

Introduction

The President notified the creation of the Department of Health Research under the Ministry of Health & Family Welfare through an amendment to the Government of India (Allocation of Business) Rules, 1961 on the 17th September, 2007.

The Department of Health Research was formally launched on 5th October, 2007 by the Minister for Science & Technology and Earth Science in a function presided over by the Minister for Health & Family Welfare, in the presence of the Minister of State for Health & Family Welfare.

The first Secretary of the Department who is also the Director General of the Indian Council of Medical Research, was appointed in November, 2008.

The following work has been allocated to the Department of Health Research:

1. Promotion and co-ordination of basic, applied and clinical research including clinical trials and operational research in areas related to medical, health, biomedical and medical profession and education through development of infrastructure, manpower and skills in cutting edge areas and management of related information thereto.
2. Promote and provide guidance on research governance issues, including ethical issues in medical and health research.
3. Inter-sectoral coordination and promotion of public - private - partnership in medical, biomedical and health research related areas.
4. Advanced training in research areas concerning medicine and health, including grant of fellowships for such training in India and abroad.
5. International co-operation in medical and health research, including work related to international conferences in related areas in India and abroad.
6. Technical support for dealing with epidemics and natural calamities.
7. Investigation of outbreaks due to new and exotic agents and development of tools for prevention.
8. Matters relating to scientific societies and associations, charitable and religious endowments in medicine and health research areas.
9. Coordination between organizations and institutes under the Central and State Governments in areas related to the subjects entrusted to the Department and for the promotion of special studies in medicine and health.

10. Administering and monitoring of Indian Council of Medical Research.

Of the work allocation given above, the work relating to ICMR was the only ongoing scheme to have been transferred to the Department. There was almost no systematic work on the remaining areas allocated, although some ad hoc work was taken up during emergencies like the H1N1 out break. This has necessitated the taking up of new schemes in view of the major gap in programmes and infrastructure that exists today with respect to health research.

Since the creation of the Department wide scale consultations have been initiated in order to finalize and firm up the interventions and policies required in order to establish and facilitate a vibrant, well functioning and relevant health Research system.

Based on consultation four schemes have been prepared the details of which are given in following chapters.

Infrastructure Development for Health Research

There is a need to promote basic, applied research for the improvement in the health care services in the country. Normally the health research is confined to Medical Colleges/Institutions providing education in allied subjects and other research Institutions. Medical Colleges are the back bone of both teaching and providing specialized services to patients in India. They are also expected to set the trends in the thinking process and innovations to improve our understanding of the diseases and their management. However, over the years it has been noticed that majority of medical colleges have confined themselves to routine patient care and teaching based on conventional methods. Presently, quality Medical Research is largely confined to a handful of institutions and medical colleges in the country that too in few States only. The standard of papers published/ research projects undertaken by the students of post-graduate courses/PhD in most of the Medical Colleges are not inspiring. This can be attributed both to the lack of appropriate facilities for conducting research and a lack of motivation and knowledge on the part of faculty and students in Medical Colleges for conducting research.

Consequently, the Medical Colleges are not pursuing newer methods of investigation for understanding the pathological diagnosis, treatment and management practices. This has not been perceived as a priority area for States and even for many Central institutes. This also affects the quality of clinical services being provided. There is, therefore, an urgent need to promote and encourage quality medical research in the country and provide assistance to the Medical Colleges to set up appropriate facility.

Though Medical Research is part of the Medical Education and Animal House facility is a basic requirement for undertaking research by the students in the Medical Colleges, most of the medical colleges do not have well established animal house facility meeting the requirements of the regulatory authorities under the Prevention of Cruelty to Animals Act. Since having a well established animal house facility is essential for promoting medical research in any institution, there is a need to provide support to the medical colleges for establishing a good animal house facility meeting the basic requirement of the regulatory authority.

Similarly medical professionals in the public health system, especially those working in the periphery, lack access to information on modern advances in a regular fashion in their settings, the transfer of technology to the end users becomes very difficult. As

the medical doctors working in the public health system do not get opportunity to get orientation on modern advances in a regular fashion in their settings, the transfer of technology to the end users becomes very difficult. Further wide variations exist in the pattern of diseases prevalent, the local conditions which require development of state/area specific, disease specific strategy to provide better health care facilities ensuring the modern technology is made available to the general public.

