Dedicated to Tuberculosis Research
1956-2010

NIRT

National Institute for Research in Tuberculosis

TRC

Tuberculosis Research Centre

TCC

Tuberculosis Chemotherapy Centre

TRC FOUNDATION DAY
1st August, 2011
&
ICMR CENTENARY CELEBRATIONS
1911-2011

DEDICATED TO TUBERCULOSIS RESEARCH (1956-2010)

CONTENTS

सत्यमेव जयते

कार्यालय सचिव, भारत सरकार
स्वास्थ्य अनुसंधान विभाग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय एवं
महानिदेशक, आई सी एम आर
Office of the Secretary to the Government of India
Department of Health Research
Ministry of Health & Family Welfare &
Director-General, ICMR

भारतीय आयुर्विज्ञान अनुसंधान परिषद
स्वास्थ्य अनुसंधान विभाग
(स्वास्थ्य एवं परिवार कल्याण मंत्रालय)
वी. रामलिंगस्वामी भवन, अंसारी नगर
नई दिल्ली - 110 029 (भारत)
Indian Council of Medical Research
Department of Health Research
(Ministry of Health & Family Welfare)
V. Ramalingaswami Bhawan, Ansari Nagar
New Delhi - 110 029 (INDIA)

Message

It is my privilege to greet entire staff of Tuberculosis Research Centre (TRC). The TRC is our flagship institute for research in TB. During its over 50 years of existence, the Institute has progressed very well and is globally recognized for its pioneering research in the chemotherapy, epidemiology and laboratory aspects of TB. It is a WHO collaborating Centre for Tuberculosis Research and Training and also serves as a reference laboratory for mycobacteriology for South-East Asia. The TRC was selected as an International Center for Excellence in Research (ICER) by the NIH in 2002. The focus of the ICER grant is on expanding facilities for tuberculosis, filariasis and HIV/AIDS research. It is a supranational as well as one of four National Reference Laboratories for tuberculosis in the country. TRC has made important research contributions that form the basis for TB control programme in this country as well as over the world. TRC is currently the world's largest single centre for integrated tuberculosis research. The Centre is playing a pivotal role in promoting the basic principles of the DOTS strategy and demonstrating its epidemiological impact for the first time in the country. The TRC has used scientifically sound methodology to compute the burden of tuberculosis in the country. These realistic estimates will be very helpful to policy makers, planners and programme managers. The Centre has also established the standards for quality assurance and monitoring of the TB programme in the country,

The future is still wide open and there is considerable scope for diversifying the research activities of the Centre in the field of TB. It has slowly made forays into the area of HIV-TB research and is emerging as a leading player in that field also. The Centre also boasts of a world-class state-of-the-art HIV Vaccine Trial Unit that will harness the rich experience of the TRC in the area of controlled clinical trials, both in the clinic and in the field. The fight against TB continues relentlessly and the last word has not been said so far. We are confident that the Institute will maintain its leadership role.

I would like to express our gratitude to TRC's former Directors, Dr. N. K. Menon, Dr. S. P. Tripathy, Dr. R. Prabhakar, Dr. P. R. Narayanan and Director-in-Charges Dr. C.N. Paramasivam, Dr. V. Kumaraswami, who had the foresight and vision to put the TRC on solid foundations, and to the current Director-in-Charge, Dr. Aleyamma Thomas who is continuing to provide excellent leadership in keeping the Centre in the forefront of TB research. I offer all the staff of TRC, both former and present, my best wishes for the TRC Foundation day and Centenary celebrations.

(V. M. Katoch)

Tele. : (Off.) 26588204, 26589620; Fax : 91-11-26588662, E-mail : dg@icmr.org.in; secydhr@icmr.org.in

PREFACE

Little did anybody realize that the recommendation of the British Medical Research Council in 1956 to set up a Tuberculosis Chemotherapy Centre as a five-year project would lead to the establishment of a centre that would one day blossom into a premier institute for research in Tuberculosis (TB). In keeping with the mission of conducting scientific research and applying science for the benefit of the community, TRC has made significant contributions in clinical, operational, applied and basic research. During the first two decades, the centre focused all its attention on chemotherapy of TB and mycobacteriology that resulted in extraordinary results that helped to evolve the principles of chemotherapy of TB. In the third decade, results of the largest BCG trial conducted by TRC helped the Governemnt of India shaping its policy on BCG vaccination in the country. The attention of TRC in the fourth decade was on establishing the ground rules for management of extrapulmonary TB. In the fifth decade, TRC joined hands with Central TB Division of Ministry of Health, Govt. of India, in strengthening the Revised National TB Control Programme (RNTCP) in the country. In the last few years, TRC strengthened the infrastructure for basic research, initiated HIV-TB related studies, established HIV vaccine trial centre and NIH centre for excellence in research. Placed against the backdrop of the national and global TB control programme, it is heartening to look back and feel proud that TRC has always addressed issues in research that has direct implication in benefiting the TB patients in the community. This monograph presents the account of the hard work and untiring efforts of all the scientific, technical and administrative staff of the centre during the last 55 years. TRC will continue its journey in its fight against TB, maintaining the momentum of research and preserving the quality of scientific work. TRC will remain ICMR's flagship institute for TB research.

Dr. Aleyamma Thomas
Scientist 'G' & Director-in-Charge

DIRECTORS

Dr. Menon
(1964-69)

Dr SP Tripathy
(1969-83)

Dr R. Prabhakar
(1983-95)

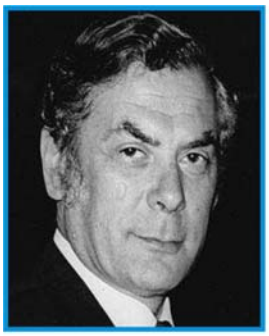
Dr CN Paramasivan
Officer-in-Charge - 1995-96

Dr PR Narayanan
(1996-2008)

Dr V Kumaraswami
Director-in-Charge - 2008-10

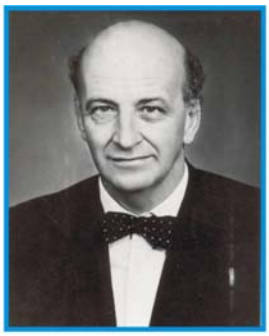
Dr Aleyamma Thomas
Director-in-Charge 2010

TRC is indebted to their significant contributions …



Dr Wallace Fox

Dr DA Mitchison



Dr Hugh Stott

Dr C.V. Ramakrishnan

Dr. S. Velu

Dr.S.Devadatta

Dr.SR Kamath

Dr PRJ Gangadharam

Dr S. Radhakrishna

Mr.PR Somasundaram

Dr R. Parthasarathy

Dr T Santha Devi

Dr G Raghupati Sarma

Ms J Monga

Ms. Williams

MAJOR ACHIEVEMENTS OF TRC

- Conducted more than 50 randomized control clinical trials in tuberculosis, extra-pulmonary TB, HIV and HIV-TB
- Revolutionized the treatment of TB chemotherapy by establishing the value of domiciliary treatment of TB
- Provided the evidence base for the globally used DOTS strategy by demonstrating the role of supervision and documentation in TB treatment.
- Demonstrated the utility of short course chemotherapy for extra-pulmonary TB
- Conducted the largest BCG vaccine trial ever (Chengleput trial).
- Demonstrated the epidemiological impact of the DOTS strategy in a community setting.
- Provided the nation the first reliable estimate of the burden of TB
- Trained over 5000 RNTCP personnel during the last decade
- Completed two Phase I HIV preventive vaccine trials recruiting a total of 48 HIV-negative healthy volunteers of which 22 were women
- Addressed a number of operational research issues that were of relevance for the RNTCP
- Published about 1100 research articles in the field of TB, HIV, Leprosy and Filariasis.

HISTORY OF TRC

Prepared by
Dr. S Radhakrishna
Former Director, Institute of Research in Medical Statistics (ICMR)

In 1950s, India's TB disease burden was 2½ million active cases of which 1½ million were infectious. The accepted method of treatment was isolation in sanatorium, but only 23,000 sanatorium beds were available for the entire country, and resources for the TB control programme were scanty. In this scenario, treatment at home with effective anti-TB drugs was an attractive proposition. However, the Government of India was worried that inadequate therapy might result in large numbers of chronic excretory of drug-resistant bacilli, engendering a serious public health risk. It therefore sought advice and assistance from the World Health Organization (WHO), which sponsored a visit to India of three representatives of the British Medical Research Council (BMRC), Drs. P.D'Arcy Hart, J.G.Scadding and Wallace Fox, in October 1955. The trio had several discussions with Indian authorities, attended a meeting of the Tuberculosis Sub-Committee of the Indian Council of Medical research (ICMR), and visited numerous venues in India. It was thereafter decided that, in the existing state of knowledge, it was premature to initiate immediately a mass domiciliary treatment programme and that controlled comparative trials needed to be undertaken in patients and their contacts. Madras City was chosen for the purpose as the local authorities were proactive, and English was widely spoken in the City. A Research project named Tuberculosis Chemotherapy Centre commenced activity in May 1956, with Dr. Wallace Fox (MRC Tuberculosis Research Unit, London) as the WHO Senior Medical Officer-in-charge until January 1961. Its initial mandate was for 5 years, and the first randomized control trial, often referred to as the Madras Classic, was a comparison of domiciliary chemotherapy with treatment in sanatorium, and commenced in September 1956, with a wide array of objectives, namely:

1. Determination of the success rate of home/sanatorium treatment with a daily regimen of isoniazid plus PAS for one year, and the relapse rate over 4 years.
2. Measuring the extent to which the infectivity of patients treated at home can be reduced by standard daily chemotherapy.
3. Estimation of the prevalence of TB in close family contacts, and the incidence of tuberculous disease over a 5-year period thereafter, with special reference to the drug sensitivity of the strains.
4. Determining the identity and virulence of the causative organisms, and comparing with strains of tubercle bacilli from England.
5. Evolving practical procedures in the mass application of chemotherapy, for sputum collection for monitoring drug compliance.
6. Evaluating the impact of traditional factors such as a well-balanced diet, plenty of rest and airy, well-ventilated accommodation on treatment outcome.

At the invitation of the ICMR and the WHO, the BMRC undertook scientific responsibility for the trial, and the WHO provided eight international staff and equipment and supplies (jeeps, ambulances, anti TB drugs).The local State Government provided the premises for the clinic and the laboratory and 100 beds in Government Tuberculosis Sanatorium, and shared the expenses with the ICMR. A Project Advisory Committee, comprising representatives from the four collaborating agencies (WHO, ICMR, BMRC, Madras State Government) and the WHO Senior Medical Officer, met at periodic intervals to guide the research activities.

To ensure universal acceptance of the findings of the Madras clinical trials, great efforts were made to preserve high quality in all aspects. Thus, detailed study protocols and procedures were drawn up with advice from Dr.I.Sutherland (MRC Statistical Research Unit, London). As bacteriology constituted a key index of progress, a first-rate laboratory was set up by Prof.D.A.Mitchison (MRC Group for Research in Drug Sensitivity in Tuberculosis, London), with assistance from WHO technician, Ms.E.Holst. X-rays were initially taken at the neighbouring State TB Institute, until an in-house x-ray unit was set up by WHO x-ray technician Mr.E.Borg. The clinical assessment of patients was undertaken by Dr.Wallace Fox and Dr.R.H.Andrews, besides two national doctors. Efficient appointment and reminder systems and an effective domiciliary visiting service were put in place by two WHO

public health nurses. Ms.C.M.Lomasney and Ms.A.M.Gerhardson, and the overall administration and liaison activities of the Centre were looked after by a WHO Administrative Officer, Mrs.K.Daniels.

The results of the first trial demonstrated that domiciliary chemotherapy was by no means inferior to institutional treatment in terms of therapeutic efficacy during drug intake, relapse during a 4-year follow-up period, and incidence of TB over 5 years in close family tuberculosis. These startling findings peremptorily dismissed several time-honoured beliefs, and laid the foundation for India's policy of mass domiciliary chemotherapy. Next, as many medical authorities had recommended monotherapy with isoniazid for developing countries and as this was being widely practised in the country in any case, the second randomized trial compared three regimens of isoniazid alone with a control regimen of isoniazid plus PAS. This study established substantial superiority of combined chemotherapy, but suggested that isoniazid in a single dose was more effective than in two divided doses. (The latter finding led to the evolution of a *fully supervised* twice-weekly regimen of high-dosage isoniazid plus streptomycin, the precursor of WHO's current Global DOTS strategy). However, despite these major achievements and against all expectations of a proclamation of an extended mandate for the Centre, newspaper headlines flashed on one dark morning in 1962 announcing the imminent closure of the TRC. It required trenchant editorials in the local newspapers such as The Hindu and The Mail, and an intervention at the level of the Prime Minister, Mr.Jawaharlal Nehru, by no less a person than Dr.P.V.Benjamin, the Government of India's TB advisor, to stay this closure.

Subsequently, in 1964, the Centre was made a permanent establishment under the ICMR. Thereafter, in conformity with the general policy of the WHO regarding the provision of technical expertise, WHO staff members were gradually withdrawn as and when national counterparts were identified and trained. The last WHO Medical Officer and the last WHO bacteriologist left the Centre towards the end of 1965. In April 1966, the staff members initially recruited by the Madras State Government were absorbed by the ICMR, and the last WHO Senior Medical Officer (Dr. Hugh Stott) was withdrawn in July 1966, whereupon the scientific direction of the research became entirely a national responsibility. WHO, however, continued its

active interest in the Centre's research activities, and arranged for consultants and supplies that were not readily available within the country.

Thereafter, randomized control trials of once-weekly regimens following an initial phase of chemotherapy of 4 weeks, and short-course chemotherapy regimens of 6 months duration with powerful anti-TB drugs were also undertaken at the TRC, as also numerous trials of maintenance chemotherapy in patients with initially successful outcomes and in treatment failures of primary chemotherapy. Although the main aim of all these trials was to evolve effective, nontoxic, inexpensive and acceptable modalities of treatment, the logical sequence of investigations, together with supportive high-class laboratory investigations, resulted in invaluable knowledge of the principles of chemotherapy and the bacteriology of TB.

In collaboration with the State Tuberculosis Institute, the methodology of randomized trials was employed to evolve successful methods for obtaining home addresses from illiterate patients and for retrieving patients who defaulted on their clinic attendance, both of which are critical for successful case-holding. Finally, in collaboration with medical college hospitals and nonprofit organizations in the city, randomized control trials in patients with spinal tuberculosis, TB meningitis and TB lymphadenitis were successfully undertaken.

An Ethical Committee was constituted in July 1976, to meet increasing concern over the ethical aspects of clinical trials in human beings. Clearance by this Committee was made mandatory for all new trials. Donation of one hectare of vacant land by the Madras State Government in 1978 and simultaneous release of funds by the ICMR led to the construction of a new 4-storeyed building for the Centre, which was then renamed as TUBERCULOSIS RESEARCH CENTRE (TRC). Soon after, two other temporary ICMR Projects, 'Tuberculosis Prevention Trial' and 'Leprosy Prevention Trial', were merged with the TRC, and labeled as the 'Epidemiology unit'. In 1981, the Centre celebrated its Silver Jubilee in a befitting manner with an International Symposium on 'Chemotherapy and Management of Tuberculosis', and a cultural programme, the highlight of which was a scintillating dance recital by the noted danseuse, Smt. Chitra Visweswaran.

In December 1981, a sophisticated pulmonary function laboratory was inaugurated. In order to increase intake to its clinical trials, the TRC opened up several peripheral clinics in Madras City, and one at the Lady Wellington Hospital, Bangalore, that was subsequently shifted to the Government Rajaji Hospital, Madurai.

One of the oft-repeated criticisms of the TRC was that its studies were all conducted in 'near-experimental' settings, divorced from the existing stark realities in the country. To address this issue, the TRC decided in 1983 to pilot-test various short-course chemotherapy regimens under Programme conditions In 18 districts of the country, as a precursor to the introduction of short-course chemotherapy on a national scale. This monitoring experience, coupled with the role played by TRC staff in the Comprehensive Programme Review in 1992, assisted in the formulation of the Revised National Tuberculosis Control Programme (RNTCP). Finally, in 2006, an air-conditioned state-of-the-art patient care facility was inaugurated.

In May 1999, a DOTS demonstration centre was set up in a population of about 580,000 in Tiruvallur district, in collaboration with the State Government and with assistance from USAID and the WHO. The objective was to conduct operational research on key aspects of the DOTS for mid-course corrections and to undertake epidemiological surveys to establish the potential impact of DOTS on TB burden in the community. Periodic prevalence surveys and ARTI surveys in this area over a 71/2-year period have demonstrated a substantial epidemiological impact of the DOTS programme on the disease burden in this community.

There have been a number of other significant developments in associated areas. Thus, in 2000, a separate HIV/AIDS division was established at the main premises of TRC in Chennai for conducting clinical trials in HIV/AIDS patients. Under the aegis of a memorandum of understanding (MoU) between the National AIDS Control Organization, the International AIDS Vaccine Initiative and the ICMR, a Phase I preventive AIDS vaccine trial was initiated thereafter. A Vaccine trial Centre, established at the TRC, comprises a clinical facility, a data management unit and a state-of-the-art HIV immunology, virology and routine medical laboratory.

The year 2003 marked another milestone in the history of the TRC. A MoU was signed by the ICMR with the National Institutes of Health (NIH), USA for setting up an International Centre for Excellence in Research (ICER) at the TRC. The goal of the ICER program is to develop a sustained research program in areas of high infectious disease burden through partnerships with scientists and physicians in developing countries in three countries, Mali, Uganda, and India. The stated goal of the ICER program was to partner with in-country scientists to address major endemic diseases and foster research in areas such as malaria, HIV, filarial infections and tuberculosis. The hope was to build sustainable research programs by providing a long-term commitment, thus allowing difficult research challenges to be addressed, and, importantly, to train local scientists so that they are prepared to tackle emerging and re-emerging infectious diseases into the future. During the initial five year period of the ICER (2003-2008), apart from renovating and equipping a 4000sq ft laboratory building, a modern IT backbone was established that enabled a secure computer network with both high speed connections to the NIH's online resources and software for clinical and basic laboratory research. Videoconferencing facility was put into place that not only enabled sharing of research presentations and regular dialogue among the scientific staff in India and at the NIH, but also has been used for interactive training. Furthermore, redundant systems (from air handling to backup generators) and preventative maintenance for equipment and the infrastructure built as part of the overarching ICER approach. A senior scientist is detailed to the site to oversee the laboratory operations related to the ICER program and to act an on-the-ground liaison between the NIAID and the TRC.

Because training was always an integral part of the ICER concept, there were a large number of on-the-ground training forums as well as short term training opportunities for collaborating members of the TRC staff. In Chennai, training sessions were based on the perceived needs of the TRC staff and included courses in GCP and GLP, biostatistics, biosafety, good accounting practices, clinical trials design, antiretroviral therapy, and HIV care among others. Three to six month laboratory based collaborative research was undertaken by a number of staff and students at the TRC that included work on multicolor flow cytometry in HIV, pharmacokinetics, human genetics of extrapulmonary TB, proteomics of mycobacteria, pulmonary immunology, advanced clinical microbiology in HIV, and

mycobacterial genetics. Short term training was made available to several members of the clinical research staff in the United States, South Africa and in Uganda.

The Centre is currently recognized for post-graduate training (leading to the Ph.D. degrees in bacteriology, biochemistry, immunology and statistics) by the Madras University, and by the Inter-University Board of India and Sri Lanka. It is also a training centre for WHO fellows, as well as medical undergraduates and post-graduates of the University of Madras and of the neighbouring states.

Looking back over five decades, something that started off as a temporary clinical unit with a staff of about 80 in May 1956 and a one-point inquiry regarding the efficacy of domiciliary chemotherapy has grown over the years in to a mammoth research institute with approximately 590 staff members and a plethora of activities. Throughout this period, the most important cause of success has been *team work*, a trait generously gifted by the Centre's founding father, Dr.Wallace Fox, and best described by Henry Ford's famous quote:

"Coming *together* is a beginning.

Keeping *together* is progress.

Working *together* is success".

TRC'S CONTRIBUTION TO TB-RELATED RESEARCH OVER FIVE DECADES

Contribution to globally accepted DOTS strategy for managing TB

- TB patients can be treated as effectively at home as in the hospital, reducing the cost of treatment
- No additional risk to contacts by treating patients at home
- Treatment taken thrice a week proved to be as effective as daily treatment
- Duration of treatment can be reduced to six months by using rifampicin and pyrazinamide
- Patients who relapse after successful treatment can be treated with the same drugs
- All forms of TB can be successfully treated within a duration of six to nine months
- Treatment completion when SCC was given for self administration under the programme was only 50 percent, stressing the need for direct observation of drug administration

Epidemiological contributions

- The largest BCG trial evaluating the efficacy of the vaccine in preventing TB demonstrated that BCG did not offer any protection against bacillary forms of TB
- Epidemiological data collected during this trial has given a wealth of information
- Decline in TB was only 1.4 percent per annum between 1968 and 1985. DOTS has accelerated this decline further during the period 1999-2009
- Molecular epidemiological studies suggest that the majority of the TB cases are from an already infected pool – hence the need for long term commitment for TB control

Operational research

- Identified vulnerable groups for poor treatment outcome to enable targeted IEC
- TB is more prevalent among males. Contrary to popular belief, more women approach health facilities, get diagnosed and are more compliant despite facing more stigma
- Community volunteers can provide reliable and accurate assistance for TB control
- Estimated that the economic loss due to TB is Rs.13,000 crores annually
- Estimated that 300,000 children in India drop out of school every year due to parental TB
- DOTS has resulted in 50 percent reduction in patient cost

Laboratory

- Using the LOT quality assurance method and checking eight slides per microscopy centre assures quality with minimal resources and time
- Drug resistant surveillance has shown MDR-TB among newly diagnosed TB patients to be less than 2 percent
- TRC is assisting the government in establishing culture and drug susceptibility testing at state level

Capacity building

- Pre-tested and finalized the training modules on RNTCP for the country
- A nodal centre for training, having trained around 4000 health personnel

Setting the research agenda

- Attempts to reduce the duration of treatment further using newer drugs
- Basic and operational research to develop tools for improving DOTS strategy (diagnostics, implementation, monitoring and evaluation)
- Rapid transfer of technology from the clinic / laboratory to the field to benefit the community at large
- Packages for sustainable programmes

VISION STATEMENT

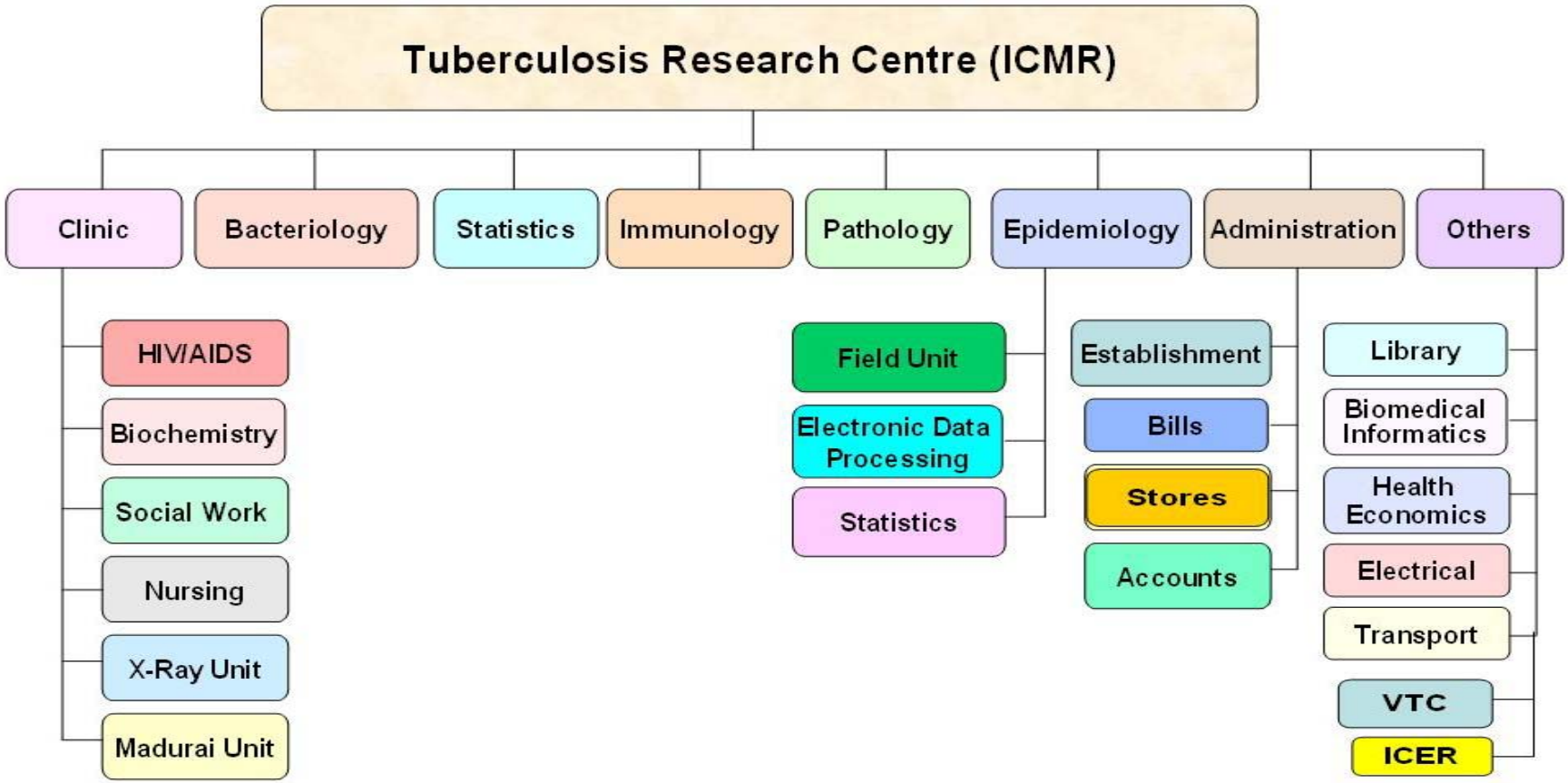
To develop the Tuberculosis Research Centre into:

- a centre of excellence for research in TB
- an opinion leader on TB control policies
- a core facility for training for TB research and control
- a nodal agency for advocacy for TB control in India

MISSION STATEMENT

- TRC is mandated by the Indian Council of Medical Research to provide scientific understanding and technologies needed to support the fight against TB
- TRC supports and promotes Directly Observed Treatment Short-course (DOTS) in the Revised National Tuberculosis Control Programme (RNTCP) of the Government of India by providing better tools and refining existing tools for diagnosis, treatment and monitoring of TB through controlled clinical trials and scientific research
- TRC strives for integrity, quality and relevance of its research by constantly improving its scientific programs through external peer review and competitive funding
- TRC utilizes tools from clinical, biological and social sciences to understand the parasite, patient and the programme associated with TB
- TRC recognizes its obligation to patients with TB and promotes and practices the highest standard of patient care in the course of its research activities
- TRC develops statistically reliable protocols for the evaluation of intervention strategies for the control of TB
- TRC endeavours to provide excellent training programs to researchers and programme personnel in both basic and clinical sciences
- TRC aims to bridge the gap between the public establishment and private enterprise, to promote advocacy required for the control of TB
- TRC is committed to the dissemination of knowledge and leads in the development and use of the technologies needed to synthesize, analyze and disseminate information about TB
- TRC enters into partnerships with local, national and international agencies to develop sustainable strategies for the control of TB
- TRC respects the ethical principles associated with research and strives to safeguard its intellectual property rights and protect the rights of others

ORGANIZATIONAL STRUCTURE OF TRC



DEPARTMENT OF CLINICAL RESEARCH

Overview

The Department of Clinical Research is the fulcrum around which the TRC revolves. The department specializes in the conduct of randomized clinical trials in the treatment of TB. The strength of the department is its infrastructure, consisting of physicians, nursing staff, social workers and health visitors, which is ideally geared for carrying out treatment trials in TB. Over the years it has earned a well-deserved reputation for high quality research. Many landmark research studies in TB, such as the efficacy of domiciliary treatment, intermittent treatment regimens and short course regimens for pulmonary and extra-pulmonary TB have been carried out by the department, with active support from other departments of TRC. These studies have helped to influence treatment practices for TB worldwide. After carrying out a large number of clinical trials to establish the scientific foundation for rational treatment regimens, the department is now focusing its attention on evolving treatment regimens that are directly relevant to the TB control programme.

Research Focus

- Shortening the duration for treatment of TB
- TB control programme oriented clinical trials
- Multidrug and Extensively drug resistant TB (MDR/ X DR)

Landmark Controlled Clinical Trials

Trial in pulmonary TB in adults: In 1956, concurrent comparison of the home and sanatorium treatment of pulmonary TB (PTB) with isoniazid plus p-aminosalicyclic acid over a period of 12 months, showed that despite the manifest advantages of sanatorium care such as rest, adequate diet, nursing and supervised treatment, the merits of domiciliary chemotherapy were comparable to those of

sanatorium treatment, and that it would therefore be appropriate to treat the majority of patients at home, provided an adequate service were established.[1]

In 1961, to evaluate a suitable intermittent regimen, the effectiveness of a combination of isoniazid and streptomycin given twice-weekly under supervision was evaluated which concluded that twice weekly regimen was as effective as daily treatment.[2]

From 1974 onwards short course chemotherapy regimens with rifampicin were evaluated. A controlled clinical trial of 3 and 5 month regimens in the treatment of sputum-positive PTB documented the efficacy of 5 month rifampicin containing regimen.[3]

During 1980-85 fully intermittent regimens which required less frequent patient attendance were evaluated. Oral short-course regimens for the treatment of sputum-positive PTB that could be more easily implemented under field conditions were evaluated during 1986-90 which concluded that a fully unsupervised ethambutol-containing regimen given daily for 8 months was found to be very effective even in the presence of isoniazid-resistant bacilli.[4]

In 1995, the TRC initiated a randomized clinical trial of 3, 4, 5 months regimens with ofloxacin as one of the drugs in the intensive phase of treatment for the treatment of patients with smear positive PTB. This trial showed for the first time that it is feasible to shorten the duration of TB treatment to 4 or 5 months.[5] The publication of results of this trial in 2002 resulted in a global interest in the role of quinolones in TB treatment.

