeoxycholic acid and retinoic acid on pulmonary tuberculosis in mice model.	3 Years	The results so far have indicated that while developing the animal model of tuberculosis, Swiss albino mice developed visible illness only on 3rd month after inoculation of 0.1X10 <sup>6</sup> of <i>M. tubercle</i> bacilli. The study is ongoing.	Postgraduate Institute of Medical Education and Research, Chandigarh

4	Susceptibility to ocular tuberculosis: tlr-2, tlr-4, il-6, il-10, interferon $\gamma$ and tumour necrosis factor- $\alpha$ polymorphisms and the development of ocular tuberculosis	The study aims to determine the cytokine profile ( <i>i.e.</i> IL-6, IL-10, TNF- $\alpha$ and IFN- $\gamma$ ) in peripheral blood and if possible in vitreous fluid of ocular tuberculosis subjects (antigen induced) polymorphisms of TLR-2, TLR-4, IL-6, IL-10, IFN- $\gamma$ and TNF- $\alpha$ and their relationship with intracellular and extracellular cytokine profile in subjects with ocular tuberculosis and pulmonary tuberculosis.	3 Years	The study is expected to provide information regarding the role of cytokine profile in development of ocular TB in cases of pulmonary TB.	Postgraduate Institute of Medical Education and Research, Chandigarh and S.S.K.M. Hospital, Kolkata
5	Understanding the mechanism of action of histidinol dehydrogenase from <i>M. tuberculosis</i> .	The study aims to clone Histidinol dehydrogenase (HD) gene of <i>M. tuberculosis</i> in various expression vectors such as pDEST15, pDEST17, pPAL7, pMAL <i>etc</i> using recombinant DNA technology and to crystallize & determine the three dimensional structure using X-ray crystallographic technique.	3 Years	With the aim to develop inhibitors against PRPP & PRAC, In silico compound screening approach will be followed. The lead compound identified from this approach, will be purchased (ZINC contains purchasing information of the compounds in the library) from the relevant companies. Attempts will be made to determine enzyme/ inhibitor complex structure; will provide a platform for structure based inhibitor enhancement.	National Institute of Immunology New Delhi
6	Role of Ispa gene in the biology and pathogenesis of <i>M. tuberculosis</i>	<ul style="list-style-type: none"> <li>To explore the possible cholesterol binding activity of the purified recombinant Mce (Mce1A and Mce4A) proteins of <i>Mycobacterium tuberculosis</i>.</li> <li>To investigate uptake and utilization of cholesterol during phagosome- lysosome fusion within <i>M. tuberculosis</i> internalized macrophages.</li> <li>To explore the regulatory role of Mce1A and Mce4A proteins on the activity of intracellular calcium level inside the macrophages engulfing <i>Mycobacterium tuberculosis</i>.</li> </ul>	3 Years		Vallabhbai Patel Chest Institute University of Delhi, Delhi