There is, therefore, a need to create structures which function as an interface between the new technologies developers (Researchers in the Medical Institutions; State or Centre), health systems operators (Centre or state health services) and the beneficiaries (community Rural, Urban slums). There is need to create a structure in a rural setting which would act as a model unit to transfer the technology to the state health system where research under basic, applied and clinical discipline will be undertaken to transfer the technology for use of rural population of that area.

Objectives:

The objectives of the present scheme are to:

- bridge the gap in the infrastructure which is inhibiting health research in the Medical Colleges by assisting them to establish multidisciplinary research laboratory and animal house facility with a view to improving the health research and health services.
- create infrastructure for transfer of technology to the end users which would ensure an interface between the new technologies developers (Researchers in the Medical Institutions; State or Centre), health systems operators (Centre or state health services) and the beneficiaries (community Rural, Urban slums)
- to ensure the geographical spread of health research infrastructure by selecting judiciously the institutions to be supported under the scheme.
- This scheme, with the components detailed below are essential since there are no other schemes at present, which address these issues either in the Ministry of Health & Family Welfare or in other Ministries.

Components :

1. Establishment of Modern Biological Lab/ Multidisciplinary research units in Government Medical Colleges and institutions
2. Establishing Animal House facilities in Govt. Medical Colleges
3. Developing of Model Rural Health Research Units (MRHRU) in states

Details:

A. Setting up of modern biological labs/ multi-disciplinary research units in State Govt. medical colleges

At present there are about 300 medical colleges in the country of which 143 are in Govt. sector. In order to revitalize medical colleges as centres for bio medical research, it is proposed to provide financial assistance upto Rs. 5 crores to each medical college for setting up appropriate infrastructure for medical research, depending on

the infrastructure gap/ requirement of the institution This will include funds for civil works, equipments and furniture considering the availability of existing infrastructure in each of the Medical College, the requirements in terms of equipments, civil work for medical colleges etc. will vary. During the project period of 3 years, it is proposed to take up 100 State Government Medical Colleges. The project will be extended thereafter to cover the remaining government medical colleges and others. The total project cost for this purpose would be Rs. 500 crores.

Apart from the non-recurring grant of Rs. 5 crores per college, recurring grant will also be extended for a period of 5 years for engaging trained technical man power on contractual basis, for training, consumables and contingency expenditure.

Achievements :

1. The scheme has been approved in principle by the planning commission and expenditure finance concurrence has been prepared.
2. 27 medical colleges from 14 different states have sent their application for establishing multi-disciplinary research unit and animal house facilities. 15 medical colleges have been selected taken up into the first phase.
3. DHR has received concurrence and proposals from 5 states namely Himachal Pradesh, Rajasthan, Bihar, Tamil Nadu and Maharashtra and a workshop has been proposed to initiate the proposals through MRHRU of these states.

Human Resource Development for Health Research

Advances in the quality of health care and improvement of the health of people through research will require an accelerated expansion in the supply of health manpower for research. The growth of health research is directly dependent on the availability of trained medical and bio medical manpower, which is possible through the training of competent personnel, providing start-up grants for their initiation into active research and ensuring some career growth opportunities.

Apart from the overall shortage of trained personnel, with the rapid advances in medical science, there is also a need to create/ augment personnel in emerging and new areas. There is, therefore, an urgent need to support manpower development for health research in the country. The proposed support to biomedical research training includes institutional training grants, individual fellowships, training grants, research grants etc.

Objectives:

The objectives of the present scheme are to:

- To increase the availability of personnel for health research through scholarships, fellowships and career advancement scheme etc. thereby providing an incentive for people to take up medical and health research
- To assist in the creation of a cadre of skilful researchers in fields such as clinical trials; Toxicology; Good Clinical Practices (GCP); Good Laboratory Practices (GLP); Quality Control (QC) & QA; Genomics; Proteomics; Geriatrics; Modern Biology; Biotechnology; Stem cells; Genetics; Drugs chemistry; any other specialized area of medicine and operational research.
- To create and support multidisciplinary and multi-sectoral teams of researchers working in medical colleges, universities, research institutes and NGOs
- This scheme, with the components detailed below is essential since there are no other schemes at present, which address these issues either in the Ministry of Health & Family Welfare or in other Ministries. To create synergy an Expert group has been constituted to identify the areas in

which the DHR will complement the efforts of other science agencies in order to avoid any duplication of effort.