Trial in PTB in children: Short course chemotherapy (SCC) for PTB in children concluded that 6 months' intermittent therapy with isoniazid, rifampicin and pyrazinamide in the initial 2 months' was as effective as the 9 months' daily therapy

with isoniazid and rifampicin. Both the nodal and parenchymal lesions resolved to the same extent at the end of treatment.[6] The residual lesions continued to improve even after stopping treatment. Mortality and drop out rates were very low and adverse reactions negligible. Clinical and radiographic profile of 201 children with culture confirmed PTB showed that children with TB present with fever and cough of insidious onset. Lymphadenopathy is a common feature even in children with PTB. A significant proportion of children had normal chest X-rays despite positive gastric aspirate cultures. Drug resistance rates in children mirror the pattern seen in adults in this geographic area.[7] A 5-year follow- up of 137 children treated in randomised clinical trial of PTB showed that 50% had radiographic sequelae at the end of treatment with low relapse rate. [8]

Trials in extra-pulmonary TB

Spinal TB: A randomised, controlled clinical trial to compare ambulant SCC with anterior spinal fusion plus SCC for spinal TB without paraplegia was undertaken. The study concluded that ambulant chemotherapy for a period of six months with daily isoniazid plus rifampicin (Amb6) was an effective treatment for spinal TB except in patients aged less than 15 years with an initial angle of kyphosis of more than 30^{o} whose kyphosis increased substantially.[9]

TB meningitis in children: A SCC study in TB meningitis in children evaluated two 9 month regimens. The response to therapy was similar in both the regimens. The mortality was very high, namely 31%, despite using intensive regimens. There was a strong association between the stage on admission and the mortality rate, the latter being highest in stages II and III. This emphasised the need for early diagnosis and treatment in tuberculous meningitis.[10]

Brain tuberculoma: The efficacy of short-course regimen in the treatment of brain tuberculoma and computerised tomography scan appearance before, during and after anti-TB treatment was studied in a controlled clinical trial. Short-course

regimens of 9 months' duration were effective in the treatment of tuberculoma of the brain.[11]

Abdominal TB: The efficacy of a 6-month SCC regimen with that of a 12-month standard regimen was compared in the treatment of abdominal TB. Surgery was undertaken only for patients suspected to have obstruction or perforation of the intestine. A 6-month SCC regimen was found to be as effective as the standard 12-month regimen in the treatment of all forms of abdominal TB.[12]

Lymphnode TB: Patients with biopsy confirmed superficial lymph node TB were randomly allocated to receive either a daily self-administered 6-month regimen of rifampicin and isoniazid, or a twice weekly, directly observed, 6-month regimen of rifampicin and isoniazid plus pyrazinamide for the first 2 months. Both the self-administered daily regimen and the fully observed twice-weekly regimen were highly efficacious for treating patients with lymph node TB and may be considered as alternative options to the recommended regimens.[13]

Skin TB: Bacteriological and histological correlates of the three predominant clinical forms of cutaneous TB and the efficacy of a 9-month daily regimen containing rifampicin and isoniazid were evaluated in 213 patients. Bacteriological and/or histological confirmation of TB was obtained in 88% of the cases. Ninety-two per cent of the patients showed resolution of the lesions within the first 6 months of chemotherapy; 1% failed to respond to this regimen. There was no relapse in any of the cases during the follow-up period of 3 years. The study concluded that clinical findings were adequate to identify major forms of cutaneous TB as evidenced by bacteriological and histopathological examination. A daily regimen of rifampicin and isoniazid for 9 months was effective in treating cutaneous TB.[14]

Management of Multidrug resistant TB (MDR-TB): The feasibility of managing MDR-TB patients under field conditions where DOTS programme had been implemented was studied in 66 patients. Among them 20 (30%) were resistant to one or more second line drugs including a case of “XDR TB”. Providing injection was identified to be a major problem. Response to treatment could be correctly predicted based on the 6-month smear results in 40 of 42 regular patients. Successful

treatment outcome was observed only in 37% of cases with a high default of 24%. The findings suggested that despite having reliable drug susceptibility testing and drug logistics, the main challenge was to maintain patients on such prolonged treatment by identifying a provider closer to the patient who can also give injection, have social skills and manage minor adverse reactions.[15]

The outcomes of 38 MDR-TB patients treated with the RNTCP-recommended 24 months standardized treatment regimen (STR), under programmatic conditions was studied. The findings suggested that outcomes of this small group of MDR-TB patients treated with the RNTCP's STR were encouraging in this setting. Close attention needs to be paid to ensure adherence, and to the timely recognition and treatment of ADRs.[16]

Studies in Leprosy

In analogy with TB, TRC undertook randomized controlled clinical trials in leprosy patients. Two multi-drug regimens (clofazimine and dapsone versus clofazimine, dapsone, isoniazid and rifampicin) in multibacillary lepromatous leprosy patients with bacteria index of 2.5 or more were studied. There was no difference between the rifampicin regimens with resoect to clinical improvement or bacteriological status of the patients.[17] In another study, it was observed that addition of anti-histamine to a regimen of clofazimine and dapsone did not enhance the efficacy of the regimen as evidenced by clinical and bacteriological findings.[18]

Studies were also undertaken to obtain information on relapses during long-term follow-up with drug susceptible *M. leprae* among multibacillary leprosy patients treated with multi-drug treatment regimens[19] and also to assess the value of midfinger smears in multibacillary leprosy patients.[20]

Studies in Filariasis

The standard drug currently used to treat bancroftian filariasis, diethylcarbamazine citrate (DEC), is unsatisfactory due to severe side effects and poor compliance. Other drugs tested either have lacked sufficient efficacy or have been associated with unacceptable toxic effects. Ivermectin, a semisynthetic macrolide antibiotic that has a wide helminthicidal spectrum for parasites of animals, has recently proved to be superior to DEC and has become the drug of choice for the treatment of onchocerciasis. A comprehensive phase II trial of ivermectin showed comparable efficacy with DEC and single-oral-dose administration made it the best candidate to replace DEC as the treatment of choice for bancroftian filariasis.[21] Further, a randomized, double-blind trial in 40 south Indian men with lymphatic filariasis confirmed these results.[22]

For the first time, a direct comparison of the relative efficacies of single doses and split doses of ivermectin and DEC was done in treating malayan filariasis. The ability of single doses of either ivermectin or DEC to achieve prolonged suppression of microfileremia upto one year would be helpful in the design of better control strategies for lymphatic filariasis.[23]

In addition, a hospital based study was conducted to evaluate the efficacy, tolerability and safety of DEC-fortified salt in clearing microfilaraemias of *B. malayi*. The DEC-fortified salt was well accepted by the study population and the adverse reactions were transient and did not require any specific treatment.[24]

SOCIAL WORK SECTION

Overview

The social work section has been a part of the department of clinical research ever since the inception of TRC 55 years ago. The role of the social workers includes supporting clinical research activities by functioning as a liaison between the clinicians and the patients. This involves detailed consent procedures, sociological assessments, clarifying doubts and fears around the illness, motivation, counseling and defaulter retrieval of patients to ensure that strict follow up of patients is maintained. This is crucial for the success of any clinical trial. The section is actively involved in a number of socio-behavioral studies in TB and HIV/AIDS. These studies have addressed a number of issues such as stigma, disclosure issues, health seeking behavior patterns, factors influencing adherence and feasibility studies such as vaccine preparedness and routine referral of TB patients for HIV screening. Furthermore, the section has also been involved in international collaborative studies targeting sensitive hard-to-reach populations such as MSM (Men having sex with men), alcohol dependants, migrants and mothers living with HIV/AIDS.

Research Focus

- Socio-behavioral studies in TB and HIV

Landmark Socio behavioural studies

Feasibility of provider-initiated HIV testing and counselling of TB patients under the TB control programme: The study findings highlighted that routine referral of TB patients for HIV screening is feasible and was carried out in 80% of TB patients. There was a need to integrate HIV screening in TB clinics and to consider barriers such as distance availability of health providers, avoidance of frequent visits by patients to clinics for investigations and results. The challenge of this study however is the need to assure that TB patients diagnosed with HIV have to be enrolled and followed up in ART clinics.[25]

Factors influencing the care-seeking behaviour of chest symptomatic: This study was done before and after implementation of RNTCP. There was a significant difference in care seeking of chest symptomatic pre and post RNTCP. It was observed that the initial point of contact to the public health facilities had increased from 38% (Pre RNTCP) to 50% (post RNTCP). While this was encouraging, shifting of facilities from public to private facilities was a matter of concern. The reasons for this were patient dissatisfaction with the health providers and delay. The major reasons to choose private care were proximity to residence and their perception that good-quality care was provided.[26]

Alcohol use disorders (AUD) among TB patients: Screening of TB patients for AUD is not done as a matter of routine in RNTCP clinics. This is crucial as AUDs among TB patients is associated with non adherence and poor treatment outcomes. The study findings revealed that 56% of TB patients who consumed alcohol had AUD. This was found more in Category 2 patients. One third required specific treatment for alcohol abuse as they were hazardous drinkers. Alcohol use disorder is a problem that needs to be addressed in the TB control programme.[27]

Knowledge, attitude and practice of a person at risk in relation to a future HIV vaccine trial: The study aimed to find out the willingness of populations at risk to participate in future preventive HIV vaccine trials and to assess the factors that enhance or deter them from participation. A cross-sectional study was conducted in Tamil Nadu, India among 501 participants from six different risk groups. In total, 82% were willing to participate and the desire to be protected from HIV was the main reason for willingness to participate. Perception of not being at risk was the major reason for refusal among married women.[28]

Community-based approach to designing an AIDS program for mothers living with HIV: The purpose of this study was to explore the perceptions and needs of mothers living with HIV (MLH) to gain greater insights into the challenges they face in relation to their health seeking behaviour, fears around disclosure, and issues related to stigma and discrimination. Discrimination by physicians and other health care workers has been a major impediment expressed by MLH in accessing quality

health care. MLH are increasingly concerned about how and when to disclose their HIV status to their children and the repercussions which could result from disclosure. The study findings helped to develop a short film titled "**Archana**". The study findings have also led to a pilot intervention study addressing the needs of MLH.[29]

Behavioral risk factors and HIV sero -prevalence among men who have sex with men:

In India, men having sex with men (MSM) is a particularly high-risk group for HIV and is considered a bridge population transmitting HIV and STDs to their partners. The study findings revealed that more than one fifth (46/210) reported unprotected anal intercourse in the past 3 months, 8% tested positive for HIV, and only 26% had previously participated in an HIV prevention intervention programme. MSMs stressed that they were saturated with messages on HIV/AIDS and condom distribution and called for interventions to address their psychosocial needs which are not addressed in the intervention programmes.[30]

HEALTH ECONOMIC STUDIES

Socio-economic impact of TB on patients and family in India (1997): The objective of this study was to quantify the socio-economic impact of TB on patients and their families from the costs incurred by patients in rural and urban areas. The study documented the overall costs of Rs.2052/- incurred by patients. Direct costs were lowest among patients attending government health facilities, and were 6.5 times higher among patients attending private health facilities. This is the most authentic estimate available on the socio economic burden of TB in India and is cited by national and international agencies and has also been specified by the Prime Minister of India while launching the programme on TB. Based on these findings, WHO has projected the economic burden of TB for the country.[31]

Perceptions of TB patients about their physical, mental and social well being: Data on perceptions of TB patients on their illness before the onset of illness and during the treatment period were collected, using a modified SF36 questionnaire. The reaction of patients to the disclosure of the diagnosis was worry (50%) and suicidal thoughts (9%). 'Good health status' was perceived initially in less than 7% of patients; there was significant improvement after treatment compared to the status at the onset of illness. Only 54% of patients perceived 'happy mental status' at the end of treatment, and there was no change in social stigma in both men and women. Tuberculosis control programmes should address these issues and provide social support, timely counseling and health education.[32]

Socio-economic profile of TB patients registered in TB control programme: The aim of this study was to focus on whether the TB programme is outreaching the poorer segment of the community. Based on the information collected, standard of living index was measured using the NFHS definition. This study clearly showed that two thirds of TB patients who have access to the TB programme were poor and meets the health need of the most vulnerable segment of the population. This finding substantiated that the programme was outreaching the poor.[33]

Prevalence of TB in different economic segments of the population: During an ongoing community survey, the data on standard of living was collected. The estimated standard of living index (SLI) such as low, medium and high was related to the prevalence of TB in these groups. TB prevalence was 343, 169 and 92 per 100 000 population in low, medium and high SLI groups respectively.[34]

Evaluation of post-treatment health-related quality of life (HRQoL) among TB patients: The purpose of this study was to assess the HRQoL of TB patients one year after treatment completion. The well-being scores were significantly related to age, sex, education, employment and persistent symptoms. There was a significant association between economic and social well-being. This study suggested that the HRQoL of TB patients one year after successful completion of treatment under the TB control programme was normal for most of the domains studied.[35]

HIV / AIDS SECTION

Overview

The HIV/AIDS section was established in February 2000 with a view to translate the commitment of TRC towards an increase in the quantum of research activity in the field of HIV/AIDS. This section is composed of a multidisciplinary team of scientific and technical staff who undertake both clinical and laboratory studies in the field of HIV with special emphasis on the interaction between HIV and tuberculosis. The section is conducting controlled clinical trials for the treatment and prevention of TB in HIV infected individuals, in collaboration with various state Government hospitals. Laboratory support for the diagnosis, monitoring and management of HIV patients enrolled in the clinical trials of TRC is provided by a self-sufficient laboratory, which is accredited by the NIH-VQA program for all virologic assays. It is one of WHO's National Reference Laboratories for HIV-1 drug resistance testing in the country. It is also a Regional Reference Laboratory for HIV-1 viral load testing and HIV-1 DNA PCR for NACO. In addition, studies have been initiated to understand the complex interplay between HIV and TB on the cell mediated immune response and also to study the role of immune activation markers in assessing response to treatment and prognosis in patients with HIV and TB.

Research Focus

- Chemotherapy of tuberculosis in HIV infected persons
- Immune status, viral load and cytokine profile in patients with HIV/TB

Landmark HIV/AIDS studies

Randomized clinical trial to assess the efficacy of short course intermittent regimens for the treatment of HIV-associated TB: A prospective randomized controlled clinical trial was conducted to compare the efficacy of an intermittent 6-month regimen consisting of 2-month of isoniazid, rifampicin, ethambutol and pyrazinamide followed by 4 month of isoniazid and rifampicin versus a 9-month regimen in HIV -infected patients with newly diagnosed pulmonary or extrapulmonary TB. Primary outcomes included favorable responses at the end of treatment and recurrences during follow-up, whereas the secondary outcome was death. Intent-to-treat and on-treatment analyses were performed. This study showed that the 9-month regimen resulted in a similar outcome at the end of treatment but a significantly lower bacteriological recurrence rate compared with a 6-month thrice-weekly regimen.[36]

Evaluation of safety and efficacy two different once-daily anti-retroviral treatment regimens along with anti-TB treatment in patients with HIV-1 and TB: The safety and efficacy of once-daily nevirapine (NVP) was compared with efavirenz (EFV) (standard), both in combination with two nucleoside reverse transcriptase

inhibitors. This was an open-label, non-inferiority, randomized controlled clinical trial conducted at three sites in south India. HIV-infected patients with TB were treated with standard short-course anti-TB regimen ($2EHRZ_3$/ $4RH_3$) and randomized to receive once-daily EFV or NVP with didanosine and lamivudine, after two months. Sputum smears and mycobacterial cultures were performed every month. CD4 count, viral load and liver functions were monitored periodically. Primary outcome was composite of death, virological failure, default or serious adverse event (SAE) at 24 weeks. Favorable TB treatment outcomes were observed in 93% of

patients in the EFV arm and 84% in the NVP arm. The NVP regimen was observed to be inferior with more frequent virologic failure and death.[37]

Food assistance to improve treatment outcome for HIV patients: A prospective interventional study was undertaken to evaluate the effects of an oral macronutrient supplement among HIV-infected adults in south India. Significant increases in body weight, body mass index, midarm circumference, fat-free mass, and body cell mass were observed in the supplement group but not in the control group at 6 months; gains were greater in patients with CD4 cell counts <200 cells/microL. No changes were observed in lipid levels, whereas the CD4 cell count decreased in the control group. Macronutrient supplementation did not result in significantly increased weight gain compared with standard care (including nutritional counseling) among patients with moderately advanced HIV disease.[38]

Validation of a WHO diagnostic algorithm for smear negative TB among patients with advanced HIV disease in India: a prospective, multicentric study: This study was undertaken to determine the utility of initial CXR and sputum culture (by LJ media) in the TB diagnostic algorithm among HIV-infected symptomatic sputum smear negative patients. HIV-infected patients with cough >2 weeks and three negative sputum smears were enrolled at two sites in Chennai and Pune. Patients had a CXR and sputum cultures performed, received a course of broad spectrum antibiotics, and were reviewed with a repeat CXR after 15 days. The study showed that radiographic abnormalities among HIV-infected chest symptomatic were not specific for TB and do not contribute to early diagnosis of smear negative PTB.

Innate and adaptive immunity in children starting antiretroviral drugs in India: This study aimed at investigating immune status and disease progression prospectively in a pediatric HIV-infected cohort in Chennai, India. Our observations suggested that a majority of perinatally HIV-infected children who survive infancy without ART remain clinically stable in the short term, but have demonstrable immunologic abnormalities indicative of defects in innate and adaptive immune system with impairment of DC activation and function, along with skewing of maturation T-cell subsets, altered immune activation and elevated immune exhaustion. Children initiated on ART showed improvement in CD4 counts but did

not show improvement in DC function or change in CD8 immune activation. These defects of immunity point to a need for earlier treatment initiation.

Immune activation in HIV-infected TB patients: In order to investigate the impact of active TB and its treatment in HIV-infected individuals, changes in markers of systemic immune activation such as plasma neopterin, beta-2-microglobulin and soluble TNF-receptor 1 (sTNF-RI) were assayed in ART-naïve HIV positive TB patients undergoing treatment for TB. Our findings revealed that plasma levels of neopterin, beta-2-microglobulin and sTNF-RI were elevated in both TB and HIV patients, with the highest levels seen in individuals with dual infection. This increase was related to the stage of HIV disease. Though anti-TB treatment resulted in a significant decrease in plasma neopterin and soluble TNF-receptor 1, the levels at the end of ATT were still higher than that seen in the controls, indicating that underlying immune activation persists despite TB treatment.[39]

Characterization of drug resistant mutations in HIV-1 isolates from anti-retroviral treatment-naive as well as treated adults in south India: A study was undertaken to delineate drug resistant mutations in ART-naïve HIV+ patients in South India. Significant polymorphisms were observed in both RT gene and protease genes in all naïve patients, but only one individual each had naturally occurring resistance mutations to NRTI (M184V), NNRTI (Y181C) and protease (L90M).

All patients who failed treatment had resistance mutations to at least one of the RT inhibitors while none of them had mutations in the protease gene. The commonest mutations observed were M184V (Lamivudine), Y181C (Nevirapine/Efavirenz), and G190A and L74V (NRTIs). Knowledge on the existing patterns of mutations will be useful in the design of appropriate regimens for HIV-infected individuals in India.[40,41]

Impact of antiretroviral treatment on nutritional and immunological status of HIV-infected children: This study was designed to investigate the impact of antiretroviral therapy (ART) on growth (BMI and plasma leptin) and immune response (CD4+ T cell counts, cytokine production, apoptosis and nitric oxide production) in HIV-infected children. There was a significant elevation in body weight, CD4+ T cells percentage and plasma leptin levels following six months of

ART. This was associated with a decline in plasma nitrate, plasma nitrite, IFN-γ, IL-6 and apoptotic index. On the other hand, there was no significant difference in any of the above parameters in children who did not receive ART, except an increase in weight. These findings imply that HIV-associated immune activation and concomitant inflammation can be reduced by anti-retroviral treatment and this may have long-term beneficial effects.

CD4/CD8 ratio as a surrogate marker for HIV infection in infancy: In the first 18 months of life serologic tests for HIV infection do not differentiate between exposure and infection due to maternally acquired antibodies. Virologic tests like DNA or RNA PCR are confirmatory but difficult to perform in resource-constrained settings. This study aimed at examining whether CD4 count, CD4% or CD4/CD8 ratio could serve as a surrogate marker for HIV infection in infants less than 18 months of age. A significant difference was observed in the mean CD4%, CD4 count and CD4/CD8 ratio between HIV-infected and uninfected infants. These findings suggest that CD4/CD8 ratio may be used as surrogate markers for HIV infection in infants born to HIV positive women in resource-limited settings with facility for CD4/CD8 counting but not for virological assays.

EPIDEMIOLOGY UNIT

Overview

The activities of the Epidemiology division of the centre dates back to 1968 when the BCG trial in TB was started in Chingleput district. Since then the BCG Trial area has been successfully utilized as the population laboratory for the study of the epidemiology of TB. After the BCG Trial, disease prevalence surveys were undertaken by TRC, in Raichur, (Karnataka) and North Arcot (Tamil Nadu) to estimate the caseload in these districts to assist in the evaluation of implementation of the National TB programme in these districts. This division has over the years built up considerable capability in conducting large scale epidemiological field trials and surveys. It has developed qualitative as well as quantitative methodologies for carrying out epidemiological studies in TB. These have been successfully adopted by other national and international centres. This expertise has also been found useful for the study of other infectious diseases such as leprosy, lymphatic filariasis and typhoid in the same area. The strength of the department is the availability of a large number of staff who possess specialized skills requisite for field epidemiology and their proven ability to involve the communities in all aspects of the study. The department conducted a large study involving 580,000 population to assess the epidemiological impact of DOTS. In a consultative capacity, the department is assisting the Government of India in carrying out a National sample survey to estimate the burden of TB.

Research Focus

- Tuberculosis Epidemiology
- Disease Survey
- ARTI Survey
- Intervention strategies
- Assessment of risk factors

Landmark Epidemiological Studies

Trial of BCG vaccine in south India for TB prevention, (BCG Trial) : A community based double blind, randomized controlled trial to evaluate the protective efficacy of BCG against bacillary forms of pulmonary TB was carried out from 1968-1986. The incidence rates in the three vaccination groups namely high dose, (0.1mg/0.1ml) low dose, (0.01mg/0.1ml) and placebo were similar showing undoubtedly that BCG did not offer any protection against adult forms of pulmonary tuberculosis. The incidence of disease among non-reactors at intake was very low whereas the incidence was very much higher among reactors at intake. Young adults who were recently infected rarely progressed to manifest disease. But the incidence of disease was high among middle aged and old men who must have been first infected many years ago suggesting that the occurrence of new cases was not due to primary infection but due to either endogenous reactivation or exogenous re-infection.[42,43]

TB prevalence survey in Kashmir valley: TB prevalence survey was conducted in the Kashmir valley from June to November 1978. The objective of the survey was to estimate the prevalences of infection, of nonspecific sensitivity and of pulmonary TB. The prevalence of TB infection was 38% (all ages), of culture positive TB was 3/1000 and of non-specific sensitivity was 59%. The TB situation in Kashmir valley was quite different from that of the Chingleput trial area. The significant finding from this survey was that the prevalence of disease was similar in the two sexes contrary to the usual experience of higher prevalence among males.[44]

Prevalence study of TB infection over fifteen years in a rural population in Chingleput district (south India): In the BCG trial, the entire study population was tuberculin tested. After the initial tuberculin testing, repeat tuberculin testing was done twice at intervals of 10 and 15 years among children aged 1-9 years residing in a random sample of panchayats in two panchayat unions. The objective of the study was to see whether over a follow-up period of 15 years there was any change in the TB situation, in terms of prevalence of infection in children in the study population. The results showed that the overall prevalence of infection in the three surveys was

9.0, 10.2 and 9.1 respectively. The average annual risk of TB infection was estimated to be 1.7%, 1.9% and 1.7% respectively. There was no change in the TB situation in terms of prevalence of infection in the study population over a period of 15 years.[45]

Critical assessments of smear positive PTB patients after chemotherapy under the district TB programs: This study was undertaken in the North Arcot District to quantify the treatment completion and bacteriological status of patients started on anti-TB chemotherapy for smear positive PTB. The objective was to relate the bacteriological status to the amount of chemotherapy given. Overall mortality was 28%. A significant finding was that even among those who had taken less than 50% of treatment, 56% were bacteriologically negative. Inadequate and irregular chemotherapy resulted in over four times the mortality as compared to those who had adequate chemotherapy.[46]

Prevalence survey in Raichur District: Before the introduction of SCC at the national level, Government of India introduced the SCC in 18 districts monitored by TRC. In Raichur district, a sample survey was undertaken to estimate the prevalence of disease in the district so that the case finding efficiency of the District TB Programme can be evaluated. The survey was carried out from November 1988 to March 1989. The prevalence of bacillary TB (smear or culture) was 10.9/1000. Smear positive prevalence was 7.6/1000.[47]

Prevalence survey in North Arcot District: North Arcot district in Tamil Nadu was one of the 18 districts in which the SCC was monitored by TRC. A population of 1, 05, 339 persons were registered from a random sample of 35 villages and 102 town streets from the urban area. All children aged 0-9 years were tuberculin tested. Persons aged 15 years were screened by chest symptoms and one third of the sample was screened by X-ray of chest as well. The prevalence of infection among children upto 9 years of age without BCG scar was 6.7%. The prevalence of bacillary disease estimated by symptom screening alone was 4.3/1000. The

prevalence of bacillary disease by symptom and X-ray screening in the one-third sample was 7.9/1000.[48]

Trends in the prevalence and incidence of TB in south India: In 1968–70, about 1, 00, 000 subjects were surveyed for TB and followed up for 15 years by re-surveys once in 30 months. Tuberculin tests were done initially on all and at 4, 10 and 15 years in selected samples of those aged 1-9 years. The results showed that the prevalence of culture positive TB decreased by 1.4% per annum but prevalence of smear positive TB did not show any significant decrease over the 15 years of follow-up. The incidence of culture positive TB and that of smear positive TB decreased by 4.3% and 2.3% per annum respectively. The annual risk of TB infection was initially 2% and showed no sign of decline over the follow-up periods.[49]

Survey for TB in a tribal population in North Arcot District: The objective of this survey was to estimate the prevalence of TB infection and disease in the tribal population living in Jawadhu Hills in south India. The study sample for the disease survey was 16017 individuals aged 15 years and above. The prevalence of disease was 8.4/1000. The annual risk of TB infection in children aged 0-9 years was 1.1%. The prevalence and pattern of TB in this tribal population was similar to that observed in a tribal population.[50]

Tobacco smoking and PTB: A case – control study was carried out to determine whether there was an association between tobacco smoking and PTB. Study population consisted of 85 men aged 20-50 years with bacteriological TB as cases (smear and / or culture positive) and 459 age matched men without TB selected randomly as controls. The study analysis showed that there was a positive association between tobacco smoking and pulmonary (bacillary) TB (age adjusted odds ratio 2.24). The association also showed a strong dose response relationship.[51]

National sample survey to estimate annual risk of tuberculous infection in south India:

The objective of this survey was to estimate the annual risk of TB infection (ARTI) among children aged 1–9 years in the south zone of India. Six districts were selected

through systematic random sampling. Four hundred and twenty rural clusters and 180 urban clusters were selected from these districts on the basis of the rural–urban ratio in the entire zone. The ARTI was computed from the estimated prevalence of TB infection among children without a BCG scar. Among 52 951 children registered for the study, 50 846 (96%) had a tuberculin test result. The BCG coverage for the study population was about 65%. Among 17 811 children without a BCG scar, the prevalence of infection was 5.9% (95%CI 4.0–7.7%); the corresponding ARTI was 1.7% (95%CI 0.7–1.4%).The estimated ARTI for the south zone was 1%, as compared to the national average of 1.7% used for programme evaluation. This baseline information would be useful for the assessment of future trends.[52]

Epidemiological impact of DOTS strategy: The BCG trial area, Tiruvallur district (previously known as Chingleput district) has been successfully utilized as a population laboratory to study the epidemiology of TB from 1968 onwards. The RNTCP was introduced in this area in 1999. To assess the impact of RNTCP on the incidence and prevalence of disease four serial prevalence surveys were carried out. The results of the first three surveys showed that TB prevalence declined by about 50% in 5 years, from 609 to 311 per 100 000 population for culture-positive TB and from 326 to 169/100 000 for smear-positive TB. The annual rate of decline was 12.6% (95%CI 11.2–14.0) for culture-positive TB and 12.3% (95%CI 8.6–15.8) for smear-positive TB. The decline was similar at all ages and for both sexes. The findings from this study showed that with an efficient case detection programme and the DOTS strategy, it was feasible to bring about a substantial reduction in the burden of TB in the community.[53]

Estimation of burden of TB in India for the year 2000: Data on the burden of TB in India are vital for programme planners to plan the resource requirements and for monitoring the nation-wide TB control programme. This study estimated the burden of disease for the year 2000 based on recent prevalence of TB and annual risk of TB infection estimates. Data on prevalence generated among adults by the Centre, among children by National Tuberculosis Institute (NTI), Bangalore, and the ARTI estimates from the nation-wide sample survey by NTI and TRC were used for the estimation. The estimates of bacillary, abacillary and extrapulmonary cases were then combined to get the national burden. The estimated number of bacillary cases was 3.8 million (95% CI: 2.8 - 4.7). The number of abacillary cases was estimated to be 3.9 million and that for extrapulmonary cases was 0.8 million giving a total burden of 8.5 million (95% CI: 6.3-10.4) for 2000. The current estimates provided baseline information for advocacy and planning resource allocation for TB control activities. Also, these estimates can be compared with that in future years to measure the long term impact of TB control activities in India.[54]

Sample mortality surveys in Andhra Pradesh and Orissa: At the request of Central TB Division, TRC undertook sample mortality surveys to collect baseline TB mortality data in these two states. The objectives were (i) to estimate crude mortality rate for the states of Andhra Pradesh & Orissa (ii) to estimate the TB mortality rate among the general population in the two states. A sample of 3, 80, 000 population was surveyed in both the states. Using a retrospective follow up methodology, mortality data were collected. The cause of death was ascertained using verbal autopsy. The crude death rates (proportion) in A.P and Orissa were 5.9/1000 persons and 5.2/1000 persons respectively. The TB mortality rates in A.P. and Orissa were 76/100000 p-years and 41/100000 p-years respectively.