7	Cloning, expression, purification and evaluation of recombinant antigens for the diagnosis, prognosis and prediction of mdr/xdr tuberculosis	The study aims to clone the genes (Rv 1827, 2145c, 2714, 2970, 1437) into a suitable expression vector, express & purify the recombinant protein expressed in E. Coli and develop immunoassays using the above novel proteins for diagnosing & predicting MDR/XDR TB, using serum samples.	3 Years	The investigators analyzed the target proteins & found their impressive antigenicity & their value in developing a novel immunodiagnostic method for detecting MDR/XDR TB directly from infected patient samples. Hence, the effective method of diagnosis can be developed with the differentially expressed antigens of sensitive & MDR TB strains. These can be exploited to develop immunoassays & other rapid test methods in diagnosing MDR cases.	AIIMS, New Delhi
8	Cloning, expression and analysis (lip j, lip k and lip s) of <i>M. tuberculosis</i> H37Rv	The study aims at cloning and expression of Lip J, Lip K and Lip S genes and to study its possible role in virulence of <i>Mycobacterium tuberculosis</i> H37Rv.		The study is expected to chemically characterize the two lipases and provide information pertaining to its possible role in virulence of <i>Mycobacterium tuberculosis</i> H37Rv.	Panjab University Chandigarh
9	Impact of foxp3+ treg cells on the host immune response among HIV-TB co-infected patients: relevance in multi-drug resistant tuberculosis (MDR-TB)	The study aims to investigate the frequency and functional dynamics of CD4+ CD25+ FoxP3+ Regulatory T cells (T <sub>reg</sub> ) among MDR-TB patients. And to define the pattern of drug resistance to <i>M. tuberculosis</i> among MDR-TB patients co-infected with HIV and its relationship with magnitude of HIV induced suppression of immunity.		The study is expected to provide information regarding the role of T-regulatory cells on the host immune system in MDR TB patients	AIIMS, New Delhi
10	Exploring global mechanisms regulating autophagy and their role in intracellular survival of <i>M. tuberculosis</i>	The study aims to characterize the autophagy process in H37Rv & H37Ra infected Thp-1 macrophage cells, study the effect of host dependency factors for intracellular <i>M. tuberculosis</i> survival (identified through our previous work) on autophagy in the H37Rv infected & uninfected Thp-1 cells.		The work proposed here would not only identify novel targets for therapeutic intervention of tuberculosis, it will also lead to a high-resolution understanding of key physiological processes of autophagy.	International Centre for Genetic Engineering and Biotechnology New Delhi

11	Whole proteome analysis of aminoglycoside resistant isolates of <i>M. tuberculosis</i>	The study aims at selection of aminoglycoside resistant <i>Mycobacterium tuberculosis</i> clinical isolates, proteomic analysis of the isolates by two-dimensional gel electrophoresis and Identification of differentially expressed proteins by MALDI mass spectrometry and characterization of selected proteins.		The interim results indicated the successful isolation of the membrane protein.	NJIL&OMD, Agra
12	Functional analysis of mce4a and mce1a proteins of mycobacterium tuberculosis: role of cholesterol transport and phago-lysosome fusion inside macrophages	The study aims at to explore the role played by Mce4A in the regulation of host cholesterol in context of phagolysosome fusion, the intracellular calcium channel and survival of <i>Mycobacterium tuberculosis</i> within the phagosome.		Calcium, one of the important signal molecules required in various cell signaling processes, also plays an important role in phagosome-lysosome fusion. An increased cytosolic calcium level is an important factor for phagosome maturation which leads to phagosome lysosome fusion. <i>M.tb</i> blocks calcium ion signaling for phagosome maturation in human macrophages via specific inhibition of sphingosine kinase. With confirmation of cholesterol utilization in presence of Mce4A, we further look into its effect on the phagolysosome fusion involving changes in intracellular calcium levels.	Vallabhbhai Patel Chest Institute University of Delhi, New Delhi
13	Sp110 gene variants in defining susceptibility to tuberculosis in north India	The study aims to study analysis of single nucleotide polymorphism (SNPs) in SP110 gene in healthy North Indian population.		Plan to examine the Single Nucleotide Polymorphism (SNP) in tuberculosis patients (both pulmonary & extra-pulmonary TB) as compared to healthy controls pertaining to genetic variations of SP110 gene. The different clinical presentation of tuberculosis such as pulmonary & extra pulmonary TB in the context of SP110 gene has not been explored in any association study so far.	Vallabhbhai Patel Chest Institute University of Delhi, Delhi