Components:

- Programme to create researchers in high focus, high skill areas.
- Programme to promote medical research as a career among young scientists and medical students.
- Programme to promote research in young and mid career faculty of medical colleges.
- Creation of a national initiative in partnership with relevant stakeholders to attract and retain the young to a career in health research
- Development of human resource policy with focus on career development scheme for young researchers
- Strengthening research through the establishment of online courses and web portal on health research for students, faculty and other researchers.

Details :

- **Development of researchers in critical and high focused areas:** This would be done through the adoption of a multi pronged strategy.
 - ♦ **Through the identification of institutions working in identified areas,** and by providing access to researchers to work in frontline areas in such state- of- the- art facilities. Under this programme, selected researchers would be placed in state-of-the-art facilities both within and outside India, as required in cutting edge areas, so as to enhance their skills and knowledge and to ensure a core group with skills in important areas. In order to implement this scheme, Department of Health Research would identify state of the art facilities within and outside India. It will provide funds to the institutions in India for up gradation of facilities & consumables etc. and to the researchers; to develop core teams in selected areas.
 - ♦ **To provide technology support to investigators** who plan to work on frontline areas of medical and health research, mechanisms will be built to make such facilities available to them locally or anywhere within the nation.
- **Programme to promote medical research as a career among young scientists and medical students:** This will be ensured through the provision of fellowships and scholarships as follows:
 - ♦ **Fellowships for training:** Researchers in identified advanced fields would be provided fellowships so as to enhance their skills in deficit areas. **DHR** would provide fellowships for trainings in frontline and emerging areas for training within India and abroad.

These fellowship trainings will be preferably for relatively young investigators who are working on health related areas and where the plans for utilizing the training are well focussed and concrete.

- ◆ **Provision of scholarships at the Post graduate level:** Support for producing man power in newer areas which are essential for development of health research like Postgraduate degrees in clinical research, health technology, Regenerative Medicine, Ethics in medical research, patents relating to health, etc.
- ◆ For the creation of a national initiative in partnership with relevant stakeholders to attract and retain the young to a career in health research:
- ◆ **Institution of a young Researcher programme:** The Young Researcher Programme is designed for highly qualified and motivated individuals skilled in areas relevant to bio medical research, who wish to take up medical research as a career option. The programme would be open for potential researchers who have completed their undergraduate medical degree or post graduate degrees in medical and biomedical fields. This is proposed to be achieved by providing special training programmes.
- ◆ Selected researchers would participate in specially designed orientation and given an opportunity for on-the-job learning and mentoring. They would be provided an opportunity to participate in seminars, short trainings and workshops. They would also be provided specialized training through scholarships where required.
- ◆ At the end of their training/ fellowship, selected researchers would be provided **startup grants** to enable them to take up projects based on their training.
- ◆ As highlighted above the proposed programme would identify **young and mid career researchers in medical colleges & other health research institutions** and then provide support through fellowships and subsequently a start up grant so as to attract and retain the young in a career of health research.

Achievements :

1. The scheme has been approved in principle by the planning commission and expenditure finance concurrence has been prepared.

Grant-in-Aid for Health Research

At present number of Institutions/Universities are undertaking projects in Health Research relating to basic, clinical, operational areas. Some of the leads, by chance, are also get translated to products. However, these research projects are being taken up in isolation and there is no coordination between these researchers in basic, clinical etc. and the community clinician, clinical practitioners, professional society, industries etc. so that the research undertaken is focused, broader and with an aim to develop products and processes for the benefit of society. A bench-to-bedside approach to translational research is really a two-way street. Basic scientists provide clinicians with new knowledge about biology and tools for use in patients and for assessment of their impact, and clinical researchers make novel observations about the nature and progression of disease that often stimulate basic investigations.