OTHER ACTIVITIES

Training of health workers in survey methodology: The epidemiology unit of T.R.C. has trained health workers in survey methodology for conducting Disease survey and Tuberculin survey, from the following National Institutes:

N.T.I, Bengaluru
AIIMS, New Delhi
JALMA, Agra
PGIMS, Chandigarh
MGIMS, Wardha
RMRCT, Jabalpur
New Delhi TB Centre
LRS Institute, New Delhi
CMC, Vellore

DEPARTMENT OF BACTERIOLOGY

Overview

This Department is one of the largest facilities of its nature and serves as a Supra National Reference Laboratory for South East Asian Countries under WHO. The Department has been in existence since the inception of the centre. The laboratory routinely provides support for all controlled clinical trials, programme based studies and evaluates drug resistance for referral samples. It also supplies standard strains and clinical isolates of mycobacteria to other investigators. The department conducts important research in basic fields such as drug resistance, applied fields such as improved smear microscopy, phage based rapid diagnosis and drug susceptibility testing for *M. tuberculosis*, phage genomics, applications of phages in the study of mycobacteria, drug discovery and evaluation of emerging methods (technology/ kit) for rapid diagnosis or drug susceptibility testing. A team of well trained scientific and technical staff are involved in conducting several basic studies. The Department forms a major component of the TRC, functions as a training centre for mycobacteriological techniques and for training medical and para medical professionals in different capacities for RNTCP. It also functions as a National Reference Laboratory under RNTCP for smear microscopy, EQA and DRS activities, and provides accreditation of laboratories for conventional / liquid culture and DST in public and private sectors.

Research Focus

- Drug resistance surveillance
- Mycolic acid analysis
- Diagnosis of tuberculosis
- Luciferase reporter phage
- Molecular mechanisms of resistance
- Drug discovery

Landmark Bacteriological Studies

Effect of storage of sputum specimens at room temperature on smear and culture results: The study was undertaken to determine the effect of storage of sputum at room temperature on diagnostic procedures such as smear and culture, with a view to simplify transport of samples from distant areas to reference laboratories. It was found that three days storage at room temperature resulted in loss of viability of tubercle bacilli, while smear was unaffected even after four weeks of storage at room temperature. The study established the need for a transport medium for sputum samples for effective diagnosis and for drug resistance surveillance studies.[55]

Drug resistance surveillance studies: The study was taken up to determine the proportion of initial and acquired drug resistance in cases of PTB in Tamil Nadu, in order to use the level of drug resistance as a performance indicator of the National Tuberculosis Programme using guidelines prescribed by the WHO/IUATLD Working Group on Anti-TB Drug Resistance Surveillance. It was found that there was gradual increase in initial drug resistance over the years in this part of the country.[56]

Phenol ammonium sulfate sedimentation smear microscopy method for diagnosis of pulmonary TB: Phenol ammonium sulphate (PhAS) sedimentation of sputum renders it safer for smear microscopy. The study was taken up to evaluate the method in comparison with direct microscopy with culture as the gold standard. It was found that both methods were comparable in terms of sensitivity and specificity. But the PhAS method was better accepted by the laboratory technicians being safer, but necessitated an overnight sedimentation, with delay in reporting of results by a day.[57]

Pot staining of tubercle bacilli: Conventionally, sputum smears are prepared on glass slides before being stained for acid fast bacilli (AFB) microscopy. In the current study, an attempt was made to stain the tubercle bacilli in the container itself before the smears were made. This method not only reduces the work load and time but also renders the sample safer for handling. Well stained AFB were demonstrated in

smears prepared from pot stained sputum and smear results were comparable with conventional ZN method. In a second study, sputum was pot stained by the addition of phenol ammonium sulfate basic fuchsin solution and stored for 2 hours at room temperature. The smear results were comparable with conventional ZN method.[58,59]

Isolation and characterization of the first temperate phage Che12 capable of lysogenising *M. tuberculosis*: In an effort to develop luciferase reporter phage (LRP) constructs with high sensitivity of detection, attempts were made successfully for isolating a temperate mycobacteriophage capable of infecting and lysogenising *M. tuberculosis.* Such a phage Che12 was isolated, characterized and LRPs constructed. The efficiency of the construct was found to be higher than the existing LRPs with cultures as anticipated. The attempt marked the beginning of diverse attempts to improve the LRP diagnostic assay.[60]

LRPs for the rapid detection of dormant tubercle bacilli:

The LRP show great promise for diagnostic mycobacteriology. Since the TB cases among HIV infected population result from the reactivation of latent bacilli, development of LRPs capable of detecting dormant bacteria would be useful. In a milestone study, 3 LRP constructs were developed using promoters of genes functioning during dormancy. These LRP constructs exhibited detectable luciferase activity in dormant as well as in actively growing *M. tuberculosis*.[61]

Phagebiotics cocktail as substitute for antibiotic supplements in liquid culture of *M. tuberculosis*: Organisms of the normal flora that survive the action of the decontaminating agent during sputum processing can cause heavy contamination of the culture, especially liquid culture. Antibiotic supplements are used in liquid cultures to control such growth despite reports that these agents have deleterious effect on the tubercle bacilli. This study demonstrated a novel hypothesis that a

cocktail of phages that infect and lyse these organisms could be used in liquid cultures instead of the antibiotic supplements with better decontaminating efficiency and *M. tuberculosis* retrieving capacity. Further study established the feasibility of using phage lysin supplement to phagebiotics in decontaminating processed sputum samples in liquid culture of *M. tuberculosis*. The study opened up new possibility of developing a novel biofriendly method of sputum processing.[62,63]

Novel anti-TB compound from marine actinomycetes: Since the introduction of rifampicin forty years ago, no effective anti-TB drug has been discovered. The rate of multidrug resistance is also on the increase. New drugs are desperately needed to overcome this situation. An attempt was made to identify effective anti-TB compound from marine habitat. This is the first report on a novel anti-TB compound, Transitmycin isolated from actinomycetes of Indian marine origin. It is unique and first of its kind in its activity against *M. tuberculosis* and HIV.

Other activities

Another significant contribution from the department has been to the RNTCP program of the Central TB Division imparting training to MDs, microbiologists, technicians, Senior Tuberculosis Laboratory Supervisor etc. The department functions as a National Reference Laboratory under RNTCP supervising nine states and four Union Territories. It is mainly responsible for training of microbiologists for smear, culture and DST and ensuring external quality assurance of sputum microscopy. Further, the department undertakes accreditation of laboratories of the intermediate reference laboratories of the 9 states and in private sectors. So far, 8 labs have been accredited and 9 are under different stages of the process. Drug resistance surveillance was undertaken in Gujarat as a model state. This activity is being extended to Tamil Nadu and West Bengal.

DEPARTMENT OF BIOCHEMISTRY

Overview

The Biochemistry section of the Tuberculosis Research Centre was established in 1960 and offers biochemical support to the controlled clinical trials. In the past, extensive work was carried out to determine acetylator phenotyping using blood, urine and saliva. The mechanism of development of toxicity to rifampicin, isoniazid and pyrazinamide has been investigated. It was established that non-invasive method of estimating salivary levels of drugs could replace plasma. Assay of anti-TB and antiretroviral drugs in pharmaceutical preparations to check for their quality is an important activity. Pharmacokinetic studies to address key issues in TB and HIV are undertaken. Most of these studies are the first of its kind in Indian patients, and provide useful information.

Research Focus

- Pharmacokinetics of anti-TB and antiretroviral drugs in adults and children
- Quality check of anti-TB and antiretroviral drugs

Landmark Biochemical Studies

Analysis of anti-TB and antiret1oviral drugs in pharmaceutical preparations Deterioration of cycloserine in the tropics: During a therapeutic study of cycloserine-containing regimens at the centre, a major deficit in the stated content of cycloserine in tablets was detected. Detailed studies undertaken in the department suggested that high humidity, rather than high temperature, prevailing in the tropical regions is the main cause for deterioration. Laboratory experiments indicated that this could be prevented by storing the drug in tightly closed glass bottles at 18^{o}C. In

the absence of such facilities, if the drug has to be stored at ambient temperature and in humid conditions, the use of air-tight polyethylene bottles will serve to delay the deterioration.[64]

Inactivation of isoniazid by condensation in a syrup preparation: Gross and rapid condensation of isoniazid in commercial black-currant flavoured syrup was observed. *In vitro* studies showed that the condensation was due, at least partly, to the glucose, namely D (+)-glucose isonicotinyl hydrazone contained in the syrup. It was suggested that sugars such as glucose, fructose and sucrose should not be used in isoniazid syrup preparations, and that sorbitol, a stable non-carbonyl, might be a suitable substitute.[65]

Analysis of generic antiretroviral formulations manufactured in India: In the absence of data describing the integrity of generic antiretroviral drugs manufactured in India, studies were undertaken to analyze the drug content of certain antiretroviral drugs, alone and in combination, from three Indian sources and compared the values with proprietary medications manufactured in the United States. The study findings for the first time demonstrated that all the generic drugs from India compared well with those from the United States, and were within 5% range of the stated contents.[66]

Monitoring treatment adherence: Tuberculosis and HIV infections require treatment for long periods of time. Some of the controlled clinical trials use regimens that are administered unsupervised. This requires the need to check the regularity of drug intake. Tests for detection of anti-TB and antiretroviral drugs in urine are of great value in monitoring patients' adherence to self-administration of drugs. The department has reported several simple tests for detection of isoniazid, its primary metabolite, acetyl isoniazid, rifampicin, ethionamide, pyrazinamide and cycloserine in urine. Likewise urine tests to detect certain antiretroviral drugs, such as nevirapine and lamivudine by High Performance Liquid Chromatography (HPLC) were also standardized.[67-71]

Isoniazid acetylator phenotyping:

The department has developed several tests/methods to ascertain the isoniazid acetylator status. These tests are based on estimation of isoniazid and acetyl isoniazid in urine, blood or saliva after administration of a single dose of isoniazid. Use of saliva in determination of isoniazid acetylator status would be particularly useful in children and in individuals with renal impairment, where timed urine collections may not be possible. The department had carried out a series of studies to evaluate the impact of isoniazid acetylator status on response to treatment.[72-76]

Studies related to development of adverse reaction to anti-TB drugs

Peripheral neuropathy: This is a well known complication arising due to treatment with isoniazid containing regimens. It was shown that occurrence of peripheral neuropathy increases with isoniazid dosage and that the incidence is higher among slow than among rapid acetylators of isoniazid.

Arthralgia: Arthralgia during pyrazinamide therapy is a common adverse event and is probably due to hyperuricaemia caused by inhibition of urinary excretion of uric acid by pyrazinoic acid, the primary metabolite of pyrazinamide in man. It was observed that arthralgia was considerably less in patients who received rifampicin concomitantly. Studies were undertaken to investigate the effect of rifampicin on the pyrazinamide-induced changes in the renal elimination of uric acid. The findings demonstrated that rifampicin enhanced the renal excretion of uric acid and also that of pyrazinoic acid. This effect caused a decrease in the deposition of uric acid in joints, and consequently to a lower incidence of arthralgia.[77]

Hepatitis: This is a rare adverse reaction during treatment of TB with regimens containing isoniazid. The incidence of hepatitis was observed to be higher in those who received rifampicin in addition to isoniazid than in those who did not, and this

occurred more often in slow than in rapid acetylators of isoniazid. It was shown that this was due to increased formation of hydrazine, a known hepatotoxic agent in animals. The study findings further showed that the proportion of isoniazid metabolised through the direct pathway was higher when rifampicin (6%) was also given than when isoniazid alone (3%) was administered, and that the proportions were considerably less in rapid acetylators.[78]

Pharmacokinetic drug interaction studies

Effect of predinisolone and rifampicin in isoniazid metabolism:

Corticosteriods are known to affect the biodisposition of a number of drugs. The effect of prednisolone and rifampicin, alone and in combination on the blood and urine levels of isoniazid was studied.

The study findings demonstrated that prednisolone caused a significant decrease in the plasma isoniazid concentrations and enhanced renal clearance of isoniazid in slow and rapid acetylators. It also increased the rate of acetylation of isoniazid in slow acetylators only. However, it was observed that rifampicin largely counteracted the prednisolone effect of lowering plasma isoniazid concentrations in rapid acetylators only. This was due to the fact that rifampicin causes a more rapid metabolism of prednisolone leading to an abolition of prednisolone effect on plasma isoniazid concentrations in rapid acetylators.[79]

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) – rifampicin: The findings demonstrated that rifampicin caused a significant decrease in the pharmacokinetics of nevirapine, but not efavirenz. The decreased bioavailability of nevirapine could be overcome by increasing the dose of nevirapine.[80,81]

Absorption of anti-TB drugs in HIV & HIV-TB infected patients: Pharmacokinetic studies of rifampicin, isoniazid, ethambutol and pyrazinamide in HIV-infected patients with and without TB demonstrated significant malabsorption of these drugs. The

bioavailability of isoniazid was affected more in rapid acetylators. Decreased urinary levels of rifampicin and isoniazid in asymptomatic HIV-infected individuals with CD4 cells counts >350 cells/mm^3 was suggestive of malabsorption in this group.[82-84]

Pharmacokinetics of salivary isoniazid and rifampicin concentrations: Studies using salivary levels of isoniazid and rifampicin showed that diffusion of isoniazid into saliva was quite rapid and the salivary concentrations were similar to those in serum, suggesting that saliva could be used in place of serum for all pharmacokinetic studies with isoniazid. The salivary concentrations of rifampicin were much lower than those in serum, since a high percent of circulating rifampicin is bound to plasma proteins. Further, there was evidence of a significant delay in the diffusion of rifampicin from serum to saliva.[85]

Study of *CYP2B6* polymorphism (G516T) and *ABCB1* polymorphism (C3435T) in HIV-1-infected individuals from south India: The influence *CYP2B6* 516G>T and *ABCB1* 3435C>T gene polymorphisms on plasma efavirenz and nevirapine concentrations in HIV-infected patients in south India was studied. The study findings showed that frequency of *CYP2B6* 516G>T and *ABCB1* 3435C>T polymorphisms are high in the ethnic south Indian population. TT genotypes of the *CYP2B6* polymorphism have elevated plasma concentrations of efavirenz and nevirapine. With respect to *ABCB1* 3435C>T polymorphism, a trend in plasma efavirenz concentrations was observed; patients with the CC genotype having the highest values followed by CT and TT genotypes. These findings suggest that inter-individual variations in plasma concentrations of efavirenz and nevirapine could be due to genetic variations in the *CYP2B6* gene and to a lesser extent *ABCB1* gene.[86,87]

Plasma NNRTIs in HIV-infected children: The influence of age, sex, drug dose, nutritional status and *CYP2B6* G516T polymorphism on blood levels of nevirapine in children treated with generic antiretroviral drugs was studied. A combination of factors such as young age, *CYP2B6* GG/GT genotype and stunting could result in sub-therapeutic nevirapine levels in children. The study findings suggest that higher dose recommendations may be required for malnourished (stunted) children and those below three years of age.[88]

DEPARTMENT OF IMMUNOLOGY

Overview

The Department of Immunology focuses on the biological, immunological and molecular biological aspects of mycobacterial infections and helminthic diseases. The department is involved in studies on basic pathogenic mechanisms that may lead to better diagnostic tools and development of vaccines and other immune interventions for prevention and control of infection and disease. The department has adopted a multidisciplinary approach that includes immunology, molecular biology and epidemiology to study TB. Immunologic studies focus on genetic regulation of the immune response, the role of both HLA and non-HLA polymorphisms, and cellular immune responses in TB. Antigen purification and immunodiagnosis are other major areas. More recently, the department is using molecular epidemiology to study the impact of DOTS implementation in a rural area.

Research Focus

- Immunodiagnosis
- Molecular Biology of Mycobacteria
- Molecular Epidemiology
- Immunogenetics
- Cellular Immunology

Landmark immunological studies

Immunodiagnosis

Production of monoclonal antibodies for diagnosis of active TB: Ten monoclonal antibodies (TRC 1-10) against *M.tuberculosis* secreted culture filtrate antigens were raised in BALB/C mice. Employing TRC 8 in sandwich ELISA, *M.tuberculosis* antigen was detected in sera from pulmonary tuberculosis patients with 68% sensitivity and 85% specificity. TRC 8 was found to be useful in detecting antigens specifically in *M. tuberculosis* and *M. leprae* infected tissues, by immunoperoxidase staining and may prove useful in immunodiagnosis of TB.[89]

Purification and characterization of serodiagnostically important antigens: The following *M tuberculosis* protein antigens have been isolated and characterized

• Native 38kDa	secreted	species specific
• Native 16kDa	cytosolic	species specific
• Native 30kDa	secreted	early, immunodominant
• Recombinant 27kDa	cell wall	specific
• Recombinant CFP-10	secreted	species specific, RD1
• Recombinant ESAT-6	secreted	species specific, RD1

Serum antibody response (IgG, IgA and IgM) using ELISA was measured in adult TB, [90-92] childhood TB[93-95] and HIV-TB patients[96,97] and controls. While single antigens offered a sensitivity of 68-82% and specificity of >95%, combination of antigens offered better results.[98]

Circulating immune complexes: Since either antigen or antibody detection in isolation did not offer a test of high sensitivity and specificity, an alternative approach was taken to measure the circulating antigen-antibody immune complexes, which was better than serum results.[99-101]

Identification of novel human T-cell antigens of *M. tuberculosis* by immuno-proteomics: For the identification of the T-cell antigens, culture filtrate proteins of *M. tuberculosis* were resolved by using 2D-liquid phase electrophoresis (2D-LPE). Separated fractions were subjected to immunological analysis in healthy contacts

and TB patients. It was identified that 10 fractions were specifically recognized by contacts alone. Proteomic analysis revealed that 16 proteins were present in the 10 "contact specific" fractions. Thus, novel "Contact specific" T-cell antigens inducing IFN-γ have been identified.[102,103]

Innate immunity in HIV infection:

The aim of the study was to investigate the role of innate immune functions exhibited by NK cells, particularly when co-infected with TB. Downregulation of iNKRs, upregulation of activating NKRs and coreceptors indicate immunomodulatory effect on NK cell subsets from HIV-infected individuals. Co-stimulation with IL-15 + IL-12 may have potential to normalize NK cell functions in HIV infection but had limited effect in HIV-TB co-infection – probably due to the influence of TB.[104-107]

Cytotoxic cell response in *M. tuberculosis* infection: Proliferative and Interferon gamma (IFN-γ) responses to early secreted antigenic target-6 (ESAT-6) peptides were studied. Healthy household contacts (HHC) recognized Esp1 and Esp6 peptides. In culture filtrate protein-10 (CFP-10), the proliferative response and IFN-γ secretion was found for C-terminal peptides of the protein. Esp1, Esp6, Cfp7, Cfp8, and Cfp9 were the immunogenic peptides recognized by the alleles HLA DRB1*04 and HLA DRB1*10 among HHC.[108,109]

Cytotoxicity responses were studied for selective peptides in HHC and PTB groups. The results revealed that cytolytic molecule positive CD4+ and CD8+ T-cells were increased in HHC in response to Esp1, Esp6, Cfp8 and Cfp9 immunogenic peptides compared to PTB. Functional cytotoxicity results showed higher cytotoxicity to be exhibited by the peptide Esp6 than Cfp8 in the HHC.[110]

Monocyte chemoattractant protein-1 (MCP-1) positive monocytes increased in response to the peptides Esp1, Esp6, Cfp8, and Cfp9 in PTB.[111] These peptides deserve attention for inclusion in a vaccine against TB in our geographic region.

Role of Interferon gamma assay for latent TB in HIV infection: The sensitivities and specificities of Quantiferon Gold in-tube assay (QFT-IT), Interferon gamma inducing protein-10 (IP-10) assay and tuberculin skin test (TST) in detecting active TB cases were assessed in HIV sero-negative TB patients and healthy controls. QFT-IT, IP-10 and TST yielded the diagnostic sensitivities of 90.6%, 92.5% and 68.9%; and specificities of 55%, 48% and 75.5%, respectively. The combination of any of the two tests showed 98% sensitivity among smear negative cases. Thus the QFT-IT and IP-10 were highly sensitive in detecting active TB cases in our settings.[112]

The sensitivity of QFT-IT in active TB patients with HIV infection was compared with TST. QFT-IT was positive in 65%, negative in 18% and indeterminate in 17% of patients and was not affected by low CD4 count. TST yielded a sensitivity of 31%. All the TST positives were QFT-G positives. However, unlike TST, QFT-IT yielded fewer false negative results even in individuals with low CD4 count.[113] IP-10 detects a greater number of HIV–TB cases than IFN-γ and suggests that IP-10 may be a better alternative marker for latent TB infection diagnosis among immunocompromised individuals.[114]

In vitro response to *M. tuberculosis* ESAT-6 and CFP-10 peptides selected by computational analysis was measured. IFN-γ response to RD1 selected peptides was significantly higher in active TB patients than in HHC and community controls and was associated with active TB with a higher specificity than QFT-IT and TST.[115,116] Further, IFN-γ and IP-10 in response to ESAT-6 and CFP-10 peptides were assessed as biomarkers for monitoring TB treatment.[117]

Molecular Biology of Mycobacteria

Development of DNA probes for *M. tuberculosis:* A genomic library of *M. tuberculosis* was made and a clone which is specific for *M. tuberculosis* complex was selected. This clone was found to be an insertion like repeat element with seven inverted repeats and several direct repeats. The clone was sequenced and several sets of primers were designed. One set of primer amplified 173 base pairs and found to be useful in detecting *M. tuberculosis* from clinical specimens. This set of primers (TRC4) were evaluated with widely used IS 6110 primers in about 400 strains and found that TRC4 primers were more sensitive and also identified strains lacking IS 6110 copy.[118-121] This is patented with no. 235025.

Cloning and expression of *aceA* gene encoding isocitrate lyase from *M. tuberculosis:*

M.tuberculosis aceA gene encoding isocitrate lyase was cloned and confirmed by restriction mapping and sequencing. This *aceA* gene consists of 2300 nucleotides encoding a protein of 765 amino acids. Expression of the cloned gene was confirmed by enzymatic assay.[122]

Transcriptional analysis of inducible acetamidase gene of *M. smegmatis:* In the present study, the transcriptional start site of the inducible acetamidase gene of *M.smegmatis* was mapped and its regulation was studied.[123] The binding affinity of each operator with its cognate regulator was significantly different from the other. This observation supported not only the previous model of acetamidase gene regulation in *M. smegmatis* but also explains the role of these operators in controlling the expression of respective promoters under different growth conditions.[124]

Macrophage mycobacterium interaction: The ability of adenosine triphosphate (ATP) in reducing the intracellular viability of mycobacteria was tested. Infected

monocytes upon ATP treatment underwent cell death, but no loss in the intracellular viability of *M. tuberculosis* or *M. smegmatis* could be observed.[125] *In vitro* changes in the protein synthesis pattern in guineapig peritoneal macrophages following infection with virulent *M. tuberculosis* H37Rv were studied. A mycobacterial protein of molecular weight 17 kDa was expressed exclusively in the cytosolic fraction of *M. tuberculosis* infected guineapig macrophages *in vitro.*[126]

Recombinant BCG based HIV-1 epitope delivery system: The genetic engineering of *M. bovis*-bacillus Calmette-Guérin (BCG) to express foreign epitopes is an attractive strategy in the field of epitope vaccines. An 'epitope-trap vector' with *M. tuberculosis* chaperonin-10 as a carrier antigen was constructed and used to express the HIV-1 principal neutralizing determinant epitope. A new chaperonin-10 promoter that was hyper-expressive compared with the heat shock protein-65 promoter was identified. The rBCG group exhibited mild delayed-type hypersensitivity reaction and a high frequency of CD3+CD45RA low-activated T-cells, together with high titer of anti principal neutralizing determinant immunoglobulin G antibodies. Thus, this epitope delivery system induced strong epitope-specific Th-2 polarization.[127]

Serine/threonine protein kinases of *M. tuberculosis* H37Rv: Serine/threonine protein kinases form important components of signal transduction elements in mycobacteria and have been reported to play important roles in bacterial growth and/or virulence. The PknI gene (Rv2914c) was cloned, over-expressed and characterized as a fusion protein with an N-terminal histidine tag. Phosphoamino acid analysis showed that the proteins were found to be phosphorylated at the serine and threonine residues and not at tyrosine residues.[128,129]

Another serine/threonine protein kinase PknE was cloned, expressed, purified and characterized biochemically. The gene-disrupted mutant induced profound apoptosis, and impaired secretion of pro-inflammamtory cytokines. Thus PknE regulates the apoptosis to enable the survival of bacilli inside the host.[130] The knock out mutants of pknE, pknF and pknL were generated in *M.bovis* BCG and these mutants showed different growth profiles *in vitro* and in a macrophage model of infection.[131,132]

Heat shock promoters of mycobacteria: Heat shock promoters of mycobacteria are strong promoters which get rapidly upregulated during macrophage infection and thus serve as valuable candidates for expressing foreign antigens in recombinant BCG vaccine. *M. tuberculosis* groE promoter was characterized and found that it controlled expression of bicistronic groESL operon and showed differential regulation under stress conditions.[133]

Activation of mitogen activated protein (MAP) kinases by *M. tuberculosis* strains in monocytes/macrophages: The differential induction of the MAP kinases was observed in the human macrophages and THP-1 cell line upon challenge with a virulent clinical isolate and a low virulent strain of *M. tuberculosis*. It was shown that ERK1/2, p38 MAPK and NF-κB were involved in the signaling of IL-6 production during mycobacterial infection of monocytes. The activation kinetics of MEK1/2 by all the strains was different.[134]

Molecular epidemiology of mycobacteria: Large number of *M. tuberculosis* isolates of TB patients from south India showed either no copy or only a single copy of IS6110. This poses a limitation for DNA fingerprinting with an IS6110-based probe to determine the frequency of exogenous reinfection versus that of endogenous reactivation. In the present study, this limitation was overcome by using an alternate probe, the direct-repeat element. In India, a TB-endemic country, most recurrences after successful treatment were due to exogenous re-infection in HIV-infected and endogenous re-activation in HIV uninfected persons. Strategies for prevention and treatment of TB must take these findings into considerationsn.[135,136]

Intraspecies differentiation was studied on 68 *M. tuberculosis* strains obtained from 6 states of India by restriction fragment length polymorphism (RFLP) using a direct repeat probe (DR probe).[137] Most strains showed polymorphism, were more heterogeneous and were differentiated depending on their geographical origin by DR fingerprinting.

The DNA fingerprinting of *M. tuberculosis* strains was done in a rural community from high prevalence area in south India with an ongoing DOTS programme. IS6110 based RFLP showed high degree of discriminatory power among high copy number

strains. The combination of DR and PGRS probes differentiated 50% of the high percentage (41%) of IS6110 single copy isolates.[138] Large scale molecular epidemiological studies provide a better understanding of the dynamics of tuberculosis transmission between geographic regions and suggest rational measures to interrupt such transmission links.[139]

Results of spoligotyping of 1200 *M. tuberculosis* isolates from south India showed that the major clade belong to the Group IV of Baker's classification and is named East-African Indian Lineage which is close to the spoligo pattern of Manila isolates with the deletion at RD239. Genomic deletion analysis of these isolates revealed that 85.2% belonged to the ancestral lineage of *M. tuberculosis*. Additional six new genomic regions that were variably deleted were identified within this lineage. These findings emphasize the need to consider global strain variation during TB product development.[140]

Immunogenetic Studies

HLA and non-HLA gene polymorphism studies in TB: Host genetic factors such as Human Leucocyte Antigens (HLA) and non-HLA (other than HLA) genes that are associated with susceptibility or resistance to TB may serve as genetic markers to predetermine the development of tuberculosis. HLA studies in pulmonary TB revealed the association of HLA-DR2, specifically HLA- DRB1 *1501 and –DQ1 with susceptibility to pulmonary TB in south Indian population.[141,142] Several non-HLA gene polymorphisms such as Mannose Binding Lectin (MBL),[143] Vitamin D receptor (VDR), [144,145] Natural resistance associated macrophage protein-1 (NRAMP1), various Cytokines[146,147] and Toll like receptor[148] were studied and their association was observed in pulmonary TB.

Immunoregulatory role of HLA and non-HLA gene polymorphisms on immunity to TB: The regulatory role of HLA-DR antigens on tuberculin status,[149] antibody response[150] and lymphocyte response to *M.tuberculosis* antigens[151] and HLA-DRB1 alleles on intracellular perforin positive cells,[152] macrophage phagocytosis[153] and various cytokine responses to *M. tuberculosis* antigens[154] were studied in healthy controls and pulmonary TB patients. These studies suggested that HLA-DR

antigens and their genes/alleles regulate the innate and adaptive immune functions in tuberculosis.

Further studies revealed that vitamin D_3 enhances macrophage phagocytosis of *M.tuberculosis*,[155] suppresses cytokine responses[156] and increases the production of antimicrobial peptide cathelicidin in macrophages.[157] Though vitamin D deficiencies have been associated with development of TB, the study in south Indian population revealed no association with vitamin D deficiency.

Vitamin D receptor gene variants BB and tt and the extended genotype BBAAtt play a regulatory role on vitamin D modulated macrophage phagocytosis. [158] However, the suppressive effect of vitamin D3 on single cell expression of IFN-γ and TNF-α was not regulated by vitamin D receptor genotypes.[159]

HLA and non-HLA gene polymorphism studies in HIV and HIV-TB:

HLA study in south Indian HIV-1 and HIV-TB infected patients suggested that HLA-B40 and –DR2 were associated with susceptibility and HLA-A11 with resistance to HIV-1 and HIV-TB infection[160,161] and further studies on molecular sub-typing at the allelic level revealed that HLA -A* 1101 may be associated with resistance while HLA-B* 4006 might be associated with susceptibility to HIV and development of PTB in HIV patients.[162] Molecular sub typing of HLA -DR2 revealed the association of HLA -DRB1* 1501 with susceptibility to HIV and DRB1* 1502 with susceptibility to PTB in HIV patients. Further studies on HLA- DQ and -DP suggested that HLA–DQB1*050301 may be associated with susceptibility to HIV-1 infection and HLA–DPB1*1501 may be associated with resistance to TB in HIV infected patients.[163]

The studies on mannose binding lectin (MBL) gene polymorphism revealed that plasma MBL levels were significantly higher in HIV+TB+patients compared to HIV+TB- patients. High MBL levels and diplotypes associated with increased MBL levels might have a predisposing effect in the development of TB in HIV-infected

individuals and diplotypes associated with low MBL levels may be a risk factor for development of TB in HIV negative individuals.[164]

Vitamin D receptor (VDR) gene polymorphisms in the coding region (*Fok*I) and 3' untranslated (UTR) region (*Bsm*I, *Apa*I and *Taq*I) were studied. The results suggested that VDR gene 3'UTR haplotype bAT may be associated with protection against HIV infection while BAt haplotype may be associated with susceptibility to development of TB in HIV-1 infected patient.[165]

Dendritic-cell-specific intercellular adhesion molecule-3 (ICAM-3)-grabbing non integrin (DC-SIGN), a pattern recognition receptor, is exploited by HIV-1 and *M.tuberculosis* as a part of their immune evasion strategy. It was found that variants in the DC-SIGN encoding *CD209* gene were associated with susceptibility to or protection against HIV-1 infection and development of TB in HIV-1 infected patients.[166,167] All these studies suggest that genetic susceptibility or resistance to HIV and HIV-TB is polygenic.