14	Impact of HLA-G on host immune response in human tuberculosis	<ul style="list-style-type: none"> <li>To define the levels of HLA-G both on T cell surface &amp; soluble forms various forms of human tuberculosis.</li> <li>To evaluate the role of interaction between HLA-G &amp; its receptors in determining host T cell response among various forms of tuberculosis.</li> </ul>		The study is expected to determine the host factors responsible for the different forms of TB.	AIIMS, New Delhi
15	Study of antimicrobial effect of Havan and its chemical characterization	<ul style="list-style-type: none"> <li>To study the in-vitro antibacterial effect of smoke emanating during the process of Havan on bacteria pathogenic to man</li> <li>To chemically characterize and undertake quality evaluation of the smoke emanating during the process of Havan</li> </ul>		The study is expected to scientifically validate the Indian ancient therapies.	J.N. Medical College, Ajmer & Sri Ram Centre, Delhi
<b>Epidemiological/Operational Research</b>					
1	Molecular analysis of MDR and XDR strains of <i>M. tuberculosis</i> isolated from a tertiary care hospital.	The study aims to assess genetic polymorphism of the resistant isolates by Restriction Fragment Length Polymorphism (RFLP) using IS6110 probe & Spoligotyping., identify the region within the genome of drug resistant isolates as gene(s) responsible for resistance to isoniazid & rifampicin and multi drug resistance if any.	3 Yrs	The study is expected to provide information regarding the MDR and XDR <i>M. Tb</i> strains diagnosed using the RFP technique and identify the genome of the drug resistant isolates and the role of <i>gyrA</i> gene in quinolone resistance.	LRS Institute of TB And Respiratory Diseases, New Delhi
2	Drug resistance profiling and molecular typing of <i>M. tuberculosis</i> isolates from different community settings in north Delhi	<ul style="list-style-type: none"> <li>To study the prevalence of drug resistance, multidrug resistant and extensively drug resistant <i>M. tuberculosis</i> isolates from 500 patients in North Delhi being treated a) in the private setting, b) through a DOTS centre and c) in the non-DOTS government centre, in a follow up study</li> <li>Genotypic characterization of the isolates obtained from the three groups of patients under study by MIRU typing Spoligotyping and IS6100 RFLP.</li> </ul>	3 yrs		Vallabhbai Patel Chest Institute, University of Delhi, Delhi

3	Molecular epidemiology and genetic characterization of <i>M. tuberculosis</i> from HIV seronegative and HIV seropositive patients	<ul style="list-style-type: none"> <li>• To determine prevalent/predominant genotypes of <i>M. tuberculosis</i> in HIV positive &amp; negative patients attending tertiary care hospital using Spoligotyping.</li> <li>• To determine prevalent/predominant genotypes of <i>M. tuberculosis</i> in HIV positive &amp; negative patients attending tertiary care hospital using MIRU-VNTR technique</li> <li>• To do RFLP analysis of the strains, which will not be resolved by MIRU-VNTR and Spoligotyping, using IS 6110 as probe as this is one of the most widely applied and standardized molecular typing method</li> </ul>		The study will help in establishing the utility of molecular tools to determine the predominant MTB genotype in HIV positive & negative patients	LRS Institute of Tuberculosis and Respiratory Diseases, Delhi
4	Study on drug resistance among sputum positive tuberculosis patients in rayagada district Orissa		2 yrs		Regional Medical Research Centre, Bhubaneswar
<b>Translational Research</b>					
1	To compare the efficacy of yoga and pulmonary rehabilitation on dyspnea, muscle strength, inflammatory markers and quality of life in patients with chronic obstructive pulmonary disease		4 yrs		AIIMS, New Delhi



2	To study the effects of physiotherapy in preventing & reducing the chest infections and other related chest diseases in tea garden workers of west 305engal	The study aims to see the effect of the physiotherapy in preventing the chest infections and other chest diseases.	3 yrs	The study has so far shown that the regular physiotherapy is useful in preventing the chest diseases and infections.	AIIMS, New Delhi
3	Study of drug resistance in pulmonary tuberculosis cases with and without HIV co-infection in udipi district, coastal karnataka	The study is planned to study the drug resistance in MTB and TB-HIV co-infection in Udupi district, Karnataka and also to see the clinical outcome of these managed cases.	2 yrs	This information will have public health importance for improved management of pulmonary tuberculosis cases in this area.	Kasturba Medical College And Hospital Manipal University Manipal
4	Therapeutic efficacy of moxifloxacin and econazole based drug regimen against MDR-tuberculosis	The study aims at evaluation of chemotherapeutic efficacy of PLG-NPs encapsulated with moxifloxacin and econazole, alone or in combination, in mice infected with sensitive and drug resistant strains of <i>M. tuberculosis</i> H37Rv.	2 yrs	It is hypothesized that combination of PLG-nanoparticle encapsulated moxifloxacin and econazole will serve as a new drug regimen to combat drug resistant tuberculosis.	NJIL&OMD, Agra
5	Vestibulotoxicity of amino- glycosides in antitubercular treatment: defining prevention policy	The study aims to aim to determine the incidence & establish the clinical and laboratory determinants of 'manifest' and 'occult' vestibulotoxicity in patients undergoing STM therapy.	3 yrs	This study would be first of its kind and is specially relevant in Indian context where the maximum global burden of TB exists and the increasing resistance to ATT is due to non-compliance arising from is toxicity.	Chhatrapati Shahuji Maharaj Medical University Lucknow