Accordingly there is an immediate need to bridge the gap between various stakeholders involved in Research/Services so that there is coordinated efforts to accelerate the development of appropriate technologies/innovations in the health field. Further there is no collated data available in respect to the research undertaken in the country, number of research institutions and the researchers in various fields and evaluation of research projects to ensure that they are aligned to National Health Policy, National Health Research Policy, National Science technology policy etc.

The main aim of scheme is for supporting (to create a mechanism/platform) for collection of data of research undertaken in various medical fields, evaluate them to identify the leads unattended due to want of resources or otherwise and take them to logical conclusion for development of products by fostering link with industries, support for additional information/data required in identified areas leading to development of leads and ensuring that the basic/clinical research in future is more focused and towards development of leads for translating them into products/processes for benefit of society by bringing together the academic and Industry. For this purpose a mechanism/platform/agency will be created which will support number of activities for achieving these objectives.

In addition support is also required to be extended for undertaking projects in close coordination with other departments/agencies, to attract health research personnel serving abroad to come back to India, to pursue research in areas which are very relevant to the country with special focus on knowledge management, technology access to marginalized and under privileged section of society, gender specific issues relating to women and health, to support researcher and research activities for sharing the experiences and expertise with the developed and developing countries.

Objectives :

- i. To support and encourage clinical and translational science by catalyzing the application of new knowledge and techniques to clinical practice and public health; knowledge management.
- ii. To support studies addressing the problems of technology access to marginalized and underprivileged groups by focusing on issues pertaining to gender and health, tribal health, maternal and child health.
- iii. To create synergy among various stakeholders – national and international agencies, investigators, institutions, regulators, NGOs and civil society for acceleration of knowledge generation, its translation and implementation.

Components :

Financial support will be intended for the following projects/activities for the purpose of development of leads/products etc.:

- i) **To map the health research institutes in the country, research done by them, publication, technologies etc.** There is a need to create collated data with regard to various institutions involved in health research, research publications and technologies etc. so as to analyze, identify the available material /lead that could be developed further to products in close coordination with the industry and also to undertake further research in identified projects for creation of additional data/information for development of leads for further processing.
- ii) **To evaluate the health research undertaken by various scientific departments including ICMR** with a view to ensuring that they are aligned to National Health Policy, National Health Research Policy, National Technology Policy etc. A unit will be established for evaluating and recommending technologies for improving the health care. Critical funding will be provided in the identified areas for further development.
- iii) **To establish a mechanism for coordination between the academic and the industry** so that the leads could be translated into products and processes fast. Start up funds, when required, will also be provided for encouraging Public Private Partnership mode by focusing on proposals which have a promise of developing a product or process.
- iv) **To attract health research personnel (NRI, PIO, OCI) serving abroad** in critical areas to come back to India for undertaking research in identified areas by extending financial support .
- v) **To support programmes in Medical Colleges** for carrying out innovative research.

Under this component of the scheme and start up fund will be provided to various scientific departments, industry in either in isolation or academia, individuals including NRI,PIO,OCI, institutions etc. for development of leads, translation of leads/ product development. Further in order to promote/encourage translational research National awards in various fields relating to translational research will be instituted.

In addition financial support will be extended to the following :