Cellular immune responses in TB

Immune response in tuberculous pleuritis: TB pleuritis is the best model to understand the host immune response at the site of infection. In vitro studies on correlates of protective immune response showed a shift in immune response towards TH0/TH2 type with enhanced compartmentalization of Th1 T-cells at the site of infection.[168-170] Thus correlates of protective immune response in TP demonstrated differential T-helper cytokine response, suggestive of TH1 *in vivo* and TH0 *in vitro.* Further, TLR expression was also differentially modulated on the different subsets of T-cells depending on their activation status and cytokine expression. The down-regulation of TLR2 and -4 on the natural regulatory T-cells despite their higher number at the site of infection indicated a mechanism to maintain their suppressive activity.[171] A dual-signal hypothesis of cell proliferation and apoptosis was tested using mycobacterial antigens and was found to be operative in tuberculous pleuritis.[172]

Modulation of immune response and apoptosis by the prevalent clinical isolates of *M. tuberculosis* and its antigens:

The sonicate antigens from the most prevalent strains of *M. tuberculosis* harboring single copy of IS6110 showed differential protein expression on SDS-PAGE,[173] and had potential to induce T-cell activation in normal PPD positive population.[174] The antigen S7 modulated the immune response towards Th2 type by suppressing Th1 protective immune response in this population indicating its virulence associated immunosuppressive activity.[175] Further, apoptosis of human THP-1 monocytes by these antigens showed significant increase in necrotizing cells/ late apoptotic cells indicating its role in cytotoxicity.[176] A correlation between phagocytosis and apoptosis in infected THP-1 cells 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.[177]

The role of B7 class of co-stimulatory molecules in CD95-mediated Th1 apoptosis during tuberculous infection and its effect on disease susceptibility was studied. The findings indicated that T-cell apoptosis is perhaps a host regulatory mechanism to limit inflammation, rather than a pathogen-induced immune deviation.[178]

Role of chemokines and chemokine receptors in TB: Initial studies on expression profiles of chemokines and its receptors on the immune cells obtained from tuberculous pleuritis patients established their role in driving activated and memory T-cells to the site of infection and their involvement in immune response polarization.[179] In PTB, the results showed a balanced chemokine and cytokine relationship at the periphery which may aid in amplified effector immune cell

trafficking and retarded monocyte migration through differential chemokine receptor expression.[180] A significant increase of CXC chemokine (IP-10) in pleural fluid (PF) of TP patients prompted to evaluate its diagnostic utility**.** The better sensitivity and equal specificity of IP-10 assay compared with IFN-γ suggest that IP-10 is a potential diagnostic marker for evaluating TP.[181]

Innate immunity in TB: A study on phenotypic modulation in *M. tuberculosis* infected neutrophil during TB demonstrated that clinical isolates were able to inhibit the early activation of Neutrophils and thin out the killing mechanisms for their own survival.[182] Further studies on dendritic cells (DC) showed retarded migration of *M. tuberculosis* infected dendritic cells suggesting its cell trafficking ability may be a potent mechanism used by *M.Tb* to paralyze the early immune response of the host.[183] Infection with prevalent clinical strains of *M. tuberculosis* showed differential maturation of DC depending upon their virulence.[184] The function of monocyte derived dendritic cells in pulmonary TB showed the interference of monocyte differentiation into fully and competent DC suggesting an evasion mechanism of *M. tuberculosis* that could contribute to its intracellular persistence by avoiding immune recognition.[185] Thus *M.tuberculosis* clinical strains hamper the maturation and migration of DC as a strategy to survive by evading the effective immune response of the host.

IS6110 based molecular typing (RFLP): It was used for Mtb strain characterization, studying relapses vs reinfection, mixed infection, Transmission Dynamics and genetic evolution of these strains. The results showed high percentage (40%) of IS6110 single copy strains of *M. tuberculosis* in south India.[186] This highly cited (98) observation made an impact by showing the limitations of IS6110 based fingerprinting and its diagnostic potential in endemic country like India. First time, it was shown that relapses in TB in south India were by both endogenous reactivation and exogenous reinfection. An evidence of co-infection with two or three different strains of *M. tuberculosis* was established.[187] Phylogenetic analyses indicated that IS6110 single copy genotypes were closely related and might have evolved or propagated from the common ancestor.[188]

DEPARTMENT OF PATHOLOGY

Overview

The research activity of this Department is mainly concerned with understanding the pathogenetic mechanisms underlying tuberculosis. Clinical material obtained from tuberculous lesions of the lymph node and skin and tissue from an animal model using the guinea pig have been the main sources of study towards this goal. A model for understanding the fibrotic processes following TB was developed earlier. In addition, the use of third generation staining techniques using enzyme immuno-histochemistry to delineate more than 20 host and bacterial products on about 5000 samples has provided valuable insights into some of the pathogenetic mechanisms. These include a) defining the parameters for detecting *M.tuberculosis* antigen(s) in tissue, b) identifying some of the humoral immune mechanisms in the causation of necrosis in TB and c) describing for the first time, a three week reaction and some of its cellular and molecular correlates elicited by purified protein derivative.

Research Focus

- Complement system in *M. tuberculosis*
- Immunomodulatory effect of immune complexes

Landmark Pathological Studies

Protective efficacy of DNA vaccines in guinea pig TB: Development of recombinant BCG (rBCG) over-expressing promising immunodominant antigens of *M. tuberculosis* represents one of the potential approaches for the development of vaccines against TB. The protective efficacy of three candidate DNA vaccines was evaluated and the candidate vaccine expressing the superoxide dismutase (SOD)

antigen was found to be the most efficient. The DNA vaccine expressing $\alpha 1$ crystallin ranked second exhibiting a 0.5 log reduction in lung CFU. The results clearly indicate the superiority of α-crystallin based R/D regimen over BCG.[189] For the first time, ESAT-6 based recombinant BCG (rBCG) and DNA vaccine (DNAE6) was used in a prime boost approach. Interestingly, in spite of inducing an enhanced antigen specific IFN-gamma response in mice, a DNAE6 booster completely obliterated the protection imparted by rBCG against TB in guinea pigs. Analysis of immunopathology and cytokine responses suggests involvement of an exaggerated immunity behind the lack of protection imparted by this regimen.[190] The enduring protection observed with rBCG85C over BCG gives enough reason to postulate that if an open-ended study is carried out with low dose of infection, rBCG85C vaccine in all likelihood would show enhanced survival of guinea pigs.[191]

Cutaneous TB: Fibrosis is one of the major causes of post-treatment morbidity in tuberculosis. The tissue levels of collagen, elastin, fibronectin, transforming growth factor-beta (TGF-beta) and zinc in active and healed lesions of cutaneous TB were measured. Effective antituberculous chemotherapy led to a substantial reduction of fibrosis and the consequent disability that can arise in patients with TB. Clinical findings were adequate to identify major forms of cutaneous TB as evidenced by bacteriological and histopathological examination. A daily regimen of rifampicin and isoniazid for 9 months was effective in treating cutaneous tuberculosis.[192,193]

Role of complement activation and antibody in the early interaction between *M. tuberculosis* and macrophages: The complement system, which represents a chief component of innate immunity not only participates in inflammation but also act to enhance adaptive immune response. The present study suggested that complement mediated solubilization was less in patients with TB, and this defective solubilization was likely to take part in a vicious cycle involving immune complex deposition and complement activation and, thus, may lead to disease progression depending on the nature of the defect.[194]

Further studies suggested that the presence of HH genotype was high in pulmonary TB patients and the reduced complement receptor 1 in patients may be an acquired phenomenon related to disease pathogenesis.[195]

DEPARTMENT OF STATISTICS

Overview

The Statistics department plays a key role in the planning, design, conduct, analysis and interpretation of controlled clinical trials and related laboratory studies undertaken by the Centre. Randomization techniques are made use of in allocating patients to various regimens prescribed and also in constructing different groups of patients. The department assists in evolving an all-inclusive protocol of various investigations and procedures for the successful conduct of controlled clinical trials both during treatment and follow up. Large scale data on various clinical and laboratory investigations are organized after systematic scrutiny for accuracy of information and one to one identification with the subject concerned and comprehensive documentation on planned formats like analysis and treatment cards. The department organizes drug assays to keep a systematic watch on the quality of drugs supplied by the pharmaceuticals. Quality control systems for drugs used in studies and monitoring of laboratory standards are also taken care of routinely by the department. The department also plays a vital role in database management of the studies undertaken in the Centre. Monitoring of laboratory standards through quality control techniques is another highlight of this department.

Research Focus

- Basic and applied statistical methodologies
- Survival analysis, non linear regressions
- Risk analysis, artificial neural networks
- HIV/AIDS projections

Landmark studies in Biostatistics

Statistical modeling of HIV/AIDS epidemic

The important approaches for modelling the spread of HIV/AIDS are deterministic, stochastic, state space and statistical models. The back calculation method reconstructs the post pattern of HIV infection and predicts the future number of AIDS cases with the present infection status. In order to quantify the effects of incorrect specification of incubation period distributions on the back- calculation estimates, seven most commonly used models, namely gamma, log logistic, log-normal, generalised exponential, generalised log-logistic, generalised gamma, mixed Weibull and two newly proposed models, namely change point model and immune invasion model, were fitted to 5000 observations simulated from Weibull model. The simulations and comparisons were done using SAS software. Parameter estimates of alternative models when the true, underlying incubation period distribution is Weibull were studied. The results indicated that log- logistic and root exponential models gave expected AIDS cases significantly different from the simulated results. The minimum size of the epidemic, estimated by exponential and double exponential methods, was high compared to other curves. Logistic incidence, exponential and double exponential gave consistent estimates for projection of AIDS. Assuming a median of 10 years for data generated, the changes in the incubation period were very much affected by the minimum size of the epidemic. The coefficient of variation was in the order of 18% under the true model accounting for variations in the incubation period were also varied. The simulation study further revealed that the infection density had to be chosen judiciously. The same pattern of uncertainty is reflected for median incubation period with 15 years.

HIV/AIDS estimates for India: Back calculation estimates were obtained using the conditional likelihood approach for the multinomial distribution with unknown sample size. Non-linear optimisation routines were used for maximisation of the conditional likelihood. The estimates of the minimum number of AIDS case, HIV incidence and short-term projection were obtained. The important findings are: (i) Projected AIDS cases do not vary much across various infection densities and incubation period distributions, (ii) minimum size of the epidemic and HIV incidence vary across the infection densities and incubation distributions, (iii) projected AIDS cases using the log-logistic and root exponential infection densities are less as compared to the

others. The projected models- based median AIDS cases in India for the years 2003, 2004, 2005 and 2006 are around 27,000, 44,000, 70,000 and 114,000 respectively. The projections were very much lower than the projections given by national and international agencies using the comprehensive methodologies.

Stochastic models for seroconversion times of HIV transmission

This study focuses on the study of a Stochastic Model for predicting the seroconversion time of HIV transmission. As the immune capacities of an individual vary and also have its own resistance, the antigenic diversity threshold is different for different person. We propose a stochastic model to study the damage process acting on the immune system that is non- linear. The mean of seroconversion time of HIV and its variance are derived. A numerical example is given to illustrate the seroconversion times of HIV transmission. The simulation results indicate that the estimated median seroconversion time is about 3.8 months. It varies according to the number of contacts and antigenic threshold.

Mixed effects modelling of high dimensional clinical trial data using Markov Chain Monte Carlo method

Markov Chain Monte Carlo (MCMC) is a powerful technique for performing integration by simulation. In recent years MCMC has revolutionized the application of Bayesian statistics. Many high dimensional complex models, which were formally intractable, can now be handled routinely. MCMC has also been used in specialized non-Bayesian problems. The application of MCMC with a mixed model to data obtained from patients with Pott's paraplegia was illustrated. A total of 32 measurements on each patient up to 24 months were considered.

A sample of 100 points were drawn at random from the distribution and used as a starting point for the expectation conditional maximization (ECE) algorithm to search for modes as given by Gelman and Rubin. The posterior distribution was approximated by a multivariate distribution centered at the major mode of ECM with covariance matrix as the inverse of negative of the second derivative matrix of the log posterior density. Another 1000 independent samples were drawn and importance resample subset of 10 was used as a starting point for independent Gibbs samplers. After 100 iterations, the potential scale reduction factors were approximately 1 for all parameters in the model. The other hyper parameters were

also estimated. The MCMC methods provide a powerful statistical tool and have revolutionized statistical inference specifically Bayesian inference over the past few years. The ability to fit complicated models with little programming effort is in fact a key advantage of MCMC methods. The MCMC simulation should be undertaken after the problem has been approximated and explore using simple methods.

Artificial neural network model for predicting TB

Prediction models to identify patients with active TB using common symptoms are lacking. It was aimed to build a neural network model for early prediction of pulmonary TB. A total of 451 (195 culture positive, 256 culture negative) patients' data screened to the clinical trials of the Centre from January, 2006 to March, 2007 were considered for the artificial neural network (ANN) model. A prediction accuracy of exact 91% was achieved. A root mean square error of 9% and a correlation of 0.97 were achieved between the predicated and observed results. The ANN can help physicians in faster and efficient decision making in identifying TB patients based on the presented clinical symptoms. Fuzziness added to the input, further increases the accuracy of prediction. Further work is continuing to improve the performance of the model using other feature extraction techniques and to improve accuracy.

Modelling the spatial variogram of TB for Chennai ward in India

In this study, statistical measures and spatial deviational ellipse were used to determine the spatial pattern of TB within a Chennai ward population to gain insight into the disease spread. Variogram is used to describe the spatial dependence of TB in Chennai wards and it is compared with theoretical variogram model of spherical, Gaussian and exponential fitted to TB data. Arc View GIS 9.2 and SAS software were used for spatial analysis of TB spread. Data were obtained from District Hospital records for Chennai wards. The results of the spatial pattern revealed that the spread of TB in Chennai wards have been diverse, with many wards having a low rate of infection and the epidemic being most extreme in slum areas. Variogram increases with distance at small distances and then level off which implies spatial dependence exists between small distances of TB cases. Spherical model fits data better. Spatial analysis is proved to be more useful for studying spread of TB analysis and modelling of disease analysis.

ICMR-BIOMEDICAL INFORMATICS CENTRE

Overview

The Biomedical Informatics Centre (BIC) was established at TRC as an initiative of ICMR in January, 2007. The Centre is involved in research on three aspects of TB – identification of drug targets towards drug discovery, identification of biologically derived diagnostics and vaccines for tuberculosis, and development of database with biomedical relevance. There are eight systems, a server and a laptop, and software for sequence analysis, molecular modeling and docking.

Research Focus

- Identification of drug targets
- Identification of biologically derived diagnostics and vaccine
- Development of database

Landmark studies in Biomedical Informatics

DDTRP: Database for drug targets of resistant pathogens: Many athogens have developed resistance to most of the existing antibiotics. Multi-drug resistant and extensively drug resistant strains are extremely difficult to reat, emphasizing the urgent need for novel drugs. We developed a databasecalled ‘Database of Drug targets for Resistant Pathogens’ (DDTRP) which would serve as a useful resource for research in drug discovery for pathogens with emerging resistance. The database contains information on currently available drugs with reported resistance, their respective targets, metabolic pathways involving these targets, and a list of potential alternate targets for a set of organisms, *viz. Mycobacterium tuberculosis, M. leprae, Plasmodium falciparum, P.vivax, Staphylococcus aureus, Streptococcus*

pneumoniae and *Neisseria gonorrhea*. The database can be accessed freely at http://bmi.icmr.org.in/DDTRP.

***M. tuberculosis* structural database:** A database called '*M.tuberculosis* structural database' (*Mtb*SD) has been developed to serve as a resource database for 3D structures of *M. tuberculosis* proteins. MtbSD currently contains 857 three dimensional structures for 328 *mycobacterial* proteins; the structures are grouped based on coding genes, bound ligands and domain structure. The database also provides information on similarity between the bound and cognate ligands. The structural homologues for each protein structure within the genome of *M tuberculosis* are listed. This information would enable researchers to explore whether an existing or newly identified inhibitor would bind to proteins other than the drug target. The database will be of profound use for molecular modeling, docking and structure based drug designing, and can be accessed at http://bmi.icmr.org.in/ *mtbsd*.

Identification of inhibitors for pantothenate synthetase of *M. tuberculosis:*

Virtual screening plays an important role in identifying lead compound for drug discovery. Many proteins have been identified as potential drug targets for tuberculosis. We prioritized the potential targets and undertook virtual screening of highly potent targets in order to identify potential lead molecules. Pantothenate is a metabolic by product in plants and micro organisms, but not in humans. Thus, pantothenate biosynthesis pathway could serve as a potential target for *M. tuberculosis*. Pantothenate synthetase (PS), one of the enzymes in this pathway, is thought to be important for latency and virulence of *M. tuberculosis*. Added to this, the absence of an equivalent enzyme in humans makes it an attractive drug target for *M. tuberculosis*. We used *in silico* methods to identify potential inhibitors for *M. tuberculosis* PS. Two hundred and twenty eight molecules were selected from PubChem based on specific criteria and docked with PS using CDOCKER. Using scoring function PLP1 the docked compounds were ranked. A total of 37 molecules scored a higher ranked than the positive controls (known substrates and reported inhibitors). The highly ranked molecules were energy minimized. Further studies are on going towards identifying a lead compound to inhibit PS of *M. tuberculosis*.

In silico* screening for small molecules against 3-oxoacyl-[acyl-carrier-protein] synthase II of *M. tuberculosis: This study was carried out to find new inhibitors for 3-oxoacyl-[acyl-carrier-protein] synthase (FabH), which links the type I and type II FAS pathways of *M. tuberculosis*. Two hundred and two molecules were taken from different databases as well as designed analogs of a reported inhibitor were docked to FabH. Highly ranked molecules based on multiple scoring functions with a greater potential to inhibit FabH have been identified. Further *in vitro* testing of these molecules will help us to find novel drug for TB.

In silico* identification of potential antigenic proteins in *M. tuberculosis: Cellular immune responses help to control *M. tuberculosis* infection. We hypothesized that protein of *M. tuberculosis* (MTB) that do not have homologs in humans as well as human gut flora, would mount a good antigenic response in man. We employed a bioinformatics approach to identify MTB antigens capable of inducing a cell-mediated immune response. In the first step we identified 624 MTB proteins to have no homologs in humans. Comparison of this set of proteins with the proteome of 77 different microbes that comprise the human gut flora narrowed down the list to 180 proteins unique to MTB. Further analysis of the 180 unique proteins revealed that a large number of these proteins belonged to the PE and PPE family. Fifty one of these proteins have been reported by other investigators as well, pointing to their significance. Hence, their potential as vaccine candidates and/or diagnostic markers should be further explored.

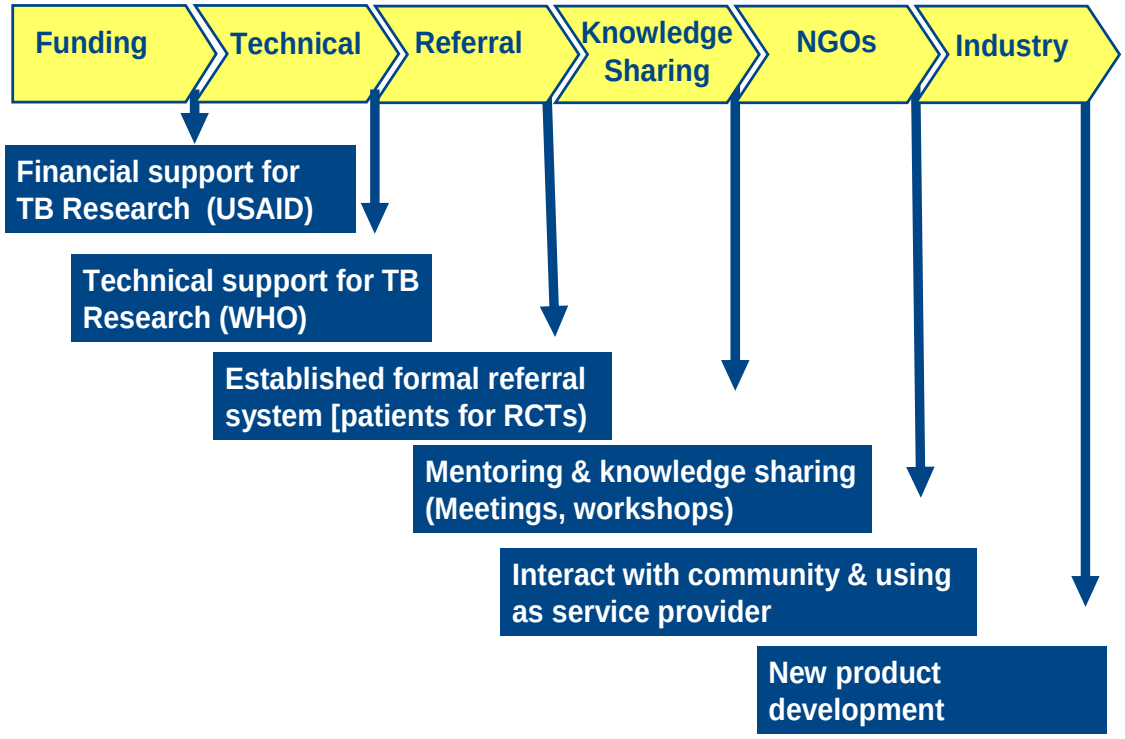
Structural comparison of fold usage in *M. tuberculosis* proteins: Advancement in technology has helped us to solve structures of several *M. tuberculosis* proteins and aided in studying fold and active site similarity between MTB proteins. In this study, we analyzed the structural similarity within the proteome of *M. tuberculosis*. From a practical perspective, identification of structural homologues within the genome will play a role in directing the identification of appropriate drug targets without any off-targets, designing of small molecules/inhibitors, prediction of cross reactivity, etc.

Ligand induced conformational changes in protein structures of *M.tuberculosis:*

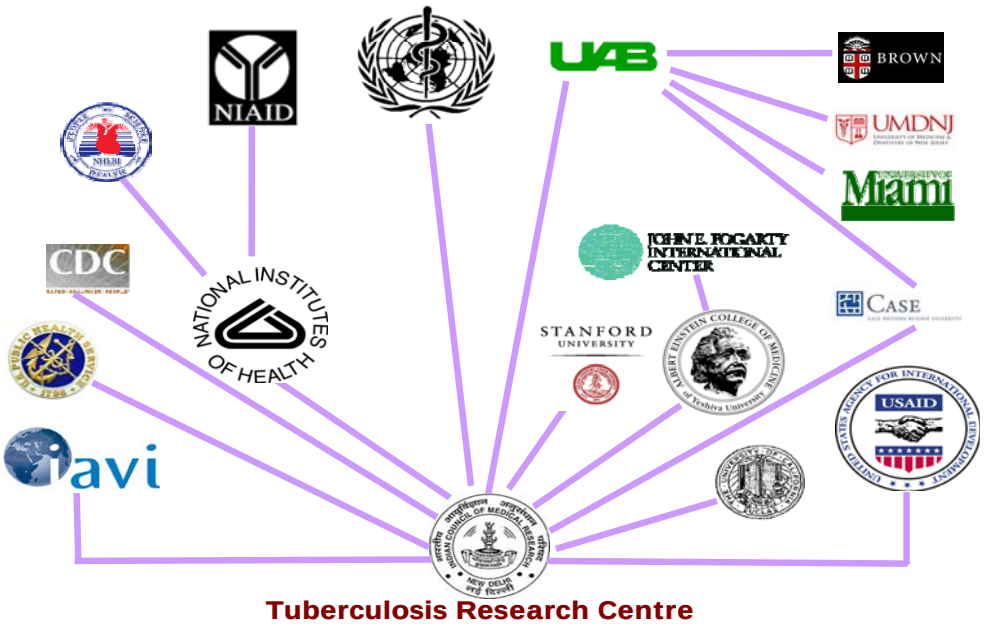
Currently there are 828 crystal structures available for 323 proteins of *Mycobacterium tuberculosis* solved in different experimental conditions. About 683 protein structures are in complex with ligands. The present study aims to analyze the level of conformational changes in protein structures due to their binding to cognate ligands. Understanding the conformational changes among different structures available for candidate genes will aid in selecting the ideal template for mutational studies, docking and structure-based drug designing.

PARTNERSHIP IN RESEARCH

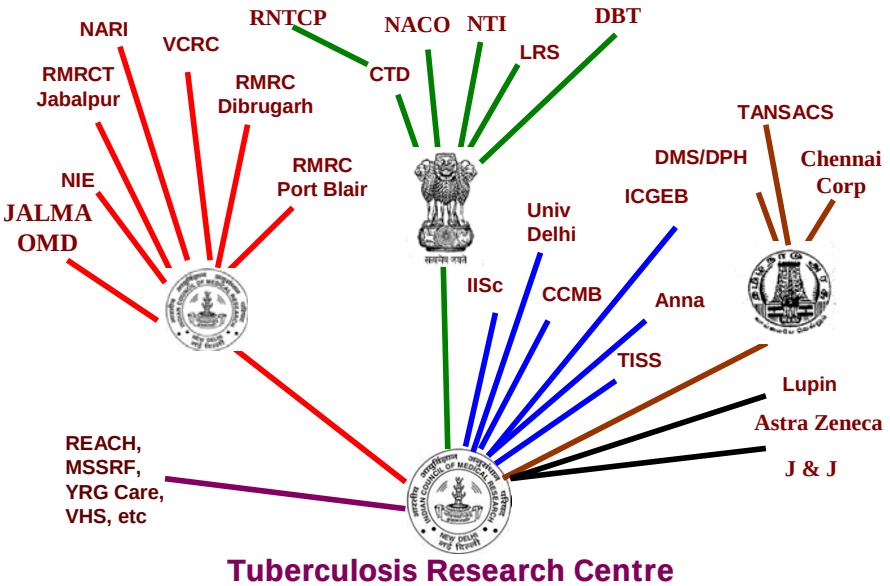
Type of partners



OUR INTERNATIONAL PARTNERS



OUR NATIONAL PARTNERS



Rewards of partnership

How the programme and partners benefited

- Programme restructured
- Capacity building
- Module development
- Extensive geographical coverage
- External quality assurance
- Training for research methodology for RCTs & OR
- Strengthening laboratories of other ICMR institutes

How TRC benefited

- Establishing methodology for RCTs
  WHO, BMRC, ICMR, Govt. TN & USPHS
- Methodology for Epidemiological Surveillance
  WHO, CDC, ICMR, Govt. TN & USPHS
- Upgradation of Laboratories
  British ODA, WHO, USAID & NIH
- Vaccine trial for HIV
  IAVI, YRG Care, NARI, NACO
- Model DOTS Project
  USAID & WHO
- Capacity building and Technology transfer through exchange programmes
  WHO, British ODA, NIH, USAID, Fogarty

INTERNATIONAL CENTRE FOR EXCELLENCE IN RESEARCH (ICER)

Overview

The goal of the ICER program is to develop a sustained research program in areas of high infectious disease burden through partnerships with scientists and physicians in the developing countries like Mali, Uganda, and India. The research was focused on major endemic diseases such as malaria, HIV, filarial infections and TB. As the main focus of the ICER program is on research, both basic and clinically-relevant, a great effort was placed on establishing clinical research protocols and making inroads into the understanding of the pathogenesis of lymphatic filariasis, HIV and TB.

Because training was always an integral part of the ICER concept, there were a large number of on-the-ground training forums as well as short term training opportunities for collaborating members of the TRC staff. Three to six month laboratory based collaborative research was undertaken by a number of staff and students at the TRC that included work on multicolor flow cytometry in HIV, pharmacokinetics, human genetics of extrapulmonary TB, proteomics of mycobacteria, pulmonary immunology, advanced clinical microbiology in HIV, and mycobacterial genetics.

The backbone or the DIR/ICER program and a longstanding collaboration between the Laboratory of Parasitic Diseases (LPD) and the TRC yielded outstanding results not only in clinical trials but also in the basic research in Helminth Immunology.

Lymphatic Filariasis: Lymphatic filariasis can be associated with development of serious pathology in the form of lymphedema, hydrocele, and elephantiasis in a subset of infected patients. We have shown that the development of lymphatic pathology is associated with increased Th1/Th17 responses and decreased regulatory T-cells as well as regulation of Toll and Nod-like receptors in pathogenesis of filarial lymphedema.[196] In addition, chemokine receptor expression

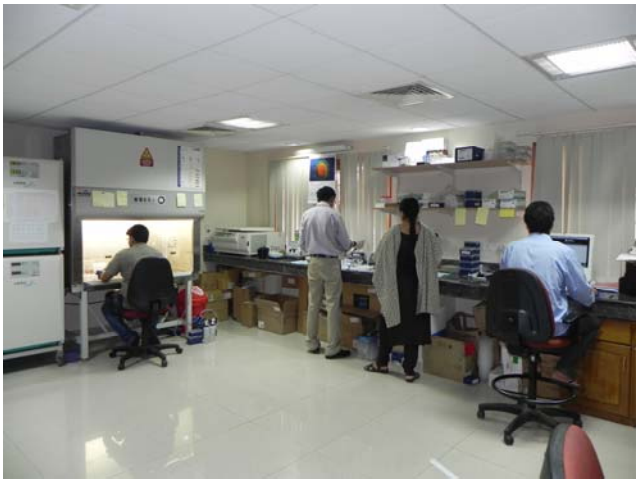
is significantly altered in lymphatic pathology, implicating a novel role for chemokine receptors in the development of pathology.[197] On the other hand, chronic, asymptomatic filarial infection is associated with a variety of immunregulatory mechanisms. First, monocytes/macrophages from filaria-infected individuals exhibit an alternatively activated phenotype compared to uninfected individuals and this phenotype is linked to the upregulation of Arginase-1.[198] Second, filarial infection is associated with downmodulation of Toll-like receptors on both APCs and T cells and this downmodulation is associated with impaired Th1 cytokine responses.[199,200] Third, the impaired Th1 responses were also shown to be associated with decreased expression of T-bet, SOCS-1, SOCS-5, and SOCS-7 and increased expression of SOCS-3 in T-cells were observed in patent lymphatic filariasis.[201] Finally, live parasites were shown to induce regulatory networks characterized by upregulation of IL-10, TGF-beta, CTLA-4 and PD-1 and these networks dampen both Th1 and Th2 immune responses.[202]

Helminth/TB co-infection studies:

M. tuberculosis and filarial coinfection is highly prevalent, and the presence of a tissue-invasive helminth may modulate the predominant type 1 T-helper response needed to control *M. tuberculosis* infection. It was observed that coincident filarial infection exerted a profound inhibitory effect on protective mycobacteria-specific Th1 and Th17 responses in latent tuberculosis, suggesting a mechanism by which concomitant filarial (and other systemic helminth) infections predispose to the development of active TB in humans.[203] The presence of filarial infections may regulate the Toll-like receptor (TLR)-dependent immune response needed to control *M. tuberculosis* infection. It was observed that coincident filarial infection exerted a profound inhibitory effect on protective mycobacteria-specific TLR-mediated immune responses in latent TB.[204] The factors governing latency in TB are not well understood but appear to involve both the pathogen and the host. In this study, tuberculin skin test positivity was used as a tool to study cytokine responses in latent TB. It was observed that tuberculin skin test positivity was characterized by increased activity of regulatory T-cells and a coincident down-regulation of the Th17 response.[205]

Helminth/ Diabetes co-infection studies:

Epidemiological studies have shown an inverse correlation between the incidence of lymphatic filariasis and the incidence of allergies and autoimmunity. However, the interrelationship between lymphatic filariasis and type-2 diabetes is not known and hence, a cross-sectional study to assess the baseline prevalence and the correlates of sero-positivity of lymphatic filariasis among diabetic subjects was carried out.