**Table 3. New proposed extramural Research activities to be undertaken in XII<sup>th</sup> Plan**

Sr. No.	Thematic area and Title of the study	Off-shoot/ De novo/New study	Justification	Time frame	Deliverables	Institution/ Centre
<b>Basic Research</b>						
1	Evaluation of various clinical, pharmacological, and immunological factors as risk factors for treatment failure and relapse in patients with pulmonary tuberculosis on category II (re-treatment) regimen	New study	The study aims to estimate the serum levels of first-line anti-tuberculosis drugs in patients on category II (retreatment) regimen and to compare the drug levels between patients labeled as cured with those who were not cured at the completion of ATT regimen The results of this analysis may have important implications for future management strategy formulation.	2013-2014	The information from the study may demonstrate if failure rates are higher in any one of the two categories due to above factors. The results of this analysis may have important implications for future management strategy formulation.	AIIMS, New Delhi
<b>Clinical Research</b>						
1	Role of Gene-Xpert MTB/RIF assay in the diagnosis of intra-thoracic tuberculosis in children	New study	In the present study on role of Genexpert/MTBRIF will be evaluated for its sensitivity and specificity in diagnosing pulmonary tuberculosis among the pediatric population taking MGIT-960 culture results as the gold standard.	2013-2014	The study will provide sensitivity and specificity of geneXpert/MTBRIF for gastric aspirates and induced sputum on intra-thoracic TB in children. Gastric aspirates and induced sputum will be collected on ambulatory basis. The results will provide data to improve diagnosis of TB in children. In long term it will reduce over diagnosis and inappropriate treatment with ATT in childhood.	AIIMS, New Delhi

Epidemiological/Operational Research						
1	Performance of light emitting microscope in different settings: a multi centric study	New study	The study aims to evaluate the performance of Primo Star iLED microscope in different settings for TB diagnosis	2013-2014	The study will provide information on the whether LED microscope can be used in different settings.	NIRT, Chennai
2	Hospital based studies on emerging drug resistant TB in Kolkata and the surrounding endemic area	New study	The study aims to identify drug-resistant (MDR or XDR) TB in patients reporting to the clinics of Bengal Tuberculosis Association (BTA) and referred to BTA by the medical institutions / practitioners from Kolkata and the surrounding endemic areas.	2013-2014	Findings of the proposed study will provide data on TB incidence and drug resistance pattern in this endemic area for dissemination to RNTCP.	Bengal Tuberculosis Association, Kolkata
3	Identification & evaluation of <i>M. tuberculosis</i> antigen as Biomarkers in Clinical samples from Pulmonary and extra Pulmonary Tuberculosis patients	New study	In the present study on role of Genexpert/MTBRIF will be evaluated for its sensitivity and specificity in diagnosing pulmonary tuberculosis among the pediatric population taking MGIT-960 culture results as the gold standard.	2013-2014	The results will provide data to improve diagnosis of TB in children. In long term it will reduce over diagnosis and inappropriate treatment with ATT in childhood.	AIIMS, New Delhi
Operational Research /Program Support						
1	Study of rapid culture and direct drug sensitivity testing of <i>M. tuberculosis</i> to isoniazid and rifampicin using liquid culture media	New study	Study is planned to standardize and evaluate rapid method for culture and direct drug sensitivity testing of <i>M. tuberculosis</i> to isoniazid and rifampicin and to support RNTCP.	2013-2014	The technique using sheep blood supplementation, liquid culture media could also be used by us for direct drug sensitivity testing of Mtb from a small number of sputum samples in seven days.	Desert Medicine Research Centre, Jodhpur