- (i) **Projects jointly developed in coordination with other Agencies** like DST, DBT, DARE/ ICAR, DSIR/CSIR, Department of Space, Ministry of Environment & Forest, National Disaster Management Authority, DRDO, National Knowledge Network (Department of Information Technology) , etc, in identified areas. For example, joint projects with DBT would be on diagnostics & vaccine developments and developments of guidelines for application of new generation technology, with DARE/ ICAR on zoonosis & nutrition, with Department of Space focus will be on technologies like use of GIS & remote sensing in relation to human health, with Department of Environment would be on climate change and health as well as impact of transgenic/ recombinant technology, with DSIR/ CSIR would be technology development & drug discovery ,with DST would be for developing basic technology/ knowledge in areas pertaining to basic biology, polymers, devices, bioinstrumentation and other life science related areas, nanotechnology. While DHR will coordinate & fund the application side of investigations with special focus on human health, the other relevant areas of technology will be funded by respective agency.
- (ii) To researchers to pursue research in areas which are very relevant to our country with special focus on **knowledge management, technology access to marginalized and under privileged section of society.**
- (iii) **To support to programme for Gender and Health:** The vulnerability of women to various situation and circumstances are different as compare to men. A gender based analysis on a continuing basis is critical to establish gender based issues like Vulnerability to disease, access to testing and health services, mobility, care and support. There is therefore a need to understand these differences and respond with public health interventions that are specific to the situation of women, which includes access to services including testing, adherence to treatment, expenditure on treatment, differences in biological vulnerability, socio cultural factors like education & access to information, mobility, care & support services. Under the scheme the project will be supported for analyzing existing data, studies to cover the gap, vote to examine the current situation and changes over time on gender specific issues relating to women and health.
- (iv) **To develop and establish for preventive, diagnosis and treatment of diseases:** While the profile of disease burden in the country is changing over time, the treatment especially in the primary and secondary sectors has not kept pace. It has therefore become critical to study the existing practice and to evolve suitable protocols and systems in order to have more evidence based treatment and diagnosis which is practicable at different levels within the country. Financial support will be extended for undertaking such studies and for devising, diagnosis and treatment protocols. Various scientific professional associations/societies/ bodies will also be involved for this purpose so as to address such vital issue in an impartial manner.
- (v) **Support to Scientific/Professionals/Association/Bodies:** Financial support to scientific societies/associations etc. will be provided to create expert groups, to develop guidelines, to evaluate any technology that the specialty field important

and provide developmental grants for implementing the recommendations, emanating from these expert groups/workshops. Support will also be extended to print the proceedings, guidelines and recommendations emerging to that scientific events as well as specially constituted expert groups.

(vi) Financial support will also be extended for

- a) participation in conferences abroad of non-ICMR researchers for presenting research papers, chairing the session or delivering a key note address in international scientific events (conferences, seminars/symposia/workshop) for promoting the research activities and researchers for sharing of experiences of scientists from various countries.
- b) organising international conference/seminars/symposia/workshop in India for sharing of knowledge and expertise of developed and developing countries for transfer of technology, for dealing with various emerging/remerging challenges.

Achievements :

1. The scheme has been approved in principle by the planning commission and proposal for expenditure finance committee has been prepared.

Establishment of a Network of Laboratories for Managing Epidemics

Viruses are one of the deadliest organisms known to cause large epidemic and pandemics in various parts of the world. Majority of emerging-reemerging infections of concern worldwide are of viral origin. Out of the 20 emerging-reemerging infections all over the world, 14 are of viral origin like Hanta, SARS, Monkeypox, West Nile, Ebola, Marburg, Yellow fever, Influenza (Avian/Swine), Chandipura, Chikungunya, Nipah, Dengue, Hendra and HIV. In India, during the last 30 years, 30 different outbreaks have been recorded, of which 21 have been due to different viruses. During the past 10 years, ICMR's National Institute of Virology at Pune has investigated and confirmed various outbreaks of Nipah virus (2001), SARS(2003), H5N1 (2006-09), Chandipura (2005, 06, 08), Chikungunya (2006-09), Acute Encephalitis Syndrome/JE (2005 onwards), Hepatitis B outbreak in Gujarat (2008) and H1N1 pandemic (2009 onwards). These epidemics/pandemics have had a major impact on the health sector and also taken a huge toll on the economy of the country.

The ability of viruses to cause devastating epidemics in human societies has led to the concern that these organisms could be weaponised for biological warfare. Because viruses use vital metabolic pathways within host cells to replicate, they are difficult to eliminate without using drugs that cause toxic effects to host cells in general. Hence there are very few effective drugs for treatment of viral diseases. The only method to stop the spread of viral diseases, in most of the cases, is timely diagnosis and implementation of proper control measures. This can only be achieved by establishing proper surveillance and diagnosis facilities in each and every part of the country so that the outbreak due to any virus can be detected and aborted as soon as it begins.