Although a direct causal link has yet to be shown, there appeared to be a striking inverse relationship between the prevalence of lymphatic filariasis and diabetes, which was reflected by a diminished pro-inflammatory cytokine response in Asian Indians with diabetes and concomitant lymphatic filariasis.[206] A cross-sectional study was undertaken in southern India to assess the baseline prevalence of seropositivity of lymphatic filariasis among persons with T1DM and there appeared to be a striking inverse relationship between the prevalence of lymphatic filariasis and T1DM in southern India.[207]

MODEL DOTS PROJECT (MDP)

Overview

Directly Observed Therapy-Short course (DOTS) is universally accepted as the treatment strategy for TB control in both developing and developed countries. DOTS strategy makes it possible to carry out case finding, chemotherapy and patient monitoring effectively without hospital care. Government of India is implementing this strategy in the Revised National Tuberculosis Control Programme (RNTCP) in a phased manner since 1993. However, there has been no information available so far on the epidemiological impact of this strategy on the TB problem in a community. To understand this, the Tuberculosis Research Centre undertook a project in collaboration with the Government of Tamil Nadu to establish Model DOTS center for DOTS implementation, Tuberculosis control, training and research. It was proposed to measure the epidemiological impact of this strategy in this community over a period of at least 10 years. The project was undertaken with the technical support from WHO and financial support from USAID.

Objectives of the project

1. Establish a Centre for DOTS demonstration and training for DOTS implementation in a population of approximately 580,000 in Tiruvallur district in Tamil Nadu, India.
2. Strengthen the infrastructure at state level, particularly in the districts surrounding the project area.
3. Assess epidemiological impact of DOTS using ARTI (tuberculin surveys), Disease surveys, RFLP and Drug resistance surveys.
4. Conduct operational research on key aspects of the DOTS strategy.

Project area: Five Panchayat unions in Tiruvallur District covering a population of 5, 80,000 were selected for Model DOTS project. This is the same area where the famous “Chingleput BCG Study” was conducted. The area has been under observation for a long period of time, hence the epidemiological impact of DOTS programme can effectively be measured here.

DOTS demonstration and training: Medical and paramedical trainees from Tamil Nadu and other states in India, and trainees from abroad were taken regularly to the area for field level training in RNTCP. In addition, medical officers, laboratory personnel from DPR Korea, Myanmar, Bangladesh of the SEAR, WHO and East Timor have been trained. More than 5000 trainees at different levels have undergone training.

State strengthening: Tuberculosis Research Centre has been providing all assistance as required by the state level officers for TB Control activities like training of the trainers, STS, STLS and Laboratory technicians from various districts in Tamil Nadu. Multi-drug resistant TB patients identified from the project area were referred to TRC for further management.

Epidemiological impact study: To assess the epidemiological impact of DOTS implementation, repeated resurveys were carried out to estimate the prevalence of TB disease and the tuberculin survey to estimate the prevalence of infection in the project area. A random sample of panchayats/urban units (where baseline survey was completed) was included for the resurveys.

Operational Research: The operational research findings were disseminated in national and international peer-reviewed journals. A total of **115 manuscripts** have been published so far and 9 more have been accepted for publication. This not only resulted in increased access of these findings to a wider audience but also brought about capacity building for TRC staff and considerably increased the visibility of the institution.

The key achievements of this project are listed in the following table:

Key operational research topics
Improving administrative commitment
Evaluation of the epidemiological impact of DOTS[208]
Evaluation of the socio-economic impact of DOTS[209]
Estimating the burden of TB in India for the year 2000[210]
Improving case detection
Comparison of ≥ 2 weeks vs ≥ 3 weeks cough to improve the yield of smear-positive cases among outpatients[211]
Examination of the role of repeat sputum smear microscopy after a course of antibiotics[212]
Feasibility and effectiveness of involving private sector in DOTS[213]
Improving sputum microscopy
Evaluation of PhAS sedimentation method[214]
Adequacy of 0.3% carbol fuchsin for ZN staining[215]
Comparison of 2 vs 3 smears for diagnosis[216]
Improving treatment observation and outcomes
Effectiveness of different types of DOT providers[217]
Evaluation of the risk factors for poor treatment outcomes[218]
Retrospective analysis of data from clinical trials to provide evidence for giving 3 months IP to patients with 2+ or 3+ smear positivity and 2 months IP patients with scanty or 1+ smear
Examination of the co-relation between duration of treatment and treatment outcome to define an optimal maximum cut-off period for completing treatment
Epidemiological and programme monitoring
Drug resistance monitoring[219,220]
External quality assurance for sputum microscopy[221]
Re-staining of sputum smears for LQAS[222]
Storing of heat fixed smears for panel testing[223]
Estimation of annual risk of TB infection[224]
Anonymous unlinked HIV testing among TB patients[225]
Examination of possible TB transmission using molecular epidemiology studies[226]

INTERNATIONAL AIDS VACCINE INITIATIVE

Phase-I Preventive HIV Vaccine Trial

In view of the existing burden of HIV infection with its medical, social and economic dimensions, it was decided that efforts should be undertaken to test a vaccine against HIV as per the joint declaration by the National AIDS Control Organization (NACO), ICMR and the International AIDS Vaccine Initiative. For this purpose, a phase I trial of a multigenic vaccine against HIV-1 subtype C using Modified Vaccinia Ankara as the vector was initiated to determine the safety and tolerability of three injections of the vaccine or placebo in two dose levels and also to determine the immunogenicity of this vaccine. Mandatory approvals from the ethical committees, Drugs Controller General of India, Genetic Engineering Approval Committee and the health ministry's screening committee were obtained. Community advocacy activities for recruitment of volunteers were initiated thereafter in collaboration with YRG Care Centre. A total of 32 volunteers were enrolled in two groups and followed up for a total of 18 months. The administration of 3 injections of MVA-TBC-M4 vaccine to healthy volunteers at two dose levels appeared to be safe.

The results of the first phase I HIV vaccine trial using a multigenic MVA vaccine conducted at this centre indicated that while this was safe and effective in inducing immune response in all the vaccine recipients, the persistence and the magnitude of the response should be improved before moving this vaccine further in human trials[227,228]. Therefore, it was decided to use this in a prime-boost regimen involving a DNA vaccine (ADVAX) to prime and the MVA vaccine to boost. This part of the study has been completed, and data are being analysed.

FACILITIES

The Tuberculosis Research Center is one of the premier medical institutions in India and is a National laboratory of the Indian Council of Medical Research. The centre has a record of high-quality research in TB and International collaborations. Apart from performing critical research, TRC provides clinical care to several thousand adult TB patients including those with HIV co-infection.

The patient care facility with over 15,000 square feet caters to the needs of patients with TB and HIV/AIDS. Separate counseling areas, treatment area, and emergency room have been designed in addition to doctors' rooms. The clinical facilities are myriad, and most of the staff members have had experience in participating in large clinical trials. The centre runs sub-centres at several Government hospitals in and around Chennai including Kilpauk Medical College and Hospital, Chennai and Government Rajaji Hospital, Madurai. In-patient facilities are available in certain Govt. hospitals and have been allotted beds to house patients as part of clinical trials. The clinical division has facilities for radiological investigations required to support the clinical studies. An image archiving system has been established that allows efficient storage and retrieval of radiological data. The HIV/AIDS division has facilities to perform viral load measurements, antiretroviral drug resistance testing and ELISPOT asays.

The clinical activities of the Tuberculosis Research Centre are ably supported by well equipped Bacteriology, Biochemistry, Immunology and Clinical Pathology laboratories. The Bacteriology laboratory is the reference centre for South-East Asia for mycobacteriology. Facilities are available for rapid species identification of *M. tuberculosis*, atypical mycobacteria, drug susceptibility testing and drug resistance surveillance studies. It has recently established Biosafety lab with BSLIII and BACTEC MGIT960 facilities. Automated analyzers are used to carry out biochemical and hematology tests. The Clinical pharmacology laboratory has facilities to undertake estimation of anti-TB and antiretroviral drugs by HPLC and LCMS. Pharmacokinetic studies in adult and pediatric populations are been conducted.

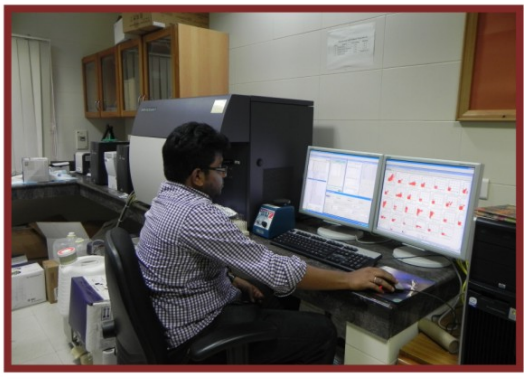
Immunology laboratories are equipped to conduct enzyme, radio-labeled assays, cellular immunological studies, hybridoma studies and flow cytometry. Molecular biological facilities allow gene cloning, expression and DNA sequencing. A confocal microscopy facility supplements the activities of the Clinical Pathology division. The Statistics department assists in evolving research protocols of various investigations and procedures for the successful conduct of controlled clinical trials and for several laboratory studies. The centre has a network of PC workstations and serves connected by LAN and supported by internet connectivity using a 1 Mbps dedicated leased line. All clinical, epidemiological and laboratory data are computerized using both commercial and in house developed software.

The training facilities at the centre include a 100 seat auditorium, a large conference hall and three smaller conference rooms. All the training and conference rooms are air-conditioned and equipped with audiovisual aids such as LCD projectors, slide and overhead projectors and sound system. A state-of-the-art “Waste water treatment plant” has been installed.

Digital X-ray

Auto analyser

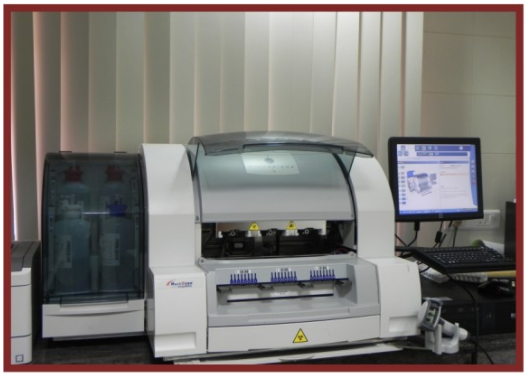
FACS Calibur



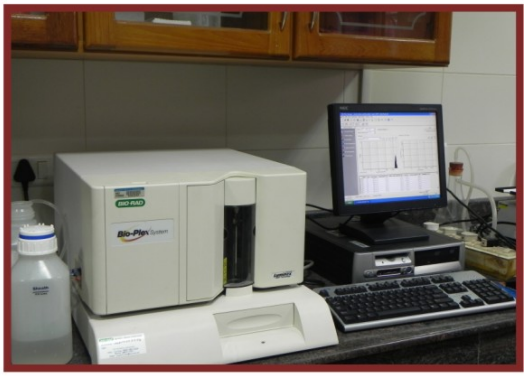
FACS Canto-II

LC MS

MALDI TOF TOF

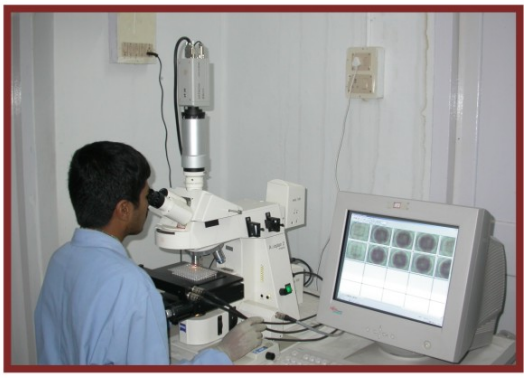


AUTOMATED DNA EXTRACTOR



LUMINEX

CONFOCAL MICROSCOPE



ELISPOT READER

WASTE WATER TREATMENT PLANT

LIBRARY & INFORMATION DIVISION

The Library & Information Division of the Centre has a fairly large collection of books and scientific journals on different aspects of TB and other related subjects. Books are classified according to the Dewey Decimal Classification Scheme (DDC). The library caters to the needs of the scientific community in and around Chennai.

The Library services were expanded with a number of value added services such as Medline, NUCSSI, UCCDH and an in–house fortnightly publication, namely, “TB ALERT”, which comprises of recent articles related to TB published in journals subscribed by TRC. A database of TRC Publications (TRCPUB) and a bibliographic database on Tuberculosis are being maintained. Library is having dial-up Internet connectivity with VSNL, where the Library acts as a Central Node for Electronic Mail co-ordination agency for all the staff of the Centre. There are plans of procuring a CD TOWER to offer the MEDLINE: CDROM search facility throughout the LAN to the staff of the centre.

Utilizing the local area network facilities and the extensive computerization of the Centre, this unit is attempting to convert to a digital library. As a first step, journal subscriptions are being converted to on-line subscriptions. All the reprints of the centre have been converted into PDF documents for easy maintenance and to decrease storage space. The centre hosts a web site that provides information not only about the activities of the centre but also is a repository of information on various aspects of the TB control programme in India and other parts of the world. This web site has been rated as the internet resource for TB in South East Asia.

ELECTRONIC DATA PROCESSING DIVISION

In 1970, Tuberculosis Prevention Trial (TBPT), at Madras saw the birth of the IBM 1401-H computer system for doing data processing work for the BCG trial. Twelve years later when the TBPT was merged with TRC, it was decided to replace the IBM 1401-H computer system with new computer to manage against an increasing amount of data and analyses. In 1984, TRC had purchased a micro computer called "Aurolec data processing system" and carried out analyses work. Later, in 1986, a VAX-11/750 computer system with 8 terminals was installed. The system was working up to 1999 and became obsolete.

In 2000, the LAN system funded by USAID through WHO/ICMR was installed. This LAN is being used for data management systems pertaining to the MODEL DOTS PROJECT undertaken by TRC. This has created facilities for researchers, students and trainees to communicate within and outside TRC.

Major Activities

The Electronic Data Processing (EDP) division provides computerized services for all departments in the TRC, which have direct access to the data with the personal computers. The EDP division is continuing to give data management support including data entry/verification to various studies undertaken in the Centre. Also, this division generates reports and prepares pre-printed forms for field activity of epidemiological studies and supply data tabulations for monitoring the studies and publication of research work. All break-down calls of computers and its peripherals are dealt with under comprehensive annual maintenance contract. This includes managing the installation of the facilities and ensuring that the computers are maintained and kept up to-date.

Data Entry and management are important functions of this unit. A software called 'Data Star' (DOS version) is used for data entry and data verification. The data entered by one operator is verified by another operator. The department also receives all documents and laboratory results through the Statistical department for data management.

Major Studies Supported

The EDP department has supported several epidemiological studies, namely, BCG trial (1968-1986) and BCG prophylaxis in Leprosy (1973–1986) in Chingleput district, DOTS - Disease prevalence survey (1999-2008) and Prevalence of TB infection surveys (1999-2008) in Tiruvallur district, Mortality surveys (2005-2007) in Andhra and Orissa states, and Operational research studies (2002-2005) in rural (Tiruvallur) and urban (Chennai city) areas to evaluate the DOTS strategy. The department has brought several research papers (1972-2011).

FUTURE DIRECTIONS

The road ahead.....

There is no reason why so many should die of TB or live with the disease when we know the blue print of the bacterium; diagnosis, in the majority of cases, is relatively easy and cheap; an array of powerful drugs are available to ensure cure, if properly used; and control programmes are in place since decades.

TB control programmes need better diagnostic tools to help detect the disease early and determine its spread in the community. They need better drugs to combat resistance and the "double-trouble" associated with HIV-TB in addition to shorter treatment regimens to ensure better compliance. A replacement for the BCG vaccine that offers unquestionable protection will be helpful. Finally they need practical solutions for the multitude of problems that crop up in field operations.

No control programme needs this as urgently as India's RNTCP. Not only is it the world's most rapidly growing TB control programme, but also the most ambitious. In addition are added concerns such as the large numbers of patients to be identified and treated, capacity building and establishment of effective monitoring and surveillance networks. All of these require effective and sustainable strategies that can only come from research.

Tuberculosis Research Centre has a unique role to play in contributing to TB research. A quarter of a century ago it was a centre for controlled clinical and field trials in tuberculosis. Today, we have consolidated our position as one of the world leaders in the chemotherapy of TB. It is in the forefront of training and dissemination of information relevant to control programmes. TRC has the unique advantage of housing basic scientists working closely with clinicians and field workers, who ultimately apply the basic research findings to control TB in the community.

We continued to build on our strengths by undertaking controlled clinical trials to explore shorter treatment regimens. We addressed key questions in the epidemiology of TB, such as assessing the annual risk of infection and the epidemiological impact of directly observed treatment, short course (DOTS).

Additionally, we took on newer responsibilities in operational research and capacity building for the TB control programme. We rapidly expanded our portfolio to establish ourselves as a significant player in molecular epidemiology, genomics and socio-economic aspects of TB research. The centre continued its effort to focus on research in evaluating the diagnostic criteria and developing strategies for the prevention and treatment of TB in HIV infected persons. We redesigned the way we build partnerships at all levels to promote development of new diagnostics, drugs and vaccines. Our model for private practitioner participation in TB control developed with ACT (Advocacy for Control of Tuberculosis) is one such example.

Tuberculosis remains neglected by policy makers, health administrators and the community. We changed the way we communicate with the TB and non-TB communities. To enhance advocacy, we disseminated several key messages about the disease, the diagnostic and chemotherapy tools available and effective ways of using them. Control programmes and health administrators, who were quick to recognise the value of TRC's endorsement of their campaigns, routinely seek our support. We have facilitated links between public health, operational research and clinical care using our web site.

However, it is not enough to rest on past successes. We recognise that our continued success is far from guaranteed unless we use newly available opportunities to build a holistic approach towards TB research. We are conscious that TB control and research are inextricably linked and research should feed the needs of control programmes. While we need to identify chinks in *M. tuberculosis'* armour to design better drugs and vaccines, we also need operational research to transfer the technology from the laboratory to the field.

Recognising the current needs of TB research and reminding ourselves of our goal of reducing morbidity and mortality due to TB, we have successfully reoriented our institute to address key issues related to health policy, systems and services research. The next steps for TRC should be to continue exploring gaps in current knowledge for TB control, to excel in Laboratory based and operational research and to disseminate its findings to programme managers and policy makers. Through this we believe that TRC will effectively shift the focus of TB research in India.

Development of strategic plans for effective utilisation of funds, identifying time defined deliverables and building sustainable partnerships will be the backbone of the centre's approach towards achievement of this goal.

Overall, TRC has made a significant impact. All medical research should have as its ultimate goal disease control, and it cannot be justified unless the new knowledge and technology are disseminated and utilized. In this sense, the TRC has excelled; its effects have been greatest in the fields where it matters most — public health, epidemiology and research methodology.

But we cannot stop with our past or current achievements, no matter how impressive. Much work remains ahead of us in TB control. This can be achieved only by forging partnerships locally, nationally and globally – an approach the TRC has consistently advocated.

TRC will continue to provide new knowledge and tools that are worthy of our status as a flagship institute of the Indian Council of Medical Research.

Moments of Pride ….

Awards and Achievements

1. Dr.R. Prabhakar - Recipient of the Dr.P.V. Benjamin Memorial Gold Medal Oration Award at the 13th Andhra Pradesh State Tuberculosis and Chest Diseases Workers' Conference, Kakinada, 5th and 6th October, 1986 and delivered an oration on "Laboratory aspects in TB – an overview".

2. Dr. Padma Ramachandran - Awarded the "R.C. Garg Memorial Award", for the best article published in 1986 in the Indian Journal of Tuberculosis for the paper entitled "Three chemotherapy studies of tuberculous meningitis in children".

3. Dr.T. Santha Devi - Awarded the "Dr.R. Krishna Memorial Award" for the best paper presented at the 41st National Conference on Tuberculosis and Chest Diseases held at Hyderabad in October, 1986 for the paper entitled "Short Course Chemotherapy under District Tuberculosis Programme".

4. Dr.R. Prabhakar - Nominated to deliver the Wander-TAI Oration on "Laboratory Diagnosis of Tuberculosis – an Overview" at the 41st National Conference on Tuberculosis and Chest Diseases held at Hyderabad in October, 1986.

5. Dr.R. Prabhakar - Nominated to deliver the P.C.I. Oration on "Short course chemotherapy for TB – rationale and application in the control programme" at the 7th National Conference on Respiratory Diseases held at Calcutta in December, 1987.

6. Dr.V.K. Vijayan - Awarded the 'Saroj-Jyothi Award' (2nd prize) for the best paper presented at the 7th National Conference on Respiratory Diseases held at Calcutta in December, 1987 for the paper entitled, 'Bronchoalveolar lavage in pulmonary tuberculosis'.

7. Dr.V.K. Vijayan - Awarded the Fellowship of the Indian College of Allergy and Applied Immunology, V.P. Chest Institute, New Delhi.

8. Dr. Rani Balasubramanian - Awarded the 'R.C. Garg Memorial Award" for the best article published in 1987 in the Indian Journal of Tuberculosis for the paper entitled "Kanamycin plus rifampicin plus ehtambutol in the re-treatment of patients with tubercle bacilli resistant to isoniazid and streptomycin".

9. Dr. Rajeswari Ramachandran - Awarded the Dr.R. Krishna Memorial Award" for the best paper presented at the 43rd National Conference on TB and Chest Diseases held at Calcutta in December 1988 for the paper entitled "Short course chemotherapy in the treatment of Pott's paraplegia".

10. Dr.R. Prabhakar - Elected as a Fellow of the International Academy of Chest Physicians and Surgeons of the American College of Chest Physicians.

11. Dr.R. Prabhakar - Awarded the Dr.N.L. Bordia gold medal by the Madhya Pradesh Anti TB Association.

12. Dr.V.K. Vijayan - Awarded the 'Prof.B.K. Aikat Oration Award' of the ICMR for research in Tropical Diseases for the year 1991.

13. Dr. Manjula Datta - Awarded the "Dr.R. Krishna Memorial Award" for the best paper presented at the 45th National Conference on Tuberculosis and Chest Diseases held in Rohtak in January 1991, entitled "Compliance and quiescence in smear positive pulmonary TB under programme conditions".

14. Dr. Prema Gurumurthy - Awarded the "R.C. Garg Memorial Award" for the best article published in 1990 in the Indian Journal of Tuberculosis, for the paper entitled "Gastro-intestinal absorption of isoniazid and rifampicin in patients with intestinal tuberculosis".

15. Dr.P.R. Narayanan – Visiting scientist in the Laboratory of Prof. Barry R. Bloom, Dept. of Immunology and Microbiology, Albert Einstein College of Medicine, Bronx. New York.

16. Dr.V.K. Vijayan - Awarded membership of the National Academy of Medical Sciences (India) in recognition of significant contribution for the advancement of medical sciences.

17. Dr.C.N. Paramasivan - Awarded the University of Madras / Tamil Nadu Tuberculosis Association Endowment Lectureship in medicine for the year 1991- 92.

18. Dr.R. Prabhakar - Awarded the “Dr. Subramaniam Suresh Memorial Oration Award” for contribution to AIDS and Tuberculosis at Madras Medical College, Madras, during November, 1993.

19. Dr.R. Prabhakar - Awarded the “Dr. Raman Viswanathan Oration Award” by the National College of Chest Physicians, during August, 1993.

20. Dr.R. Prabhakar - Awarded the “Dr. Rathnavel Subramaniam Endowment Oration” on visceral Leishmaniasis at Madras, during 1992.

21. Dr.C.N. Paramasivan - Awarded the “Dr.P.V. Benjamin Oration Award” by the Andhra Pradesh TB & Chest Diseases Society, Kurnool, for the year 1993.

22. Dr.V.K. Vijayan - Received the “Prof.B.K. Aikat Oration Award” for research in Tropical Diseases for the year 1991, in Award Function, ICMR Headquarters, New Delhi, July, 1993.

23. Dr.V.K. Vijayan - Awarded an International Governorship for India by the International Academy of Chest Physicians and Surgeons of the American College of Chest Physicians, USA for the term 1993-96.

24. Dr.V. Kumaraswami - Awarded the “Dr.M.O.T. Iyenger Memorial Award” for contributions to chemotherapy and immunology of lymphatic filariasis for the year 1992.

25. Dr. Rema Mathew - Awarded the “Dr.R. Krishna Memorial Award” for the best paper presented at the 47th National Conference on Tuberculosis and Chest Diseases held in Bombay in November 1992, entitled “Response of patients with initially drug-resistant organisms to treatment with short course chemotherapy”.

26. Dr.V.K. Vijayan - Awarded the “Calicut Medical College Alumini Oration Award”, Calicut for the year 1994.

27. Mrs. Sara Mathew - Awarded gold medal for the best paper presented at the 13th National Congress on Respiratory Diseases held at Madras, during 1994, entitled “Use of vancomycin in selective Kirchner’s liquid medium for culture of tubercle bacilli”.

28. Dr.P. Venkatesan - Awarded the “Dr.R.N. Srivastav Award” for the best paper presented by a Scientist <45 years of age at the 12th Conference of the Indian Society for Medical Statistics held at Wardha in September, 1994, entitled “Analysis of clinical trial data beyond the analysis of variance”

29. Dr.V.K. Vijayan - Awarded the “Prof.K.C. Mohanty Award” by the Tuberculosis Association of India, New Delhi, for the year 1995.

30. Dr.V.K. Vijayan - Awarded the Fellowship of the Indian College of Cardiology.

31. Mrs. Sara Mathew - Awarded the “Dr.R. Krishna memorial cash prize” for the best paper entitled “A direct rifampicin susceptibility test for tubercle bacilli”, presented at the 49th National Conference on Tuberculosis and Chest Diseases held at JIPMER, Pondicherry, during 1994.

32. Dr.V.K. Vijayan - Awarded the Amrut-Mody Unichem Prize in Chest Diseases by ICMR.

33. Dr. Geetha Ramachandran - Awarded “cash prize” for the best paper entitled “Pharmacokinetics of rifampicin, ethambutol, isoniazid and pyrazinamide following administration of the drugs individually or in different combinations in healthy volunteers” at the National Congress on Diseases of the Chest, organized by the American College of Chest Physicians, south India Chapter, Chennai, during February, 1997.

34. Dr.P. Selvaraj - Second Best Poster award for the paper entitled, “Vitamin D receptor gene polymorphisms (BsmI, ApaI and FokI) in pulmonary tuberculosis” at the XXIX Annual meeting of the Indian Immunology Society & Symposium on Immunoparasitology, Regional Medical Research Centre (ICMR), Bhubaneswar, 27-29 November 2002.

35. Ms. Cheruvu Mani - Second Best Poster award for the paper entitled “Rapid identification of multi-drug resistant tuberculosis” at the National level conference on “50 years of DNA” held at Ethiraj College for Women, Chennai, February, 2003.

36. Dr. Ranjani Ramachandran – Awarded “Prof.K.C.Mohanty award” for the best paper entitled `Mycobacteremia in TB patients with HIV infection” that was presented at the 57th National Conference on Tuberculosis and Chest Diseases held at Goa during October, 2003.

37. Ms. Radha Gopalswami – Bagged the best poster award for the paper titled “Cloning, Expression and Characterization of Serine theronine kinase *pkn*l of *M.tuberculosis*” at the 30th Annual Conference of Indian Immunology Society held at Sanjay Gandhi Postgraduate Institute of Medical Science, Lucknow during November, 2003.

38. Dr. Geetha Ramachandran – Won “Dr.C.Srinivasa Rao award” for the best paper on TB for the year 2003 for the paper titled "Vitamin A levels in sputum positive pulmonary TB patients in comparison with household contacts and healthy normals" presented at the 58th National Conference on Tuberculosis and Chest Diseases held at Mumbai during January, 2004.

39. Dr.S. Ramesh Kumar – Bagged the second prize for the best poster presentation on the paper titled "Impact of HIV infection on chest radiographic findings in patients with pulmonary tuberculosis” presented at the National Conference on Management of HIV/AIDS in Resource Restricted Settings at Mumbai during February, 2004.

40. Dr.M.S. Jawahar - Received “RC Garg Memorial award” for the best article published in the Indian Journal of Tuberculosis in 2002 at the 58th National Conference on Tuberculosis and Chest Diseases, Mumbai, Maharashtra, January, 2004.

41. Dr. Ranjani Ramachandran – Received “Prof. KC Mohanty award” for the best paper publication in Indian Journal of Tuberculosis “Mycobacteremia in a HIV infected TB patient” during 2004.

42. Dr.S. Anitha – Received “Prof.R.N. Srivastava award” for young scientists at XXII ISMS conference, JIPMER, Pondicherry - January, 2005.

43. Dr.T. Santha – Received “RC Garg Memorial award” for the best article titled “Is it worth treating Category failure patients with Category II regimen?” published in Indian Journal of Tuberculosis for the year 2005:

44. Mr.P.G. Gopi – Received the “Prof. KC Mohanty award” for the best paper entitled “A new measurable indicator for TB case detection in Revised National TB control programme” presented at the 60th National Conference on Tuberculosis and Chest Diseases held at Lucknow in February, 2006.

45. Dr.P. Venkatesan - Elected as “Fellow of Indian Society for Medical Statistics - FSMS” and the Award was given in November, 2006.

46. Dr.V. Chandrasekaran – Received “Prof. BG Prasad award” for the best paper published on Statistics in the field of Epidemiology in the journal ‘Statistics in Medicine’ for the year 2005 at the Annual Conference of the Indian Society for Medical Statistics held at Belgaum during December, 2006.

47. Dr.N. Selvakumar – Received the “Lifetime Achievement award” for promoting knowledge and research in Applied Microbiology by the Indian Association of Applied Microbiology at Kancheepuram during January, 2007.

48. Ms. Shenbagavalli – Received the “Prakash Award” for the best poster presentation at the 4th Convention of Society for Immunology and Immunopathology (SIIP) and National Symposium on immuno-biotechnology held at Chennai during February, 2007.

49. Dr.N. Selvakumar – Received 1st prize for poster presentation titled “Pot staining of sputum samples for the detection of AFB” during the NATCON 2007 held at Tuberculosis Association of India, New Delhi during September, 2008.

50. Dr. Vanaja Kumar - Received “Life Time Achievement award” from Indian Association of Applied Microbiology at SRM University, Chennai during December, 2009.

51. Dr. N. S. Gomathi – Received the 'Dr. R. Krishna Memorial award" for best paper presented in the 64th National Conference on TB and Chest Diseases, 2009.

52. Mr. V. N. Azger Dusthackeer – Received the 'Dr. Srinivasa Rao Memorial award' for best paper by young scientist presented in the 64th National Conference on TB and Chest Diseases, 2009.

53. Dr. N. S. Gomathi - Awarded the best poster presentation in the 65th National Conference on TB and Chest Diseases

54. Dr. N. Selvakumar - Conferred the 'P. K. Sen Oration award and Gold Medal' by Tuberculosis Association of India in the 65th National Conference on TB and Chest Diseases, 2010.

Patents Filed:

1. 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/137A April 2009).
2. 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)
3. 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).
4. Dr. Vanaja Kumar – Patent applied for "New anti-tuberculous antibiotic from marine actinomycete strain R2" – (P&I / IPR/TRC/ 184/ June16, 2010)

Accreditation:

1. HIV/AIDS Laboratory was accredited by the World Health Organization asa National Reference Laboratory for HIV Drug Resistance Genotyping.

Climbing to greater heights

List of candidates who were awarded Ph.D degree

Part-time

Alamelu K
Anitha S
Beena E. Samuel
Chandrasekaran K
Chandrasekaran V
Daniel Herbert
Geetha Ramachandran
Geetha Ramani Shanmugam
Gomathi M
Gomathi NS
Gopi PG
Hemanth Kumar AK
Jayasankar K
Kannapiran M
Kubendiran G
Kumaraswami V
Kuppu Rao KV
Luke Elizabeth Hanna
Mohanarani Suhadev
Muniyandi M
Ponnuraja C
Prabakaran L
Pravin N Bhat
Prema Gurumurthy
Rajeswari NS
Rajiswamy
Ramakrishnan
Selvaraj R
Subash Chandra Bose
Sulochana Somasundaram
Sujatha Narayanan
Thilakavathi Subramaniam
Vanamala CR
Vasan SK
Venkatesan P
Vijayan VK

Full-time

Alagarasu K
Anbarasu D
Aparna Rao
Aravindhan V
Arvindh Pradheep S
Basirudeen S
Chandra G
Cheruvu Mani
Daisy Vanitha
Deepak Jayakumar
Harini Laxminarayan
Kamala T
Kamalakannan V
Kanakalata
Kaustuv Nayak
Lakshmi S
Madhan Kumar M
Manivannan S
Narayana Rao V
Natarajan PL
Nirmala Raman
Nisha Rajeswari D
Nusrath Unnissa
Prabha C
Prabhu Anand S
Priya R
Radha G
Raghavan S
Raghu B
Rajashree P
Ramalingam B
Ramana Rao PV
Sahadevan R
Selvakumar S
Senthil Kumar KS
Shakila H
Shenbagavalli G
Sivadasan K
Sunil Mathan Kurian
Supriya P
Uma Devi KR
Uma H
Venkataprasad
Vidya Rani M
Vijayalakshmi P
Vishwanath V

External candidates

1. Dharuman C
2. Govindarajan R
3. Nandakumar C
4. Porchelvan S
5. Rajasekaran S
6. Ravanan R
7. Sarala Rajajee
8. Sattanathan R
9. Selvaraj V
10. Srimathi S
11. Sumathy M
12. Suresh ML
13. Suresh ML
14. Vallinayagam V
15. Vijayalatha

MERITORIOUS ACHIEVEMENT

AWARD OF D.Sc. DEGREE

Dr. V K Vijayan – The Tamil Nadu Dr. MGR Medical University, Chennai

Dr. C N Paramasivan – University of Madras, Chennai

Staff who served the centre

Abdhul Khudoos
Abdul Rahman
Achamma D
Acharyulau GS
Adikesavan V
Adimulam R.
Adiseshan V
Alamelu Narayanan
Alexander C
Ambujam Ganesh
Ananthakaranth N
Anjanappa S
Annamalai Baskaran
Annamma Joy
Annamony Palos
Ansar RS
Anthony AN
Anugraha Raj JD
Appe gowda BN
Arjunan S
Arokiasamy P
Arputhamary C
Aruldoss D
Arumaikkannu
Arumugam G
Arunachalam CJ
Aseervatham D
Ayyappan S
Babu K
Baghavandoss R
Balakrishnan D
Balambal R
Balamma
Balaraman E
Balarishna Rao
Beela Mohan
Belliappa KP
Benjamin I
Beulah Jasmine
Bhimarao KR
Boopathy S
Catherine Bosco
Chandra Immanuel
Chandrahas RK
Chandramohan R
Chandramouli G
Chandran D.
Chandrasekar P
Chinnaiah
Chirstopher
Cletus AJ
Dakshayani Govindan
Dakshinamurthy D
Dakshinamurthy M
Damodaran V
Deva doss P
Devaraj D
Dhanaraj MR
Dhanasekaran H
Diwakara AM
Duraipandian M
Ekambari P
Ellamanda P
Elumalai V
Emily Johnson
Emily Varghese
Erudayanathan A
Eswar Rao Ingale
Ethiraj V
Eusuff SI
Fathima Rahman
Fredrick KG
Gajavalli G
Gajendran P
Ganapathy A
Ganesan N
Geetharamani Shanmugam
Gejji SR
George C
George M
George T
Gopal C
Gopal Jetty K
Gopalakrishnan S
Gopalan BN
Gopi PG
Gopilingam KN
Gopinath B
Govindan M
Govindaraj MS
Govindarajulu K
Guruvaiah B
Hemavathy G
Herold Arthur Cuffry
Ibrahim A
Ilampuranan KJ
Imamsahib S
Jacob K
Jagadeesan B

Jagannatha Rao KJ
Jagannathan P
Janakiraman S
Janardhana Rao H
Janardhanam B
Jayaganga Babu R
Jaya Gopinath S
Jayalakshmi Monga
Jayarajan K
Jayaraman N
Jayaraman C
Jebamallie Valentine
Jemima Shiela Fredrick
Jesudass Jayaraj G
John Jayaraj M
Joseph N
Kailasam S
Kalavathi Chari PN
Kalimuthu K
Kalyanam S
Kamala D
Kamala R
Kamalanabhan MR
Kannapiran M
Karthikesan VS
Karunakaran K
Kathiravel K
Kembu S
Kesavalu B
Khadar Nawaz Khan
Kirupashankar AS
Kondamma
Kothandapani G
Krishnamacharya L
Krishnamurthi J
Krishnamurthy MS
Krishnamurthy V
Krishnamurthy PV
Krishnamurthy R
Krishnan S
Krishnan Nambiar
Kubendiran G
Kumaran S
Kumaraswami V
Kunhiraman K
Kunjamma PS
Kuppu Rao KV
Kursheed Ara Begum
Lakshmana Rao S
Lakshmanan V
Lakshmi Sambandam
Lakshminarayanan AR
Lakshminarayanan V
Lalitha Hari
Lalitha Victor
Leelavathy Aaron
Loganathan GK
Madhavan KRS
Madhavan PB
Magthalin P
Manickraju MR
Manjula Datta
Mano Pushparaj
Manonmany Nathan
Mari P
Marimuthu M
Marimuthu M
Masilamani
Mathibusanam TV
Mayurnath S
Md. Amanullah Khan
Meenakshi K
Meenakshi Gandhi
Meenakshi V
Meenalochani Dilip
Meera Sahib
Megavarnam P
Mirunalini R
Mohan CV
Mohan M
Mohd. Bakir K
Money E
Munichandraiah P
Munusamy E
Munusamy S
Murthy PN
Muthulakshmi P
Nabi Sahib S
Nagabhusana Rao RS
Nagamony K
Nagarajan M
Nagarathinam P
Nageswara Rao K
Nalini Sundar Mohan
Nandan R.
Narasamma Y.
Narasimhan A
Narayana ASL
Narayanan P
Narayanan KD
Narayanan PR
Narayanaswamy N
Naseema M
Natarajan J
Natarajan NS
Nimbalkar PR
Nithyanandam G
Packirisamy V

Padma S
Padma Balasubramaniam
Padma Prakash
Padma Ramachandran
Padma S Rajan
Padmanabhan M
Padmavathy K
Pakirisamy C
Pandurangan V
Paramasivan CN
Parandaman KV
Parasuraman RK
Parthasarathy R
Parthasarathy M
Parvathi Raghavan
Paul TN
Pauline Joseph
Paulraj I
Penchilamma N
Penchillayya TK
Peter P
Phaniraj BS
Philbert
Philipose P
Porgis Maria Helan
Prabhakar R
Prabhakar G
Prabhakaran I
Prakash Kumar Ch P
Prasada Rao A
Pratap Singh
Prema Gurumurthy
Radhakrishnan S
Radhakrishnan S
Radhamani MP
Radhakrishna B
Raghupathy Sarma
Raghuraman N
Rajamanohari Dason
Rajappa D
Rajarathinam KA
Rajasekara Sastry CT
Rajasekara R
Rajeswari
Rajeswari Ramachandran
Raji Swamy
Rajkumar S
Ramachandra
Ramachandran G
Ramachandran KP
Ramaiah SC
Ramakrishnan CV
Ramamirtham R
Ramamurthy VV
Raman E
Ramanathan V
Ramani Bai D
Ramanujam S
Ramdoss B
Ranganatha S
Rani Balasubramanian
Ranjit Sankar Sen
Ravichandran R
Ravoof
Rema Mathew
Sabapathy V
Sadacharam K
Sadasivam V
Sadasivan KM
Sakunthala Sundar
Sakunthala G
Sam Wilson Y
Sambandam P
Sampooranam K.
Sampurnam
Samuel Swamidoss
Sankaralingam SN
Sankaranarayanan Nair V
Santha Devi T
Santha Kumari J
Santhamma Asokan
Santhamma Chacko
Santhana Krishnan G
Sara Mathew
Saradha N
Saroja K
Sashidharan R
Sathiamoorthy S
Sathiavel E
Sathyanarayana DI
Sathyanarayana CCB
Savitri Sukumar
Seeli M
Segaran R
Selvakumar N
Selvaraj R
Selvaraju V
Seni Coin A
Senthilkumar B
Shanmugam N
Shanmugam PG
Shanthi K
Sharashwathi CK
Shivaramu N
Sigamani NG
Sivakumaran V
Sivan S
Sivasubramaniam S

Somasundaram PR
Somasekhar K
Sreenivasan PK
Sridharan NC
Srinivasan MR
Subbammal S
Subramanian G
Subramanian M
Subramanian K
Subramanian KR
Subramanian PK
Subramanian TS
Sudarsanam I
Sudeendra CR
Sudha Ganapathy
Sugumar MK
Sukumaran VS
Sulochana Achuthan
Sulochana Somasundaram
Sundaram V
Sundaramurthy G
Sundararajan S
Sundaresan G
Susairaj B
Susan Stella Bai
Suseela Soundararajan
Suthamathi S
Swaminathan TN
Syed Khadar Batsha V
Syed Noorudeen SM
Tandon JN
Thangavelu N
Tharabai G
Theresiamma Xavier
Thirugnana Sambandam T
Thirumurthy
Thyagarajan K
Umapathi KC
Usha Ramanathan
Vaidyanathan B
Valasamma KK
Valliammal Jayaraj
Valsarajan KC
Vamanamurthy T
Varadammal K
Varadarajulu ST
Varadhan M
Vasantha S
Vasantha Malathy J
Vasanthira Patturaj
Velan P
Vellayan M
Venkata Ramadevi K
Venkata Ramu KV
Venkatachala S
Venkataraman P
Venkataraman P
Venkataramana Rao B
Venkataswamy V
Venkatesan VK
Venkatesan P
Venkatesh Prasad V
Victor Mohan
Victoria Kamalam Jayaraj
Vijaya S
Vijayakumar D
Vijayal A
Vijayalakshmi Gopalan
Vijayalakshmi M
Vijayan KM
Visuvasam JS
Wahid Ahmed Ghais
Walter KP

Adding drops to the ocean. . . . . .

Staff in service

Adikesavan V
Alamelu Raja
Albert F
Aleyamma Thomas
Amavasai B
Anand kumar B
Ananda Kumar J
Anandan C
Anandan M
Anandaraj S
Anbalagan S
Anbarasan K
Anbu P
Anbudass B
Anbulingam R
Angayarkanni B
Anjaiah S
Ankaiah N
Ankaiah R
Ankamma R
Anna Anthony
Annamalai A
Anusuya KS
Arthur Sundar Singh R
Arul Mani P
Asokan M
Ayyasamy K
Azgar Dusthakeer VN
Babu.SN
Babu V
Balakalyan K
Balakoti B
Balakrishna Sharma
Balambal R
Balasubramaniam K
Balraj D
Balu R
Banu Rekha VV
Basilea Watson
BaskaranD
Baskaran G
Baskaran M
Beena Elizabeth Thomas
Benjamin D
Bharath TK
Bhavani PK
Bose D
Chalapathi Rao BVS
Chandra Suresh
Chandran K
Chandran P
Chandrasekaran K
Chandrasekaran P
Chandrasekaran V
Chellam S
Chinniah P
Chithra Sivakumar
Chitra J
Chittarasu CK
Damodharan K
Damodharan R
Daniel B
Dass S
David Raj Kumar R
David Silver Durai J
Dayalakumar RS
Dayalan AS
Devaki D
Devaki G
Devakumar MS
Devan J
Devika K
Durai Raj B
Durai G
Durairaj A
Doraiswamy B
Duraivel E
Easwaran G
Egambaram S
Elangovan A
Fathimunnisa V
Ganapathy R
Ganesan K
Gangadharsharma R

Geetha Ramachandran
Geetha R
Girijalakshmi V
Gomathy Sekar
Gomathy A
Gomathy NS
Gopalakrishnan C
Gopalakannan M
Gopinathan A
Govindarajan S
Govindaraju A
Govindarajulu N
Gowri Shankar T
Gunalan L
Gunasundari A
Hariharan R
Hariprasad Sharma
Harishankar M
Hemalatha P
Hemanth Kumar AK
Indirani V
Innamuthan S
Iswori Dhakal
Iyyappan S
Jagadeesan S
Jagadesan K
Jaganathan SS
Jagatbahadur
Jawahar MS
Jayalakshmi Vadivel
Jayapalan M
Jayaraj M
Jayaram P
Jayaraman K
Jayasankar K
Jayavel Anandan K
Jeeva J
Jeevanath Sharma
John Arokiadas Y
John Robert M
John Washington EA
Johnson Kennedy P
Joseph Raj Kumar SV
Jothi Segaran
Kabirdass G
Kalai Selvam B
Kalaiselvi D
Kalyanaragavan M
Kanaga K
Kanagamani C
Kanagasabapathy B
Kanagasabhapathy KG
Kanchana Udayakumar
Kannan .P
Kannan.M
Karthigayan P
Karthikesan M
Karunakaran K
Karunakaran S
Karunanidhi R
Kasiammal
Kasinathan.TM
Kathiravan.S
Kavidha.C
Kavitha.P
Keshabraj Paudel
Kirubakaran E
Kolappan C
Komaleswaran G
Komathi A
Kosalaraman P
Kowsalya P
Kowsalya P
Krishnamurthy C
Krishnabahadhur R
Krishnamurthy T
Krishnan K
Kumar S
Kumaravel P
Kuppuswamy K
Kosalakumaran V
Kutosh R
Kuttappan K
Lakshmanan A
Lakshmi L
Lakshmi R
Lakshmi S
Lakshmikanthan N

Lalithamma V
Loganathan J
Loganathan J
Loganathan TM
Lucia Precilla
Luke Elizebath Hanna
Madan KumarP
Mahadevan TS
Mahalakshmi R
Mahesh kumar M
Maheswari K
Mahizhaveni B
Makesh Kumar M
Malathi M
Malathy Parthasarathy
Mangalambal G
Mani M
Manikandan M
Manimegalai R
Manjula B
Manoharan A
Manoharan R
Manoharan S
Mariam George
Mary Eunice George
Meenal M
Michel Prem Kumar M
Min Bahadur
Mohamad Ghouse
Mohamad Shahabudin
Mohan Shankar M
Mohan M
Mohan V
Mohana Rani Suhadev M
Mohana M
Mohanan MB
Mohanraj R
Molly Joseph
Manoharan M
Mookkan S
Moshe G
Mubarakali M
Munivarathan P
Muniyandi M
Munuswamy K
Murali.N
Murugesan P
Murugesan S
Nagalakshmi J Reddy
Nagalakshmi MJ
Nagaraja PC
Nagarajan S
Nagaraju C
Nageswari B
Nambirajan S
Narasimhan R
Narayanan T
Narendran G
Nataraj T
Navalan V
Nazeema Beevi B
Neelavathy J
Nirmala MJ
Nirmala S
Niruparani Charles
Nithyakumar D
Nithyanandam G
Pachayappan D
Padma R
Padmapriyadarsini C
Padmavathi Asaithambi
Palaniyandi K
Pandeeswari P
Pandy A
Partheeban V
Parthiban K
Paul Kumaran P
Ponnambalam M
Ponnuraja C
Ponnuswamy TD
Ponrose H
Poongavanam E
Poongavanam K
Poongkodi A
Porselvi K
Prabakaran E
Pradeep Aravindan Menon
Prakasam S

Prakash J
Premkumar N
Purushothaman R

Raadha MN
Radhakrishnan A
Ragammal K
Raja V
Rajagopal K
Rajakumar S
Rajalakshmi AL
Rajamma KV
Rajan Babu N
Rajaram K
Rajaraman K
Rajasakthivel M
Rajasekaran K
Rajaselvasekaran R
Rajathi J
Rajavarman A
Rajendran N
Rajendran RK
Rajendran S
Rajendran V
Ramakrishnan K
Ramakrishnan K
Ramakrishnan N
Raman T
Ramanathan VD
Ramesh Babu V
Ramesh Kumar S
Ramesh AM
Ramesh K
Ramesh R
Rangamma S
Ranganathan K
Ranganathan L
Rani Bai M
Rasheetha Begum M
Rathinam M
Rathinasabapati R
Ravi A
Ravi J
Ravi N
Ravichandran KR
Ravichandran R
Ravikumar D
Ravindra Rao S
Revathy V
Rosily Edwin
Rosily K
Sakila R
Sampathkumar K
Sampathkumar V
Samuel Vasanthan Good will J
Sankaran K
Santha Sriraghavan
Santhi Velu
Santhi Viswanthan
Saraladevi R
Saraswathi D
Saravanan C
Saravanan K
Sargunan D
Seenivasan I
Sekar L
Selvakumar K
Selvam J
Selvaraj P
Selvi A
Senthamizhselvi
Senthil Kumar M
Senthil Nathan R
Senthilkumar K
Senthilkumar VS
Senthilvelan P
Shailaja Devi V
Shakila Shankar
Shanbasha A
Shanmugam D
Shanthakumar J
Sharadha D
Sheelaa T
Sheik Illiayas A

Shunmugajyothi J
Shyamala Gopu
Silambu Chelvi
Singaravelu K
Sivagama Sundari
Sivakumar AM
Sivakumar P
Sivakumar S
Sivaraj AS
Solomon Priyakumar
Soma Sundaram RS
Soumya Swaminathan
Soundararajan P
Sri Rama Chandran S
Srikanth Dhavani
Srinivasa Raju D
Srinivasan N
Srinivasan R
Srinivasulu P
Stanley Gnanadhass
Stanly Jones Raja Singh
Stella Mary A
Stella Mary S
Subbaiah P
Subhas Chandra Bose
Subramani M
Subramani R
Subramanian V
Sudha Subramanyam
Suganthi C
Suganthi R
Sugumar D
Suguna J
Sujatha Narayanan
Sulochana D
Sumathi.K
Sumathy K
Sundarajan V
Sundaramurthy D
Sundaran K
Sundari D
Surendranath TN
Suresh Kumar B
Sureswari K
Suryanarayanan D
Syam Sundar A
Tamil Selvi N
Tamizhselvan M
Thangam (a) Meenakshi
Thangaraj D
Thangaraj T
Thanigachalam M
Thanigaivel V
Theensuwai S
Thilakavathy T
ThiruKumar C
Thirumalai KN
Thirupal G
Thiruvalluvan E
Thiyagarajan M
Thiyagarajan V
Tholkappian AS
Thulasingam
Tilbahadur
Udayakumar.J
Uma A
Umapathy KC
Usha Devi Gopalan
Uthara Bahadur C
Vadivel K
Vadivu G
Vaishnavi S
Valarmathi Nagarajan
Valarmathy R
Vanaja Kumar
Vasantha M
Vasantha N
Vasu G
Vasu G
Vasudevan A
Vasudevan K
Vasudevan V
Vedhachalam A

Velmurugan V
Venkataramana PK

Venkatesan J

Venkatesan KS
Venkatesan L

Venkatesan P

Venkatesan S
Venkatesan S

Venkateswara Rao B

Venkateswaralu V

Venugopal D
Venugopal K

Vetrichselvi R
Vijai Anand A

Vijaya Lakshmi VR

Vijayabhaskara Rao D
Vijayakumar B

Vijayakumar P
Vijayakumari D

Vijayakumari L

Vijayal AK

Vijayalakshmi A

Vijayalakshmi BV
Vijayaraj S

Visalakshi R

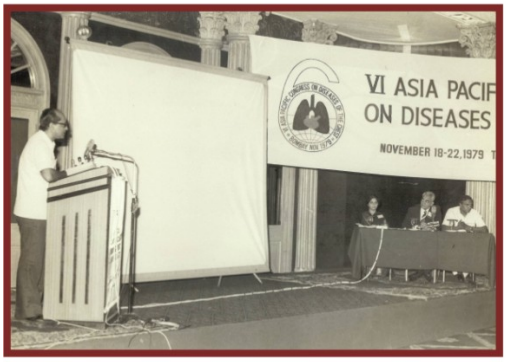
Viswambaram K
Wilkinson Mathew W

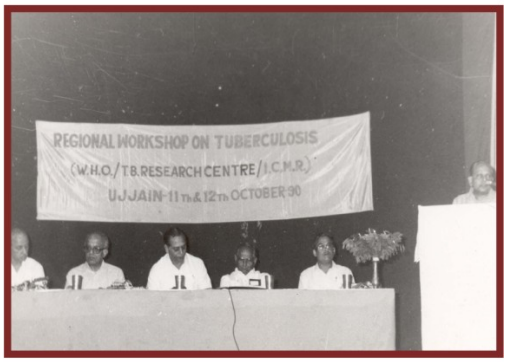
Yambahadur

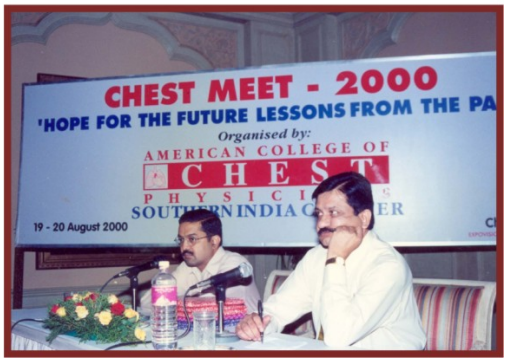
Yuvarajan R

PHOTO GALLERY

DISSEMINATION OF KNOWLEDGE








NATIONAL PROTOCOL DEVELOPMENT WORKSHOPS
"INVOLVEMENT OF PRIVATE SECTOR IN RNTCP"
&
"HIV AND TUBERCULOSIS"
Tuberculosis Research Centre, ICMR
&
Central TB Division, DGHS


National Symposium on Recent Advances
in Statistical Computing
Department of Statistics
Tuberculosis Research Centre
ICMR, Chennai - 600 031


TRC ICMR MADURAI
COLLABRATION WITH
WORLD VISION INDIA
WORKSHOP ON TB HIV
CHALLENGES AND THE ROLE
OF
NGOS


Joining hands to fight TB
இணைந்த கைகள்


NATIONAL CME ON HIV AND TUBERCULOS
11th 12th SEP 2004
TUBERCULOSIS RESEARCH CENTRE ICMR CHEN
THE NATIONAL ACADEMY OF MEDICAL SCIENCES, NEW DE


OPERATIONAL RESEARCH METHODOLOGY
WORKSHOP
Chennai
18 - 20 September 2006


TUBERCULOSIS RESEARCH CENTRE (ICMR) CHENNAI
And
WORLD FOOD PROGRAMME, NEW DELHI


Theme
"Recent Advances in the Statistical Methods for Bio Sciences"
November 15th-17th, 2007
&
Pre-conference Workshop on "Statistical Methods for Bioinformatics"
November 14th 2007
DEPARTMENT O STATISTICS
TUBERCULOSIS RESEA CH CENTRE (ICMR)


APAC-HHS
DISSEMINATION SEMINAR ON
"CHALLENGES FACING MSM IN INDIA IN THE CONTEXT OF HIV/AIDS PREVENTION AND INTERVENTION"
ARE MSM BEING REACHED?
7th January 2010
USAID

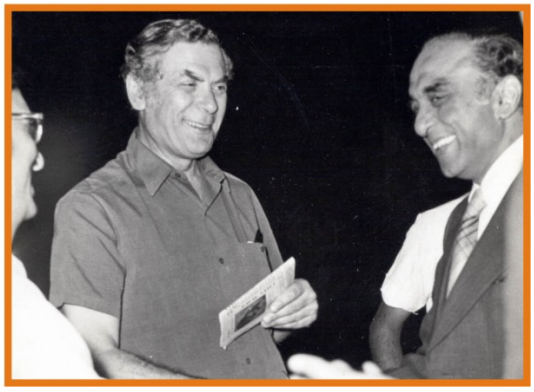

NATIONAL SYMPOSIUM


esearch Centre
berculosis Research & Training
Indian Council of Medical Research
Centenary celebrations
Nursing SYMPOSIUM on
Infection Control Practices in TB and HIV-TB

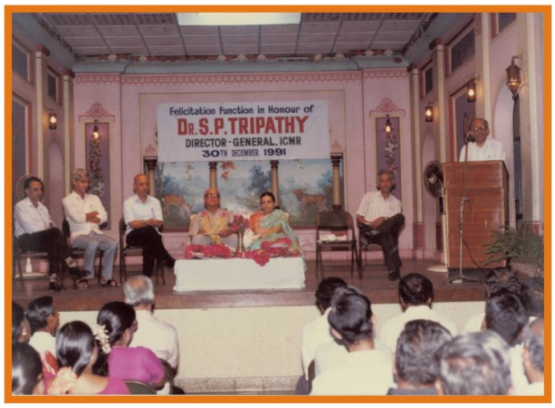
NEW VENTURES

CREATING PUBLIC AWARENESS

DOWN MEMORY LANE . . .




NATIONAL PROTOCOL DEVELOPMENT WORKSHOPS
"INVOLVEMENT OF PRIVATE PRACTITIONERS IN RNTCP
HIV and TUBERCULOSIS"
Tuberculosis Research Centre, ICMR & Central TB Division, DGHS


Felicitation Function in Honour of
Dr. S.P. TRIPATHY
DIRECTOR-GENERAL, ICMR
30TH DECEMBER 1991


INDIAN COUNCIL OF MEDICAL RESEARCH


Dr.K.S.Sanjivi
Birth Centenary Year

VISIT OF EMINENT DIGNITARIES

Shri. KK. Shah, Tamilnadu Governor, 1976

Dr MGK Menon, Planning Commission, GoI,

Prof. S.C Robins, Nobel Laureate, 1984

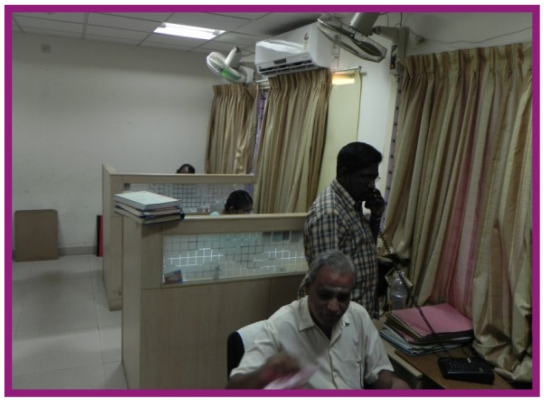
Dr HT Mahler, DG, WHO,1985

US Health Secretary

Union health minister Shri CP Thakur

SUPPORT TEAMS

Administration



Accounts

Transport

Canteen

Electrical

REFERENCES

1. Tuberculosis Chemotherapy Centre. A concurrent comparison of home and sanatorium treatment of pulmonary TB in South India. Bull World Health Organ. 1959; 21:51-144

2. Tuberculosis Chemotherapy Centre. Intermittent treatment of pulmonary tuberculosis: A concurrent comparison of twice-weekly isoniazid plus streptomycin and daily isoniazid plus p-aminosalicyclic acid in domiciliary treatment. Lancet;1963;1078-1080 and Indian J Tuberc.1963;10:117-122.