Till date there is grossly inadequate infrastructure in the country for timely diagnosis and management of populations affected with viral diseases, in times of need. There are very few laboratories all over the country which have the potential to work on viruses. Entire burden of diagnosing diseases of suspected viral etiology all across the country is mainly borne by ICMR's National Institute of Virology, Pune and National Center for Disease Control, Delhi. These apex laboratories are involved in providing diagnostic services to patients, developing laboratory contingency plan, communication with government and public, providing support to SEARO countries, establishing new diagnostic centers in various parts of the country, training, Quality control, supply of reagents and kits and doing basic, applied and translational research. These laboratories with their limited manpower and resources are unable to cater to the needs of the entire nation, despite best possible efforts. Considerably

large numbers of patients with diseases of suspected viral etiology go undiagnosed due to lack of proper surveillance and diagnostic tools available in different parts of the country.

The capacity for surveillance and diagnosis has to be strengthened at each level in every part of the country so that viral diseases are timely diagnosed and managed, cases are not missed and timely interventions can be made. Surveillance on commonly occurring viral diseases can help Government in planning proper strategies like vaccination. Thus the expenditure on these infrastructure and tool development will be evidence based. Capacity at different levels has to be developed for early and correct diagnosis, development of tools to predict viral disease outbreaks beforehand, continuous monitoring and surveillance of existing as well as new viral strains and handling viruses with a potential to be used as agents of bioterrorism.

Hence this creates an immediate need to strengthen infrastructure and capacity for handling viral diseases in the country in terms of early and correct diagnosis, development of tools to predict viral disease outbreaks beforehand, continuous monitoring and surveillance of existing as well as new viral strains and handling viruses with a potential to be used as agents of bioterrorism. The need for having well-established net work of laboratories and also to facilitate rapid mobilization of outbreak of disaster response (technology component) to infectious diseases has gained more importance in the context of biological terrorism / biological warfare. There is a need to facilitate focused research in dealing with emerging and re-emerging diseases identification of agents, development of diagnostic tests, formulation of case management modules & preventive strategies etc. Early adequate information & capacity to diagnose the viruses will lead to saving of many lives. In view of this the Department of Health Research proposes to establish a net work of laboratories across the country with capacity to handle all human pathogenic viruses as well as emerging-reemerging viral diseases and to develop tools for prevention. This will also meet the mandates of the department for providing technical support for dealing with epidemics and natural calamities and investigation of outbreaks due to new and exotic agents and development of tools for prevention.

Objectives:

- Create infrastructures for timely identification of viruses and other agents causing morbidity significant at public health level and specifically agents causing epidemics and/or potential agents for bioterrorism.
- Develop capacity for identification of novel and unknown viruses and other organisms & emerging-reemerging viral strains and develop diagnostic kits
- Provide training to health professionals.
- Undertake research for identification of emerging and newer genetically active/ modified agents.

This scheme, with the components detailed below is essential since there are no other schemes at present, which address this issue of infrastructure development and these aspects either in the Ministry of Health & Family Welfare or in other Ministries. This

will be complementary to Integrated Disease Surveillance Project and will strengthen the activity by capacity development & active research on these aspects

Components:

1. Establishing a net-work of laboratories for diagnosis of the viral and other infectious diseases
2. Setting up of revolving fund for facilitating a rapid mobilization of out-breaks/ disaster response (technology component) to infectious disease out-breaks or natural or man-made disaster.

Details:

1. Establishing a network of laboratories for diagnosis of the viral and other infectious diseases

As has been stated viral diagnosis today are a major health problem and outbreaks of new viral agents is a common phenomena. The inadequacy of specialized laboratories in the country especially of secondary and tertiary level has been noticed in the past as well as during the recent H1N1 crises that gripped the nation. In the context of biological agents being used as weapons for man-made disaster and also out breaks of new viral agents, it is considered necessary to establish a net work of laboratories for viral diagnosis. Such network and active research programme will be important to generate evidence for interventions for various viral infections which are endemic to the Country. For this purpose it is considered essential to establish net work of laboratories across the country, with NICD and NIV, with bio-safety laboratory III, acting as the apex laboratories. These labs will supplement the activities of the Integrated Disease Surveillance Project coordinated by NCDC, Delhi with special focus on viruses and will also be expected to deal with all common viruses like:

- 1) Viruses transmitted by respiratory route: Measles, Rubella, Mumps, Influenza viruses (A, B and C), Parainfluenza virus, Adenoviruses, Respiratory Syncytial Virus, Rhinoviruses, Polio, Coronaviruses.
- 2) Viruses transmitted by intestinal route: Hepatitis A, E, Rotavirus, Astroviruses, Calciviruses, Norwalk viruses, Enteroviruses.
- 3) Vector Borne Disease Viruses: Dengue, Chikungunya, Japanese encephalitis, West Nile, Kyasanur Forest Disease, Chandipura.
- 4) Zoonotic viruses: Rabies, Nipah virus, Hanta virus
- 5) Viruses transmitted by body fluids: HIV, Hepatitis B and C.