3. Tuberculosis Research Centre; National Tuberculosis Institute. A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum - positive pulmonary tuberculosis in South India. Am Rev Respir Dis.*1986;134:27-33.*

4. Tuberculosis Research Centre. A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis.Int J Tuberc Lung Dis.1997;1: 509-517.

5. Tuberculosis Research Centre. Shortening short course chemotherapy: a randomised clinical trial for treatment of smear positive pulmonary tuberculosis with regimens using ofloxacin in the intensive phase. Indian J Tuberc.2002;49;27-38.

6. Ramachandran P, Kripasankar AS, Duraipandian M. Short course *chemotherapy for pulmonary tuberculosis in children.* Indian J Tuberc.1998;45; 83-87.

7. Swaminathan S, Datta M, Radhamani MP, Mathew S, Reetha AM, Rajajee S,Mathew R, Radhakrishnan A, Raghu MB. A profile of bacteriologically confirmed pulmonary tuberculosis in children. IndianPediatr.2008;45:743–747

8. Swaminathan S, Raghavan A, Duraipandian M, Kripasankar AS, Ramachandran P. Short-course chemotherapy for paediatric respiratory tuberculosis: 5-year report. Int J Tuberc Lung Dis.2005;9:693–696.

9. Parthasarathy R, Sriram K, Santha T, Prabhakar R, Somasundaram PR, Sivasubramanian S. Short-course chemotherapy for tuberculosis of the spine. A comparison between ambulant treatment and radical surgery -ten-year report. J Bone Joint Surg.1999;81;464-471.

10. Ramachandran P, Kripasankar AS, Reetha AM, Mahalakshmi SM, Prabhakar R. Short course chemotherapy study in tuberculous meningitis in children. Indian J Tuberc.1997;44:195-200.

11. Ramachandran R, Sivasubramanian S, Balambal R, Parthasarathy R, Ramachandran R, Santha T, Somasundaram PR, Ganapathy S, Sudharsana K, Sayeed ZA, Kalyanaraman S, Prabhakar R.A controlled clinical trial of short- course chemotherapy for tuberculoma of the brain. Tubercle Lung Dis 1995;76:311-317.

12. Balasubramanian R, Nagarajan M, Balambal R, Tripathy SP, Sundararaman R, Venkatesan P, Paramasivan CN, Rajasambandam P, Rangabashyam N, Prabhakar R. Randomised controlled clinical trial of short course chemotherapy in abdominal tuberculosis: A five-year report. Int J Tuber Lung Dis.1997;1:44-51.

13. Jawahar MS, Rajaram K, Sivasubramanian S, Paramasivan CN, Chandrasekar K, Kamaludeen MN, Thirithuvathas AJ, Ananthalakshmi V, Prabhakar R. Treatment of lymph node tuberculosis – a randomized clinical trial of two 6-month regimens. Trop Med Int Health.2005;10:1090-1098

14. Umapathy KC, Begum R, Ravichandran G, Rahman F, Paramasivan CN, Ramanathan VD. Comprehensive findings on clinical, bacteriological, histopathological and therapeutic aspects of cutaneous tuberculosis. Trop Med Int Health.2006;11:1521-1528.

15. Thomas A, Ramachandran R, Rehaman F, Jaggarajamma K, Santha T, Selvakumar N, Krishnan N, Mohan NS, Sundaram V, Wares F, Narayanan PR. Management of multi drug resistance tuberculosis in the field: Tuberculosis Research Centre experience. Indian J Tuberc.2007;54:117-124.

16. Joseph P, Rao VB, Mohan NS, Fredrick JS, Ramachandran R, Raman R, Wares F, Ramachandran R, Thomas A. Outcome of standardized treatment for patients with MDR-TB from Tamil Nadu, India. Indian J Med. Res. 2011;133:529-534.

17. Thomas A, Nagarajan M, Balakrishnan A, Prabhakar R. Controlled clinical trial of the MDT regimens with or without rifampicin in highly bacilliferous BL / LL south Indian patients – A 5 year report. Int J Lepr.1990;10.

18. Thomas A, Nagarajan M, Chandrasekaran V, Hari L, Somasundaram PR, Prabhakar R, Kumar A, Bhatia VN, Roy RG. A doubleblind controlled clinical trial to assess the role of anti-histamines in the treatment of multibacillary eprosy. Indian J Lepr 1988;60:499-505.

19. Thomas A, Hari L, Nagarajan M, Prabhakar R. Relapses during long-term follow up with drug-susceptible *M. leprae* among multibacillary leprosy patients treated with multidrug therapy regimens; case reports. Int J Lep 1995;63:391-394.

20. Hari L, Suryanarayanan D, Thomas A, Nagarajan M, Prabhakar R. An assessment of the value of midfinger smears in multibacillary patints. Int J Lepr.1995.

21. Shenoy RK, Varghese J, Kuttikkal VV, Kumaraswami V. The efficacy, tolerability and safety of diethylcarbamazine-fortified salt in the treatment of the microfilaraemias of brugian filariasis: an open, hospital-based study. Ann Trop Med Parasitol.1998;92:285-293.

22. Ottesen EA, Vijayasekaran V, Kumaraswami V, Perumal Pillai SV, Sadanandam A, Frederick S, Prabhakar R, Tripathy SP. A controlled trial of ivermectin and diethylcarbamazine in lymphatic filariasis. N Engl J Med.1990;322:1113-1117.

23. Shenoy RK, Kumaraswami V, Rajan K, Thankon S, Jalajakumari. A comparative study of the efficacy and tolerability of single and split doses of ivermectin and diethylcarbamazine in periodic brugian filariasis. Ann Trop Med Parasitol.1993;8:459-467.

24. Kumaraswami V, Ottesen EA, Vijayasekaran V, Uma Devi S. Ivermectin for the treatment of Wuchereria bancrofti filariasis. JAMA.1988;259:3150-3153.

25. Vijay S, Swaminathan S, Vaidyanathan P, Thomas A, Chauhan LS, Kumar P, Chiddarwar S, Thomas B, Dewan PK. Feasibility of provider- initiated HIV testing and counselling of tuberculosis patients under the TB control programme in two districts of South India. PLoS One.2009;4:1-7.

26. Sudha G, Nirupa C, Rajasakthivel M, Sivasubramanian S, Sundaram V, Bhatt S, Subramaniam K, Thiruvalluvan E, Mathew R, Renu G, Santha T. Factors influencing the care-seeking behaviour of chest symptomatics: a community-based study involving rural and urban population in Tamil Nadu, south India.Trop Med Int Health.2003;8:336-341.

27. Suhadev M, Thomas BE, M RS, P M, V C, Charles N, R D, M A, Mathew TA, Wares F. Alcohol Use Disorders (AUD) among Tuberculosis Patients: A Study from Chennai, south India. PLoS One.2011;6:1-6.

28. Suhadev M, Nyamathi AM, Swaminathan S, Venkatesan P. Factors associated with willingness to participate in future preventive HIV vaccine trials among high-risk populations in south India. AIDS Res Hum Retroviruses. 2009;25:217-224.

29. Thomas BE, Nyamathi A, Swaminathan S. Impact of HIV/AIDS on Mothers in southern India: A Qualitative Study. AIDS Behav.2009;13:989-96.

30. Beena Thomas, Matthew J. Mimiaga, Sunil Menon, V. Chandrasekaran, P. Murugesan, Swaminathan S, Kenneth H. Mayer, Steven A. Safren. Unseen and Unheard: Predictors of sexual risk behaviour and HIV infection among men who have sex with men (MSM) in Chennai, India. AIDS Educ Prev.2009; 21:372-83.

31. Rajeswari R, Balasubramanian R, Muniyandi M, Geetharamani S, Thresa X, Venkatesan P. Socio-economic impact of tuberculosis on patients and family in India. Int J Tuberc Lung Dis.1999;3:869-877.

32. Rajeswari R, Muniyandi M, Balasubramanian R, Narayanan PR. Perceptions of tuberculosis patients about their physical, mental and social well-being: a field report from south India. Soc Sci Med. 2005;60:1845-1853.

33. Muniyandi M, Rajeswari R, Balasubramanian R. Tuberculosis control programme - is it pro poor? SAARC J TB L Dis & HIV/AIDS.2004;1:14-19.

34. Muniyandi M, Ramachandran R, Gopi PG, Chandrasekaran V, Subramani R, Sadacharam K, Kumaran P, Santha T, Wares F, Narayanan PR. The prevalence of tuberculosis in different economic strata: a community survey from South India. Int J Tuberc Lung Dis.2007;11:1042–1045.

35. Muniyandi M, Rajeswari R, Balasubramanian R, Nirupa C, Gopi PG, Jaggarajamma K, Sheela F, Narayanan PR. Evaluation of post-treatment health-related quality of life (HRQoL) among tuberculosis patients. Int J Tuberc Lung Dis.2007;11:887–892.

36. Swaminathan S, Narendran G, Venkatesan P, Iliayas S, Ramesh S, Menon PA, Padmapriyadarsini C, Ramachandran R, Ponnuraja C, Suhadev M, Sakthivel R, Narayanan PR. Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis. A randomized clinical trial. Am J Respir Crit Care Med.2010;181(7):743-751.

37. Padmapriyadarsini C, Ramesh Kumar S, Terrin N, Narendran G, Menon PA, Ramachandran G, Subramanyan S, Venkatesan P,Wanke C, Swaminathan S. Dyslipidemia among HIV-infected patients with tuberculosis taking once-daily nonnucleoside reverse-transcriptase inhibitor–based antiretroviral therapy in India. Clin Infect Dis.2011;52:540-546.

38. Swaminathan S, Padmapriyadarsini C, Sukumar B, Iliyas S, Kumar SR, Triveni C, Gomathy P, Thomas B, Mathew M, Narayanan PR. Nutritional status of persons with HIV infection, persons with HIV infection and tuberculosis, and HIV-negative individuals from southern India. Clin Infect Dis.2008;46(6):946-949.

39. Hanna LE, Nayak K, Subramanyam S, Venkatesan P, Narayanan PR, Swaminathan S.Incomplete immunological recovery following anti-tuberculosis treatment in HIV-infected individuals with active tuberculosis. Indian J Med Res.2009;129:548-554.

40. Lakshmi S, Ramesh K, Jauvin V, Schrive MH, Ranjani R, Narayanan PR, Fleury HJ, Swaminathan S. Characterization of HIV-1 isolates from antiretroviral drug-naive children in southern India. AIDS Res Hum Retroviruses.2007;23:1119-1126.

41. Rajesh L, Karunaianantham R, Narayanan PR, Swaminathan S. Antiretroviral drug-resistant mutations at baseline and at time of failure of antiretroviral therapy in HIV type 1-coinfected TB patients. AIDS Res Human Retroviruses.2009;25:1179-1185.

42. Tuberculosis Research Centre. Fifteen year follow up of trial of BCG vaccines in south India for tuberculosis prevention. Indian J Med Res. 1999;110:56-69.

43. Trial of BCG Vaccines in South India for Tuberculosis Prevention. Indian J Med Res.1980;72(Suppl):1-74.

44. Mayurnath S, Anantharaman DS, Baily GVJ, Radhamani MP, Vallishayee RS, Venkataraman P, Tripathy SP. Tuberculosis prevalence survey in Kashmir valley. Indian J Med Res.1984;80:129-140.

45. Mayurnath S, Vallishayee RS, Radhamani MP, Prabhakar R. Prevalence study of tuberculous infection over fifteen years, in a rural population in Chingleput district (south India). Indian J Med Res.1991;93:74-80.

46. Datta M, Radhamani MP, Selvaraj R, Paramasivan CN, Gopalan BN, Sudeendra CR, Prabhakar R. Critical assessment of smear-positive pulmonary tuberculosis patients after chemotherapy under the district tuberculosis programme. Tubercle Lung Dis.1993;74:180-186.

47. Gopi PG, Vallishayee RS, Appe Gowda BN, Paramasivan CN, Ranganatha S, Venkataramu KV, Phaniraj BS, Krishnamacharya L, Devan J, Ponnusamy R, Komaleeswaran G, Prabhakar R. A tuberculosis prevalence survey based on symptoms questioning and sputum examination. Indian J Tuberc. 1997; 44:171-180.

48. Datta M, Gopi PG, Appegowda BN, Rao KRB, Gopalan BN. Tuberculosis in North Arcot district of Tamil Nadu - A sample survey. Indian J Tuberc. 2000; 47:147-154.

49. Tuberculosis Research Centre. Trends in the prevalence and incidence of tuberculosis in south India. Int J Tuberc Lung Dis.2001;5:142-157.

50. Datta M, Radhamani MP, Sadacharam K, Selvaraj R, Satyanarayana Rao DL, Nagabushana Rao RS, Gopalan BN, Prabhakar R. Survey for tuberculosis in a tribal population in North Arcot District**.** Int J Tuberc Lung Dis.2001;5: 240-249.

51. Kolappan C, Gopi PG. Tobacco smoking and pulmonary tuberculosis. Thorax.2002;57:964-966.

52. Kolappan C, Gopi PG, Subramani R, Chadha VK, Kumar P, Prasad VV, Appegowda BN, Rao RSN, Sashidharan R, Ganesan N, Santha T, Narayanan PR. Estimation of annual risk of tuberculosis infection (ARTI) among children aged 1-9 years in the south zone of India. Int J Tuberc Lung Dis.2004;8: 418-423.

53. Subramani R, Radhakrishna S, Frieden TR, Kolappan C, Gopi PG, Santha T, Wares F, Selvakumar N, Narayanan, PR. Rapid decline in prevalence of pulmonary tuberculosis after DOTS implementation in a rural area of South India. Int J Tuberc Lung Dis.2008;12:916–920.

54. Gopi PG, Subramani R, Santha T, Chandrasekaran V, Kolappan C, Selvakumar N, Narayanan PR. Estimation of burden of tuberculosis in India for the year 2000. Indian J Med Res.2005;122:243-248.

55. Paramasivan CN, Narayana ASL, Prabhakar R, Rajagopal MS, Somasundaram PR, Tripathy SP. Effect of storage of sputum specimens at room temperature on smear and culture results. Tubercle.1983;64:119-124.

56. Paramasivan CN, Bhaskaran K, Venkataraman P, Chandrasekaran V, Narayanan PR. Surveillance of drug resistance in tuberculosis in the State of Tamilnadu. Indian J Tuberc.2000;47:27-33.

57. Selvakumar N, Rahman F, Garg R, Rajasekaran S, Mohan NS, Thyagarajan K, Sundaram V, Santha T, Thomas R Frieden TR, Narayanan PR. Evaluation of the phenol ammonium sulfate sedimentation smear microscopy method for diagnosis of pulmonary tuberculosis. J Clin Microbiol.2002;40:3017-3020

58. Selvakumar N, Ravikumar D, Sivagamasundari S, Gopi PG, Narayanan PR. A novel method of staining acid-fast bacilli in sputum containers. Indian J Med Res.2006;123:776-780.

59. Selvakumar N, Premkumar M, Kumar V, Gopi PG, Sivagamasundari S., Prabhakaran E, et al. Pot staining of sputum for detection of acid-fast bacilli. Tuberculosis Surveillance Research Unit Progress Report. Amsterdam: KNCV, 2007.

60. Kumar V, Prabakaran L, Gomathi S, Kriakov J, Dusthakeer A, Balaji S, Chan J, Jacobs WR Jr., Narayanan PR. Characterization of temperate phage Che12 and construction of a new tool for diagnosis of tuberculosis. Tuberculosis.2008;88:616-623.

61. Dusthackeer A, Kumar V, Selvakumar S, Gomathi S, Zhu G, Balaji S, Hassan S, Selvakumar N, Chan J, Narayanan PR. Construction and evaluation of luciferase reporter phages for the detection of active and non-replicating tubercle bacilli. J Microbiol Methods.2008;73:18-25.

62. Subramanyam B, Dusthackeer A, Rehman F, Sekar G, Sivaramakrishnan GN, Kumar V. An alternative sputum processing method using chitin for the isolation of Mycobacterium tuberculosis. World J Microbiol Biotechnol. 2010; 26:523-526.

63. Subramanyam B, Kumar V, Venkatesan P, Selvakumar N. Phage lysin to supplement phagebiotics to decontaminate processed sputum specimens. Eur J Clin Microbiol Infect Dis.2010;29:1407-1412.

64. Nageswara Rao KV, Eidus L, Evans C, Kailasam S, Radhakrishna S, Somasundaram PR, Stott H, Subbammal S, Tripathy SP. Deterioration of cycloserine in the tropics. Bull World Health Organ.1968;39:781-789.

65. Rao KVN, Kailasam S, Menon NK, Radhakrishna S. Inactivation of isoniazid by condensation in a syrup preparation. Bull World Health Organ. 1971; 45:625-632.

66. Ramachandran G, Perloff ES, von Moltke LL, Swaminathan S, Wanke CA, Greenblatt DJ. Analysis of generic antiretroviral formulations manufactured in India. AIDS Behav.2004;18:1482-1484.

67. Venkataraman P, Eidus L, Ramachandran K, Tripathy SP. A comparison of various methods for the detection of isoniazid and its metabolites in urine. Tubercle.1965;46:262-269.

68. Venkataraman P, Eidus L, Tripathy SP, Velu S. Fluorescence test for the detection of ethionamide metabolites in urine. Tubercle.1967;48:291-296.

69. Venkataraman P, Narayana ASL, Prabhakar R. Simple qualitative tests for rifampicin in urine. Indian J Tuberc.1988;35:114-116.

70. Kumar AK, Ramachandran G, Saradha B, Narendran G, Swaminathan S. Urine nevirapine as a predictor of antiretroviral adherence. Indian J Med Res. 2006; 123:565-568.

71. Hemanthkumar AK, Ramachandran G, Kumar P, Kumaraswami V, Swaminathan S. Can urine lamivudine be used to monitor antiretroviral treatment adherence? eJIAS.2006;8:53-62.

72. Sarma GR, Kannapiran M, Narayana ASL, Radhakrishna S, Tripathy SP. Determination of acetylator phenotype based on the ratio of acetylisoniazid to isoniazid in urine following an oral dose of ordinary isoniazid. Indian J Med Res. 1976; 64:1-8.

73. Sarma GR, Kannapiran M, Narayana ASL, Radhakrishna S. A qualitative test for the determination of isoniazid acetylator phenotype. Indian J Med Res.1978;68:335-340.

74. Kailasam S, Immanuel C, Nair NGK, Radhakrishna S, Tripathy SP. Classification of subjects as slow or rapid inactivators of isoniazid oral administration of a slow-release. Preparation of isoniazid and determination of the ratio of acetyisoniazid to isoniazid in urine. Indian J Med Res. 1975; 63: 323-328.

75. Kailasam S, Rahman F, Narayana ASL, Sarma GR. Determination of the acetylator phenotype employing concentrations of isoniazid in saliva. Indian J Tuberc. 1989; 36:151-155.

76. Sarma GR, Kailasam S, Datta M, Loganathan G, Rahman F, Narayana ASL. Classification of children as slow or rapid acetylators based on concentrations of isoniazid in saliva following oral administration of body-weight and surface- area-related dosages of the drug. Indian Pediatr.1990;27:134-142.

77. Sarma GR, Acharyulu GS, Kannapiran M, Krishnamurthy PV, Gurumurthy P, Tripathy SP. Role of rifampicin in arthralgia induced by pyrazinamide. Tubercle.1983;64:93-100.

78. Sarma GR,Immanuel C,Kailasam S,Narayana AS,Venkatesan P. Rifampin-induced release of hydrazine from isoniazid: a possible cause of hepatitis during treatment of tuberculosis with regimens containing isoniazid and rifampin. Am Rev Respir Dis.1986;133:1072–1075.

79. Sarma GR, Kailasam S, Nair NGK, Narayana ASL, Tripathy SP. Effect of prednisolone and rifampin on isoniazid metabolism in slow and rapid inactivators of isoniazid. Antimicrob Agents Chemother.1980;18:661-666.

80. Ramachandran G, Hemanthkumar AK, Rajasekaran S, Padmapriyadarsini C, Narendran G, Sukumar B, Sathishnarayan S, Raja K, Kumaraswami V, Swaminathan S. Increasing nevirapine dose can overcome reduced bioavailability due to rifampicin coadministration. J Acquir Immune Defic Syndr.2006;42:36-41.

81. Ramachandran G, Hemanth Kumar AK, Rajasekaran S, Kumar P, Ramesh K, Anitha S, Narendran G, Menon P, Gomathi C, Swaminathan S. CYP2B6 G516T polymorphism but not rifampin coadministration influences steady-state pharmacokinetics of efavirenz in human immunodeficiency virus-infected patients in south India. Antimicrob Agents Chemother.2009;53:863-868.

82. Gurumurthy P, Ramachandran G, Hemanth Kumar AK, Rajasekaran S, Padmapriyadarsini C, Swaminathan S, Bhagavathy S, Venkatesan P, Sekar L, Mahilmaran A, Ravichandran N, Paramesh P. Decrased bioavailability of rifampin and other antituberculosis drugs in patients with advanced human immunodeficiency virus disease. Antimicrob Agents Chemother. 2004; 48: 4473-4475.

83. Gurumurthy P, Ramachandran G, Hemanth Kumar AK, Rajasekaran S, Padmapriyadarsini C, Swaminathan S, Venkatesan P, Sekar L, Kumar S, Krishnarajasekhar OR, Paramesh P. Malabsorption of rifampin and isoniazid in HIV-infected patients with and without tuberculosis. Clin Infect Dis.2004; 38:280-283.

84. Ramachandran G, Hemanth Kumar AK, Sarala K, Padmapriyadarsini C, Anitha S, Tharani CB, Kumaraswami V, Swaminathan S. Urine levels of rifampicin & isoniazid in asymptomatic HIV-positive individuals. Indian J Med Res.2007;125:763-766.

85. Gurumurthy P, Rahman F, Narayana AS, Sarma GR. Salivary levels of isoniazid and rifampicin in tuberculous patients. Tubercle.1990;71:29-33.

86. Ramachandran G, Ramesh K, Hemanth Kumar AK, Jagan I, Vasantha M, Padmapriyadarsini C, Narendran G, Rajasekaran S, Swaminathan S. Association of high T allele frequency of CYP2B6 G516T polymorphism among ethnic south Indian HIV-infected patients with elevated plasma efavirenz and nevirapine. J Antimicrob Chemother.2009;63:841-843.

87. Bakshi S, Ramachandran G, Ramesh K, Hemanthkumar AK, Anitha S, Padmapriyadarsini C, Narendran G, Menon PA, Rajasekaran S,Swaminathan S. Study of ABCB1 polymorphism (C3435T) in HIV-1-infected individuals from South India. Br J Clin Pharmacol.2008;65:791- 792.

88. Swaminathan S, Ramachandran G, Hemanth Kumar AK, Vasantha M, Lakshmi S, Bhavani PK, Ganga Devi NP, Shah I, Ramesh K, Rajasekaran S. Factors influencing plasma nevirapine levels: a study in HIV-infected children on generic antiretroviral treatment in India. J Antimicrob Chemother. 2011; 66:1354-1359.

89. Senthil Kumar KS, Raja A, Uma Devi KR, Paranjape RS. Production & characterization of monoclonal antibodies to Mycobacterium tuberculosis. Indian J Med Res.2000;112:37-46.

90. Uma Devi KR, Rmalingam B, Brennan PJ, Narayanan PR, Raja A. Specific and early detection of IgG, IgA and IgM antibodies to Mycobacterium tuberculosis 38kDa antigen in pulmonary tuberculosis. Tuberculosis. 2001; 81:249-253.

91. Murthy MK, Parasa RR, Deenadayalan A, Sharma P, Raja A. Evaluation of the diagnostic potential of region of deletion-1–encoded antigen culture filtrate protein-10 in pulmonary tuberculosis. Diagn Microbiol Infect Dis.2007;59: 295–302.

92. Bethunaickan R, Baulard AR, Locht C, Raja A. Antibody response in pulmonary tuberculosis against recombinant 27kDa (MPT51, Rv3803c) protein of Mycobacterium tuberculosis. Scand J Infect Dis.2007;39:867-874.

93. Rajajee S, Raja A. Antibody to PPD, BCG, H37 RV and antigen 5 in tuberculous meningitis. J Trop Pediatr.1991;37:266-268.

94. Raja A, Ranganathan UD, Bethunaickan R, Dharmalingam V. Serologic response to a secreted and a cytosolic antigen of Mycobacterium tuberculosis in childhood tuberculosis. Pediatr Infect Dis J.2001;20:1161-1164.

95. Ramalingam B, Uma Devi KR, Swaminathan S, Raja A. Isotype specific antibody response in childhood tuberculosis against purified 38 kDa antigen of Mycobacterium tuberculosis. J Trop Pediatr.2002;48:188-189.

96. Ramalingam B, Uma Devi KR, Raja A. Isotype-specific anti-38 and 27 kDa (mpt 51) response in pulmonary tuberculosis with human immunodeficiency virus coinfection. Scand J Infect Dis.2003;35:234-239.

97. Uma Devi KR, Ramalingam B, Raja A. Antibody response to Mycobacterium tuberculosis 30 and 16kDa antigens in pulmonary tuberculosis with human immunodeficiency virus coinfection. Diagn Microbiol Infect Dis.2003;46:205-209.

98. Raja A, Ranganathan UD, Bethunaickan R. Improved diagnosis of pulmonary tuberculosis by detection of antibodies against multiple Mycobacterium tuberculosis antigens. Diagn Microbiol Infect Dis.2008;60:361-368.

99. Raja A, Narayanan PR, Mathew R, Prabhakar R. Characterization of mycobacterial antigens and antibodies in circulating immune complexes from pulmonary tuberculosis. J Lab Clin Med.1995;125:581-587.

100. Raja A, Uma Devi KR, Ramalingam B, Brennan PJ. Immunoglobulin G, A, and M responses in serum and circulating immune complexes elicited by the 16-kilodalton antigen of Mycobacterium tuberculosis. Clin Diagn Lab Immunol.2002;9:308-312.

101. Raja A, Uma Devi KR, Ramalingam B, Brennan PJ. Improved diagnosis of pulmonary tuberculosis by detection of free and immune complex-bound anti-30 kDa antibodies. Diagn Microbiol Infect Dis.2004;50:253-259.

102. Raja A, Ranganathan UD, Ramalingam B. Clinical value of specific detection of immune complex-bound antibodies in pulmonary tuberculosis. Diagn Microbiol Infect Dis.2006;56:281-287.

103. Anbarasu D, Sundaramurthi JC, Raja A Immunological and proteomic analysis of preparative isoelectric focusing separated culture filtrate antigens of Mycobacterium tuberculosis. Exp Mol Pathol.2010;88:156-162.

104. Anbarasu D, Heaslip D, Rajendiran AA, Velayudham BV, Frederick S, Yang HL, Dobos K, Belisle JT, Raja A. Immunoproteomic identification of human T cell antigens of Mycobacterium tuberculosis that differentiate healthy contacts from tuberculosis patients. Mol Cell Proteomics.2010;9:538-549.

105. Rao PV, Rajasekaran S, Raja A. Augumentation of natural killer activity with exogenous interleukins in patients with HIV and pulmonary tuberculosis coinfection. AIDS Res Hum Retroviruses.2008;24:1435-1443.

106. Rao PV, Kumar MK, Basirudeen S, Sharma P, Swaminathan S, Raja A. Improved diagnosis of tuberculosis in HIV-positive patients using RD1-encoded antigen CFP-10. Int J Infect Dis.2009;13:613-622.

107. Rao PV, Rajasekaran S, Raja A. Natural killer cell-mediated cytokine response among HIV-positive south Indians with pulmonary tuberculosis. J Interferon Cytokine Res.2010;30:33-41.

108. Ramana Rao PV, Ramanavelan S, Rajasekaran S, Raja A. Natural-killer cell-derived cytolytic molecules in HIV-associated pulmonary tuberculosis-Role of exogenous interleukins. J Clin Immunol.2010; 30:393-401.

109. Kumar M, Meenakshi N, Sundaramurthi JC, Kaur G, Mehra NK, Raja A. Immune response to Mycobacterium tuberculosis specific antigen ESAT-6 among south Indians. Tuberculosis.2010;90:60–69.

110. Kumar M, Sundaramurthi JC, Mehra NK, Kaur G, Raja A. Cellular immune response to Mycobacterium tuberculosis-specific antigen culture filtrate protein-10 in south India**.** Med Microbiol Immunol.2010;199:11-25.

111. Kumar M, Alamelu Raja A. Cytotoxicity responses to selected ESAT-6 and CFP-10 peptides in tuberculosis. Cell Immunol.2010;265:146-155.

112. Basirudeen SAK, Balambal R, Thomas A, Venkatesan P, Raja A. Role of QuantiFERON-TB gold, interferon gamma inducible protein-10 and tuberculin skin test in active tuberculosis diagnosis. PLoS One.2010;5:1-7.

113. Basirudeen S, Rajasekaran S, Swaminathan S, Venkatesan P, Paulkumaran P, Raja A. Role of Interferon gamma release assay in active TB diagnosis among HIV infected individuals. PLoS One.2009;4:1-7.

114. Basirudeen S, Rajasekaran S, Raja A. Comparison of interferon gamma and interferon gamma-inducible protein-10 secretion in HIV-tuberculosis patients. AIDS.2010;24:323-325.

115. Goletti D, Raja A, Basirudden S, Rodrigues C, Sodha A, Butera O, Carrara S, Vernet G, Longuet C, Ippolito G, Thangaraj S, Leportier M, Girardi E, Lagrange PH. Is IP-10 an accurate marker for detecting M. tuberculosis-specific response in HIV-infected persons. PLoS One. 2010; 5:1-9.

116. Goletti D, Raja A, Basirudeen S, Rodrigues C, Sodha A, Butera O, Carrara S, Vermet G, Longuet C, Ippolito G, Thangaraj S, Leportier M, Girardi E, Lagrange PH. IFN-γ, but not IP-10, MCP-2 or IL-2 response to RD1 selected peptides associates to active tuberculosis. J Infect.2010; 61:133-143.

117. Basirudeen SAK, Alamelu R, Balambal R, Satheesh T, Marc L, Giuseppe I, Enrico G, Lagrange PH, Delia Goletti D. IP-10 response to RD1 antigens might be a useful biomarker for monitoring tuberculosis therapy.BMC Infectious Dis.2011;11:1-9.

118. Narayanan S, Sahadevan R, Narayanan PR. Isolation and characterization of an insertion element-like repetitive sequence specific for Mycobacterium tuberculosis complex. Curr Sci.1997;73:259-266.