Priority will be given to develop infrastructure and expertise for diagnosis of viruses with a potential to cause outbreaks and/or which are responsible for significant disease burden like Measles, Influenza viruses (A, B and C), Respiratory Syncytial Virus, Polio, Hepatitis A, E, Rotavirus, Enteroviruses, Dengue, Chikungunya, JE etc.. These laboratories will be expected to develop expertise for diagnosis of specific viruses circulating in their geographic area.

At present, there are only 2 laboratories well equipped to deal with all kinds of viruses viz. NIV, Pune and NCDC, Delhi. These labs will continue to act as Apex laboratories. In addition three levels of laboratories are proposed to be established.

- (i) Regional laboratories
- (ii) State level laboratories
- (iii) District level laboratories

(i) Regional laboratories

It is proposed to establish 6 regional laboratories to deal with all kinds of viruses and other organisms causing infections, i.e. one each in North, South, East, West, Central and North-Eastern parts of India and preferably at ICMR institutes. They will be expected to carry out serology, RT-PCR, isolation, fluorescence microscopy, tissue culture and sequencing for viruses listed above or any other new viral pathogen. These labs will also be expected to develop capacity for identification of novel/unknown viruses and other organisms and emerging-reemerging viral strains etc. & develop diagnostic kits. They will receive unidentified samples from the State level labs for identification and characterization. These labs will also provide necessary training to those deployed in State level labs & support to them in building capacity. They will be responsible to do research apart from providing diagnostic facility and training. In addition, they will be equipped with facilities to identify viruses and other organisms which have the potential of being used as agents of bioterrorism.

It is proposed to create state-of-art facilities in these Regional labs so that it could achieve the objectives in research, continuous monitoring and surveillance of existing as well as new viral and other strains and handling viruses etc. with a potential of being used as agents of bioterrorism, capacity building, diagnosis, development of diagnostic kits etc.

These facilities will be created in the identified institutions under the Ministry of Health and Family Welfare and will function directly under the Department of Health Research for better coordination and would undertake continuous monitoring, surveillance, focused research on emerging and reemerging agents and develop diagnostic kits. These laboratories will be manned by regular scientific/ technical staff.

ii) State Level Laboratories:

It is proposed to establish one lab in each State & Union Territory preferably in Govt. Medical College/ hospital. These labs will be equipped with BSL2 facility and expected to carry out serology, RT-PCR, isolation, fluorescence microscopy, tissue culture and sequencing for all enlisted viruses. These laboratories are also expected to be involved in basic as well as applied research on viruses, development of kits and diagnostic reagents and identification of unknown/referred samples from the Sub-state level laboratories.

(iii) District level Laboratories:

It is proposed to create 200 district level labs. State Govt. will be requested to identify 1 such lab to cover a cluster of 3-4 districts depending upon their requirement preferably in Govt. Medical Colleges. These labs will be equipped with facility to carry out serology, PCR and fluorescence microscopy for the listed viruses. With the available infrastructure, these labs are expected to identify all common viruses by using immunological and molecular tools. The viruses which cannot be identified by these labs will be referred to the state/regional labs for identification. These labs will also be involved in diagnosis of common diseases other than that of viral etiology, which are prevalent in their respective region. This will facilitate early diagnosis of all the identified viruses so that the intervention/treatment if available could be provided without losing valuable time. It will also strengthen the surveillance/ monitoring of viral diseases.