119. NarayananS, Parandaman V, Rehman F, Srinivasan C, Gomathy D, Kumaraswami V, Paramasivan CN, Ramanathan VD, Narayanan PR. Comparative evaluation of PCR using IS6110 and a new target in the detection of tuberculous lymphadenitis. Curr Sci.2000;78:1367-1370.

120. Parandaman V, Narayanan S, Narayanan PR. Utility of polymerase chain reaction using two probes for rapid diagnosis of tubercular pleuritis in comparison to conventional methods. Indian J Med Res.2000;112:47-51.

121. Narayanan S, Parandaman V, Narayanan PR, Venkatesan P, Girish C, Mahadevan S, Rajajee S. Evaluation of PCR using TRC_4 and IS6110 primers in detection of tuberculous meningitis. J Clin Microbiol. 2001;39:2006-2008.

122. Pradheep SA, Narayanan S, Vasan SK, Narayanan PR. Cloning and expression of aceA gene encoding isocitrate lyase from Mycobacterium tuberculosis. Curr Sci.2000;79:1585-1588.

123. Narayanan S, Selvakumar S, Aarati R, Vasan SK, Narayanan PR. Transcriptional analysis of inducible acetamidase gene of Mycobacterium smegmatis. FEMS Microbiol Lett.2000;192:263-268.

124. Selvakumar S, Narayanan S. Identification and characterization of the regulatory elements of the inducible acetamidase operon from Mycobacterium smegmatis. Can J Microbiol.2007;53:599-606.

125. Vishwanath V, Narayanan S, Narayanan PR. The fate of Mycobacterium tuberculosis in activated human macrophages. Curr Sci.1998;75:942-946.

126. Narayanan S, Vishwanath V, Narayanan PR. Differential expression of a unique protein by intracellular Mycobacterium tuberculosis complex. Curr Sci.2001;81:689-692.

127. Aravindhan V, Narayanan S, Gautham N, Prasad V, Kannan P, Jacobs WR Jr, Narayanan PR. T-h-2 immunity and $CD3^{+}$ $CD45RB^{low}$ -activated T cells in mice immunized with recombinant bacillus Calmette-Guerin expressing HIV-1 principal neutralizing determinant epitope. FEMS Immuno Med Microbiol. 2006; 47:45-55.

128. Gopalaswamy R, Narayanan PR, Narayanan S. Cloning, overexpression, and characterization of a serine/threonine protein kinase pknI from Mycobacterium tuberculosis H_{37}Rv. Protein Expr Purif.2004;36:82-89.

129. Gopalaswamy R, Narayanan S, Chen B, Jacobs WR, Av-Gay Y. The serine/threonine protein kinase PknI controls the growth of Mycobacterium tuberculosis upon infection. FEMS Microbiol Lett.2009;295:23-29.

130. Jayakumar D, Jacobs WR Jr, Narayanan S. Protein kinase E of Mycobacterium tuberculosis has a role in the nitric oxide stress response and apoptosis in a human macrophage model of infection. Cell Microbiol.2008;10:365–374.

131. Lakshminarayan H, Narayanan S, Bach H, Sundaram KG, Av-Gay Y. Molecular cloning and biochemical characterization of a serine threonine protein kinase, PknL, from Mycobacterium tuberculosis. Protein Expr Purif.2008;58:309-317.

132. Lakshminarayan H, Rajaram A, Narayanan S. Involvement of serine threonine protein kinase, PknL, from Mycobacterium tuberculosis H_{37}Rv in starvation response of mycobacteria. J Microb Biochem Tech.2009;1:30-36.

133. Aravindhan V, Christy AJ, Roy S, Ajitkumar P, Narayanan PR, Narayanan S. Mycobacterium tuberculosis groE promoter controls the expression of the bicistronic groESL1 operon and shows differential regulation under stress conditions. FEMS Microbiol Lett.2009;292:42-49.

134. Natarajan P, Narayanan S. Mycobacterium tuberculosis H37Rv induces monocytic release of interleukin-6 via activation of mitogen-activated protein kinases: inhibition by N-acetyl-l-cysteine. FEMS Immunol Med Microbiol. 2007;50:309-318.

135. Narayanan S, Swaminathan S, Supply P, Sivakumar S, Narendran G, Hari L, Ramachandran R, Locht C, Jawahar MS, Narayanan PR. Impact of HIV infection on the recurrence of tuberculosis in south India J Infect Dis.2010; 201:691-703.

136. Narayanan S, Guleria JS. Reactivation and reinfection tuberculosis. Book published by Jaypee Brothers Medical Publishers (P) Ltd., New Delhi on Tuberculosis. Second Edition. Ed. Sharma SK and Mohan A.2009;656-664.

137. Narayanan S, Sahadevan R, Narayanan PR, Krishnamurthy PV, Paramasivan CN, Prabhakar R. Restriction fragment length polymorphism of Mycobacterium tuberculosis strains from various regions of India, using direct repeat probe. Indian J Med Res.1997;106:447-454.

138. Narayanan S, Das S, Garg R, Hari L, Rao VB, Frieden TR, Narayanan PR. Molecular epidemiology of tuberculosis in a rural area of high prevalence in south India: implications for disease control and prevention. J Clin Microbiol.2002;40:4785-4788.

139. Narayanan S. Molecular epidemiology of tuberculosis. Indian J Med Res. 2004; 120:233-247.

140. Narayanan S, Gagneux S, Hari L, Tsolaki AG, Rajasekhar S, Narayanan PR, Small PM, Holmes S, Deriemer K. Genomic interrogation of ancestral Mycobacterium tuberculosis from south India. Infect Genet Evol.2008;8:474-483.

141. Selvaraj P, Uma H, Reetha AM, Kurian SM, Xavier T, Prabhakar R, Narayanan PR. HLA antigen profile in pulmonary tuberculosis patients and their spouses. Indian J Med Res.1998;107:155-158.

142. Sriram U, Selvaraj P, Kurian SM, Reetha AM, Narayanan PR. HLA-DR2 subtypes & immune responses in pulmonary tuberculosis. Indian J Med Res.2001;113:117-124.

143. Selvaraj P, Narayanan PR, Reetha AM. Association of functional mutant homozygotes of the mannose binding protein gene with susceptibility to pulmonary tuberculosis in India. Tuber Lung Dis.1999;79:221-227.

144. Selvaraj P, Narayanan PR, Reetha AM. Association of vitamin D receptor genotypes with the susceptibility to pulmonary tuberculosis in female patients & resistance in female contacts. Indian J Med Res.2000;111:172-179.

145. Selvaraj P, Chandra G, Kurian SM, Reetha AM, Narayanan PR. Association of vitamin D receptor gene variants of Bsm I, ApaI and FokI polymorphisms with susceptibility or resistance to pulmonary tuberculosis. Curr Sci.2003; 84:1564-1568.

146. Vidyarani M, Selvaraj P, Prabhu Anand S, Jawahar MS, Adhilakshmi AR, Narayanan PR. Interferon gamma (IFN gamma) & interleukin-4 (IL-4) gene variants & cytokine levels in pulmonary tuberculosis. Indian J Med Res. 2006;124:403-10.

147. Selvaraj P, Alagarasu K, Harishankar M, Vidyarani M, Nisha Rajeswari D, Narayanan PR. Cytokine gene polymorphisms and cytokine levels in pulmonary tuberculosis. Cytokine.2008;43:26-33.

148. Selvaraj P, Harishankar M, Singh B, Jawahar MS, Banurekha VV.Toll-like receptor and TIRAP gene polymorphisms in pulmonary tuberculosis patients of south India. Tuberculosis (Edinb).2010;90:306-310.

149. Selvaraj P, Reetha AM, Uma H, Xavier T, Janardhanam B, Prabhakar R, et al. Influence of HLA-DR and -DQ phenotypes on tuberculin reactive status in pulmonary tuberculosis patients. Tuber Lung Dis.1996;77:369-373.

150. Selvaraj P, Uma H, Reetha AM, Xavier T, Prabhakar R, Narayanan PR. Influence of HLA-DR2 phenotype on humoral immunity & lymphocyte response to Mycobacterium tuberculosis culture filtrate antigens in pulmonary tuberculosis. Indian J Med Res.1998b;107:208-17.

151. Uma H, Selvaraj P, Reetha AM, Xavier T, Prabhakar R, Narayanan PR. Influence of HLA-DR antigens on lymphocyte response to Mycobacterium tuberculosis culture filtrate antigens and mitogens in pulmonary tuberculosis. Tuber Lung Dis. 1999; 79:199-206.

152. Rajeswari DN, Selvaraj P, Raghavan S, Jawahar MS, Narayanan PR. Influence of HLA-DR2 on perforin-positive cells in pulmonary tuberculosis. Int J Immunogenet. 2007;34:379-84.

153. Selvaraj P, Jawahar MS, Rajeswari DN, Alagarasu K, Vidyarani M, Narayanan PR. Role of mannose binding lectin gene variants on its protein levels and macrophage phagocytosis with live Mycobacterium tuberculosis in pulmonary tuberculosis. FEMS Immunol Med Microbiol. 2006;46:433-7.

154. Selvaraj P, Nisha Rajeswari D, Jawahar MS, Narayanan PR. Influence of HLA-DRB1 alleles on Th1 and Th2 cytokine response to Mycobacterium tuberculosis antigens in pulmonary tuberculosis. Tuberculosis (Edinb). 2007;87:544-550.

155. Chandra G, Selvaraj P, Jawahar MS, Banurekha VV, Narayanan PR. Effect of vitamin D3 on phagocytic potential of macrophages with live Mycobacterium tuberculosis and lymphoproliferative response in pulmonary tuberculosis. J Clin Immunol.2004; 24:249-57.

156. Vidyarani M, Selvaraj P, Jawahar MS, Narayanan PR. 1, 25 Dihydroxyvitamin D3 modulated cytokine response in pulmonary tuberculosis. Cytokine. 2007; 40:128-34.

157. Selvaraj P, Prabhu Anand S, Harishankar M, Alagarasu K. Plasma 1,25 dihydroxy Vitamin D3 level and expression of vitamin d receptor and cathelicidin in pulmonary tuberculosis. J Clin Immunol.2009; 29:470-8.

158. Selvaraj P, Chandra G, Jawahar MS, Rani MV, Rajeshwari DN, Narayanan PR. Regulatory role of vitamin D receptor gene variants of Bsm I, Apa I, Taq I, and Fok I polymorphisms on macrophage phagocytosis and lymphoproliferative response to Mycobacterium tuberculosis antigen in pulmonary tuberculosis. J Clin Immunol.2004; 24: 523-32.

159. Prabhu Anand S, Selvaraj P, Narayanan PR. Effect of 1,25 dihydroxyvitamin D3 on intracellular IFN-gamma and TNF-alpha positive T cell subsets in pulmonary tuberculosis. Cytokine.2009; 45:105-10.

160. Selvaraj P, Swaminathan S, Alagarasu K, Raghavan S, Narendran G, Narayanan P. Association of human leukocyte antigen-A11 with resistance and B40 and DR2 with susceptibility to HIV-1 infection in south India. J Acquir Immune Defic Syndr.2006; 43: 497-9.

161. Raghavan S, Selvaraj P, Swaminathan S, Alagarasu K, Narendran G, Narayanan PR. Haplotype analysis of HLA-A, -B antigens and -DRB1 alleles in south Indian HIV-1-infected patients with and without pulmonary tuberculosis. Int J Immunogenet. 2009; 36: 129-133.

162. Raghavan S, Selvaraj P, Swaminathan S, Narendran G. Short communication: association of HLA-A*1101 with resistance and B*4006 with susceptibility to HIV and HIV-TB: an in silico analysis of promiscuous T-cell epitopes. AIDS Res Hum Retroviruses.2009;25:1023-1028.

163. Selvaraj P, Raghavan S, Swaminathan S, Alagarasu K, Narendran G, Narayanan PR.HLA-DQB1 and -DPB1 allele profile in HIV infected patients with and without pulmonary tuberculosis of south India. Infect Genet Evol.2008;8:664-671.

164. Alagarasu K, Selvaraj P, Swaminathan S, Raghavan S, Narendran G, Narayanan PR. Mannose binding lectin gene variants and susceptibility to tuberculosis in HIV-1 infected patients of South India. Tuberculosis (Edin .2007;87:535-543.

165. Alagarasu K, Selvaraj P, Swaminathan S, Narendran G., Narayanan P.R,. 5' Regulatory and 3' Untranslated Region Polymorphisms of Vitamin D receptor Gene in South Indian HIV and HIV-TB Patients. J Clin Immunol. 2009; 29: 196-204.

166. Selvaraj P, Alagarasu K, Swaminathan S, Harishankar M, Narendran G. CD209 gene polymorphisms in South Indian HIV and HIV-TB patients. Infect Genet Evol.2009;9:256-62.

167. Alagarasu K, Selvaraj P, Swaminathan S, Raghavan S, Narendran G, Narayanan PR. CCR2, MCP-1, SDF-1α & DC-sign gene polymorphisms in HIV-1 infected patients with & without tuberculosis Indian J Med Res. 2009;130: 444-450

168. Jalapathy KV, Prabha C, Das SD. Correlates of protective immune response in tuberculous pleuritis. FEMS Immunol Med Microbiol. 2004;40:139-145.

169. Prabha C, Jalapathy KV, Matsa RP, Das SD. Differential T helper cell response in tuberculous pleuritis. Indian J Med Microbiol.2007;25:18-23.

170. Prabha C, Jalapathy KV, Matsa RP, Das SD. Role of TNF-α in host immune response in tuberculous pleuritis. Curr Sci.2003;85:639-642.

171. Prabha C, Rajashree P, Das SD. TLR2 and TLR4 expression on the immune cells of tuberculous pleural fluid. Immunol Lett.2008;117:26-34.

172. Das SD, Subramanian D, Prabha C. Cell proliferation and apoptosis: dual-signal hypothesis tested in tuberculous pleuritis using mycobacterial antigens. FEMS Immunol Med Microbiol.2004;41:85-92.

173. Rajavelu P, Madhumathi J, Das SD. Humoral immune responses of normals and tuberculosis patients to multiple sonicate antigens prepared from the most prevalent strains of Mycobacterium tuberculosis harbouring single copy of IS6110 from south India. Curr Sci.2006;91:918-922.

174. Rajavelu P, Das SD. Cell-mediated immune responses of healthy laboratory volunteers to sonicate antigens prepared from the most prevalent strains of Mycobacterium tuberculosis from south India harboring a single copy of IS6110. Clin Diagn Lab Immunol. 2003;10:1149-1152.

175. Rajavelu P, Das SD. Th2-type immune response observed in healthy individuals to sonicate antigen prepared from the most prevalent Mycobacterium tuberculosis strain with single copy of IS6110. FEMS Immunol Med Microbiol. 2005;45:95-102.

176. Rajavelu P, Das SD. A correlation between phagocytosis and apoptosis in THP-1 cells infected with prevalent strains of Mycobacterium tuberculosis. Microbiol Immunol.2007;51:201-210.

177. Rajavelu P, Supriya P, Umashankar P, Bhatt K, Narayanan PR, Salgame P, Das SD. Comparative evaluation of cytokines, T-cell apoptosis, and costimulatory molecule expression in tuberculous and nontuberculous pleurisy. Clin Transl Sci.2008;1: 209-214.

178. Rajavelu P, Das SD. Expression of co-stimulatory molecules B7.1 & B7.2 on macrophages infected with various strains of Mycobacterium tuberculosis & its influence on T-cell apoptosis. Indian J Med Res.2008;127:388-394.

179. Pokkali S, Das SD, Logamurthy R. Expression of CXC and CC type of chemokines and its receptors in tuberculous and non-tuberculous effusions. Cytokine. 2008;41:307-314.

180. Supriya P**,** Das SD. Augmented chemokine levels and chemokine receptor expression on immune cells during pulmonary tuberculosis Human Immunol.2009;70:110-115.

181. Supriya P, Prabha C, Das SD. Diagnostic utility of interferon-γ induced protein of 10kDa (IP-10) in tuberculous pleurisy. Diagn Microbiol Infect Dis.2008;62:186-192.

182. Supriya P, Priya R, Sudhakar R, Sulochana D. Phenotypic modulation in Mycobacterium tuberculosis infected neutrophil during tuberculosis. Indian J Med Res.2009;130:185-192.

183. Rajashree P, Supriya P, Das SD. Differential migration of human monocyte-derived dendritic cells after infection with prevalent clinical strains of Mycobacterium tuberculosis. Immunobiology.2008;213:567-575.

184. Rajashree P, Das SD. Infection with prevalent clinical strains of Mycobacterium tuberculosis leads to differential maturation of monocyte derived dendritic cells. Immunol Lett.2008;117:174-180.

185. Rajashree P, Krishnan G, Das SD. Impaired phenotype and function of monocyte derived dendritic cells in pulmonary tuberculosis. Tuberculosis. 2009;89:77–83.

186. Das S, Paramasivan CN, Lowrie DB, Prabhakar R, Narayanan PR. IS6110 restriction fragment length polymorphism typing of clinical isolates of Mycobacterium tuberculosis from patients with pulmonary tuberculosis in Madras, south India. Tubercle Lung Dis.1995;76:550-554.

187. Das S, Narayanan S, Hari L, Mohan NS, Somasundaram S, Selvakumar N, Narayanan PR. Simultaneous infection with multiple strains of Mycobacterium tuberculosis identified by restriction fragment length polymorphism analysis. Int J Tuberc Lung Dis.2004;8:267-270.

188. Das SD, Narayanan S, Hari L, Hoti SL, Thangathurai RK, Charles N, Jaggarajamma K, Narayanan PR. Differentiation of highly prevalent IS6110 single-copy strains of Mycobacterium tuberculosis from a rural community in south India with an ongoing DOTS programme. Infect Genet Evol.2005;5:67-77.

189. Dey B, Jain R, Khera A, Gupta UD, Katoch VM, Ramanathan VD, Tyagi AK. Latency antigen α-crystallin based vaccination imparts a robust protection against TB by modulating the dynamics of pulmonary cytokines. PLoS One.2011;6:1-11.

190. Dey B, Jain R, Khera A, Rao V, Dhar N, Gupta UD, Katoch VM, Ramanathan VD, Tyagi AK.Boosting with a DNA vaccine expressing ESAT-6 (DNAE6) obliterates the protection imparted by recombinant BCG (rBCGE6) against aerosol Mycobacterium tuberculosis infection in guinea pigs. Vaccine. 2009;28:63-70.

191. Jain R, Dey B, Dhar N, Rao V, Singh R, Gupta UD, Katoch VM, Ramanathan VD, Tyagi AK. Enhanced and enduring protection against tuberculosis by recombinant BCG-Ag85C and its association with modulation of cytokine profile in lung. PLoS One.2008;3:1-11.

192. Jayasankar K, Shakila H, Umapathy KC, Ramanathan VD Biochemical and histochemical changes pertaining to active and healed cutaneous tuberculosis. Br J Dermatol.2002;146:977-82.

193. Umapathy KC, Begum R, Ravichandran G, Rahman F, Paramasivan CN, Ramanathan VD. Comprehensive findings on clinical, bacteriological, histopathological and therapeutic aspects of cutaneous tuberculosis. Trop Med Int Health. 2006 Oct;11(10):1521-8.

194. Senbagavalli P, Geetha ST, Venkatesan P, Ramanathan VD. Defective solubilization of immune complexes and activation of the complement system in patients with pulmonary tuberculosis. J Clin Immunol. 2009 Sep;29(5):674-80. Epub 2009 May 27.

195. Senbagavalli P, Geetha ST, Karunakaran K, Banu Rekha VV, Venkatesan P, Ramanathan VD. Reduced erythrocyte CR1 levels in patients with pulmonary tuberculosis is an acquired phenomenon. Clin Immunol. 2008 Jul;128(1):109-15. Epub 2008 Apr 22.

196. Babu S, Bhat SQ, Pavan Kumar N, Lipira AB, Kumar S, Karthik C, Kumaraswami V, Nutman TB. Filarial lymphedema is characterized by antigen-specific Th1 and th17 proinflammatory responses and a lack of regulatory T cells. PLoS Negl Trop Dis.2009;3:1-9.

197. Babu S, Blauvelt CP, Kumaraswami V, Nutman TB. Chemokine receptors of T cells and of B cells in lymphatic filarial infection: a role for CCR9 in pathogenesis. J Infect Dis.2005;191:1018-1026.

198. Babu S, Kumaraswami V, Nutman TB. Alternatively activated and immunoregulatory monocytes in human filarial infections. J Infect Dis. 2009; 199:1827-1837.

199. Babu S, Blauvelt CP, Kumaraswami V, Nutman TB. Cutting edge: diminished T-cell TLR expression and function modulates the immune response in human filarial infection. J Immunol.2006;176:3885-3889.

200. Babu S, Blauvelt CP, Kumaraswami V, Nutman TB. Diminished expression and function of TLR in lymphatic filariasis: a novel mechanism of immune regulation. J Immunol.2005;175:1170-1176.

201. Babu S, Kumaraswami V, Nutman TB. Transcriptional control of impaired Th1 responses in patent lymphatic filariasis by T-box expressed in T-cells and suppressor of cytokine signaling genes. Infect Immun.2005;73:3394-3401.

202. Babu S, Blauvelt CP, Kumaraswami V, Nutman TB. Regulatory networks induced by live filarial parasites impair both Th1 and Th2 responses in patent lymphatic filariasis: implications for parasite persistence. J Immunol. 2006; 176:3248-3256.

203. Babu S, Bhat SQ, Kumar NP, Jayantasri S, Rukmani S, Kumaran P, Gopi PG, Kolappan C, Kumaraswami V, Nutman T. Human type 1 and 17 responses in latent tuberculosis are modulated by coincident filarial infection through cytotoxic T-lymphocyte antigen-4 and programmed death-1. J Infect Dis. 2009; 200:288-298.

204. Babu S, Bhat SQ, Kumar NP, Anuradha R, Kumaran P, Gopi PG, Kolappan C, Kumaraswami V, Nutman TB. Attenuation of toll-like receptor expression and function in latent tuberculosis by coexistent filarial infection with restoration following antifilarial chemotherapy. PLoS NeglTrop Dis.2009;3:1-8.

205. Babu S, Bhat SQ, Kumar NP, Kumaraswami V, Nutman TB. Regulatory T- cells modulate Th17 responses in patients with positive tuberculin skin test results. J Infect Dis.2010;201:20-31.

206. Aravindhan V, Mohan V, Surendar J, Muralidhara Rao M, Pavankumar N, Deepa M, Rajagopalan R, Kumaraswami V, Nutman TB, Babu S. Decreased prevalence of lymphatic filariasis among diabetic subjects associated with a diminished pro-inflammatory cytokine response (CURES 83). PLoS Negl Trop Dis.2010;4:1-6.

207. Aravindhan V, Mohan V, Surendar J, Rao MM, Ranjani H, Kumaraswami V, Nutman TB, Babu S. Decreased prevalence of lymphatic filariasis among subjects with type-1 diabetes. Am J Trop Med Hyg.2010;83:1336-1339.

208. Subramani R, Santha T, Frieden TR, Radhakrishna S, Gopi PG, Selvakumar N, Sadacharam K, Narayanan PR. Active community surveillance of the impact of different tuberculosis control measures, Tiruvallur, South India, 1968-2001. Int J Epidemiol.2007;36:387-393.

209. Muniyandi M, Rajeswari R, Balasubramanian R, Narayanan PR. Socio-economic dimensions of tuberculosis control : Review of studies over two decades from Tuberculosis Research Centre. J Commun Dis.2006;38: 204-215.

210. Gopi PG, Subramani R, Santha T, Chandrasekaran V, Kolappan C, Selvakumar N, Narayanan PR. Estimation of burden of tuberculosis in India for the year 2000. Indian J Med Res.2005;122:243-248.

211. Santha T, Garg R, Subramani R, Chandrasekaran V, Selvakumar N, Sisodia RS, Perumal M, Sinha SK, Singh RJ, Chavan R, Ali F, Sarma SK, Sharma KM, Jagtap D, Frieden TR, Fabio L, Narayanan PR. Comparison of cough of 2 and 3 weeks to improve detection of smear-positive tuberculosis cases among out-patients in India. Int J Tuberc Lung Dis.2005;9:61-68.

212. Balasubramanian R, Rajeswari R, Nayak AC, Duraipandian P, Karunakaran K, Narayanan PR. A double-blind study of oral salbutamol supplement and repeat sputum smear microscopy in enhancing diagnosis of smear-negative pulmonary tuberculosis in South India. Indian J Tuberc.2004;51:191-198.

213. Balasubramanian R, Ramachandran R, Rao VB, Jaggarajamma K, Gopi PG, Chandrasekaran V, Narayanan PR. A rural public-private partnership model in tuberculosis control in South India. Int J Tuberc Lung Dis.2006;10:1380-1385.

214. Selvakumar N, Rahman F, Garg R, Rajasekaran S, Mohan NS, Thyagarajan K, Sundaram V, Santha T, Frieden TR, Narayanan PR. Evaluation of the phenol ammonium sulfate sedimentation smear microscopy method for diagnosis of pulmonary tuberculosis. J Clin Microbiol.2002;40:3017-3020.

215. Selvakumar N, Sudhamathi S, Duraipandian M, Frieden TR, Narayanan PR. Reduced detection by Ziehl-Neelsen method of acid-fast bacilli in sputum samples preserved in cetylpyridinium chloride solution. Int J Tuberc Lung Dis. 2004;8:248-252.

216. Gopi PG, Subramani R, Selvakumar N, Santha T, Eusuff SI, Narayanan PR. Smear examination of two specimens for diagnosis of pulmonary tuberculosis in Tiruvallur district, south India. Int J Tuberc Lung Dis.2004;8:824-828.

217. Jaggarajamma K, Balambal R, Muniyandi M, Vasantha M, Thomas B, Nirupa C, Sudha G, Chandrasekaran V, Wares F. Perceptions of tuberculosis patients about private providers before and after implementation of Revised National Tuberculosis Control Programme. Indian J Tuberc.2009;56:185-190.

218. Santha T, Garg R, Frieden TR, Chandrasekaran V, Subramani R, Gopi PG, Selvakumar N, Ganapathy S, Charles N, Rajamma J, Narayanan PR. Risk factors associated with default, failure and death among tuberculosis patients treated in a

DOTS programme in Tiruvallur District, South India, 2000. Int J Tuberc Lung Dis.2002;6:780-788.

219. Santha T, Thomas A, Chandrasekaran V, Selvakumar N, Gopi PG, Subramani R, Rajeswari R, Rani B, Paramasivan CN, Perumal M, Wares F, Narayanan PR. Initial drug susceptibility profile of M. tuberculosis among patients under TB programme in South India. Int J Tuberc Lung Dis. 2006; 10:52-57.

220. Joseph P, Chandrasekaran V, Thomas A, Gopi PG, Rajeswari R, Balasubramanian R, Subramani R, Selvakumar N, Santha T. Influence of drug susceptibility on treatment outcome and susceptibility profile of 'failures' to Category II regimen. Indian J Tuberc.2006;53:141-148.

221. Selvakumar N, Prabhakaran E, Murthy BN, Sivagamasundari S, Vasanthan S, Govindaraju R, Perumal M, Wares F, Chauhan LS, Santha T, Narayanan PR. Application of lot sampling of sputum AFB smears for the assessment of microscopy centres. Int J Tuberc Lung Dis.2005;9: 306-309.

222. Selvakumar N, Murthy BN, Prabhakaran E, Sivagamasundari S, Vasanthan S, Perumal M, Govindaraju R, Chauhan LS, Wares F, Santha T, Narayanan PR. Lot quality assurance sampling of sputum acid-fast bacillus smears for assessing sputum smear microscopy centers. J Clin Microbiol.2005;43:913-915.

223. Selvakumar N, Sivagamasundari S, Prabhakaran E, Govindaraju R, Perumal M, Granich R, Wares F, Chauhan LS, Narayanan PR. Storage of heat-fixed unstained sputum AFB smears for panel testing in a tuberculosis unit in South India. Int J Tuberc Lung Dis.2005;9:223-225.

224. Kolappan C, Gopi PG, Subramani R, Chadha VK, Kumar P, Prasad VV, Appegowda BN, Rao RSN, Sashidharan R, Ganesan N, Santha T, Narayanan PR. Estimation of annual risk of tuberculosis infection (ARTI) among children aged 1-9 years in the south zone of India. Int J Tuberc Lung Dis.2004;8:418-423.

225. Ramachandran R, Chandrasekaran V, Muniyandi M, Jaggarajamma K, Bagchi A, Sahu S. Cross-referral between HIV counselling and testing centres and smear microscopy centres in Tamil Nadu. Int J Tuberc Lung Dis. 2009;13:221-225.

226. Das SD, Narayanan S, Hari L, Hoti SL, Thangathurai RK, Charles N, Jaggarajamma K, Narayanan PR. Differentiation of highly prevalent IS6110 single-copy strains of Mycobacterium tuberculosis from a rural community in South India with an ongoing DOTS programme. Infect Genet Evol.2005;5:67–77.

227. Boaz MJ, Hayes P, Tarragona T, Seamons L, Cooper A, Birungi J, Kitandwe P, Semaganda A, Kaleebu P, Stevens G, Anzala O, Farah B, Ogola S, Indangasi J, Mhlanga P, Van Eeden M, Thakar M, Pujari A, Mishra S, Goonetilleke N, Moore S, Mahmoud A, Sathyamoorthy P, Mahalingam J, Narayanan PR, Ramanathan VD, Cox JH, Dally L, Gill DK, Gilmour J. Concordant proficiency in measurement of T-cell immunity in Human immunodeficiency virus Vaccine clinical trials by peripheral blood mononuclear cell and enzyme-linked immunospot assays in laboratories from three continents. Clin Vaccine Immunol.2009;16:147-155.

228. Ramanathan VD, Kumar M, Mahalingam J, Sathyamoorthy P, Narayanan PR, Solomon S, Panicali D, Chakrabarty S, Cox J, Sayeed E, Ackland J, Verlinde C, Vooijs D, Loughran K, Barin B, Lombardo A, Gilmour J, Stevens G, Smith MS, Tarragona-Fiol T, Hayes P, Kochhar S, Excler JL, Fast P. A Phase 1 study to evaluate the safety and immunogenicity of a recombinant HIV type 1 subtype C-modified vaccinia Ankara virus vaccine candidate in Indian volunteers. AIDS Res Hum Retroviruses.2009;25: 1107-1116.

National Institute for Research in Tuberculosis
Indian Council of Medical Research
No.1, Sathyamoorthy Road
Chetpet, Chennai 600031
www.trc-chennai.org