Achievements :

1. The scheme has been approved in principle by the planning commission and expenditure finance concurrence has been prepared.
2. So far four Grade 1 Virology laboratories have been started at Regional Medical Research Centres at Port Blair and Bhubaneswar, Chhatrapati Shahuji Maharaj Medical University (Formerly KGMU), Lucknow and Kasturba Medical College, Manipal as extramural project of ICMR. It is further proposed to establish four more labs – three Grade 1 labs at Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, SMS Medical College, Jaipur, Field Station of National Institute of Virology at Allappuzha, Kerala and one Grade III lab at Pt. Jawahar Lal Nehru Memorial Medical College, Raipur (Chhattisgarh) in the year 2010-11.

Knowledge Management Policy (Draft)

Knowledge Management (KM) envisages capturing, creating, sharing and managing knowledge. KM comprises of three components (i) people who create, share and use knowledge as part of their daily work and help shape a knowledge sharing organizational culture (ii) Processes which include methods to acquire, create, organize, share and transfer knowledge to fit different situations and (iii) The technology including the mechanisms to store and provide access to data, information, and knowledge that must be integrated with the way people work, and address their real needs.

The implementation of any KM policy in Health sector will have essential ingredients and processes for improving the health of people by imparting benefits of various health programs to the targeted communities and improving the quality of education and research which will lead to evidence based policy. However, KM in health sector faces three major challenges:

Unsatisfactory quality of data

With good quality data better policies can be framed, better decisions can be made thus improving the implementation of Health care programs and quality of medical research.

Non- availability of data for knowledge generation

Most of the data being captured may not be available in a suitable form for creating databases. Availability of digitized data in unified format helps in improving data quality and developing standards for knowledge generation.

Inadequate dissemination of knowledge

There is a serious unavailability of information and knowledge to end-users which include health professionals, researchers, patients and students. Dissemination of quality information and knowledge through agencies like DAVP and appropriate media such as Internet, Information Kiosks etc. can provide relevant information to the end-users.

Health professionals should take advantage of the data, experience, and expertise available in their own and other organizations to create and share their own knowledge with others.

The policy would catalyze creation of knowledge and translation of that knowledge from research settings to real world application in order to improve the health of common man specially marginalized sector of our society.

The focus of this policy would be creating an environment for connecting knowledge related activities in health into a coherent action plan.

Mission

To develop an efficient Health Knowledge Management System for collection, dissemination and utilization of knowledge for improving the quality of Health Services, Education and Research

Policies

Service delivery

In order to create harmony among various health service providers and to impart their knowledge and services to the public at all times, the following essential components are proposed:

Empowering end user for better access to Health Service by :

1. Making available updated information about the service infrastructure such as manpower, equipment, medicines etc. available at different levels e.g. sub-centre, Primary Health Centre, Community Health Centre, District Hospital, Zonal Hospital, medical college and other tertiary care hospital etc.
2. Providing online information about functional status of the infrastructure i.e. availability of doctors, medical supplies including devices, vacant beds, surgical/ medical/ diagnostics facilities etc. at a given time
3. Providing information about geographical locations and other logistics of various health service providers
4. Promoting overall user awareness about available information sources by training of end users
5. Promoting access to financial resources including insurance
6. Ensuring access to all sections of society

Enriching health professionals with knowledge about available resources around them by standardizing and linking functional, infrastructural and logistic information available with different healthcare service providers in Government and private sectors.

Increasing accountability of healthcare professionals and services towards human life by

1. Developing a well defined referral system for efficient utilization of resources between Central, state and other public/private healthcare providing institutes.

2. Creating a mandatory forward and back referral pathway over a period of 5-10 years. Responsibilities of every individual in the pathway to be enforced to ensure perfect accountability involving human life.

Connecting remote areas and difficult terrains by effective use of telemedicine

Expert opinions of specialists need to be ensured on a structured fixed time interval basis as well as on emergency basis. The existing satellite connections and the optical-fibre-based National Knowledge Network (NKN) would be valuable in this context.

Efficiently handling health aspects of disasters by using Data Mining and Business Intelligence tools on available data for quickly finding information about available resources around disaster site and mobilizing these resources.

Establishing an user friendly but informative electronic medical record system.

This record system should be in a standardized, internationally compatible format.

Education

In order to improve the quality of medical education uniformly across the country with help of knowledge network, following policy guidelines are proposed:

Sharing knowledge by :

1. Establishing an efficient physical network, connecting all medical/dental/nursing/ other health related professional colleges
2. Creating tele-education portal to house resources which can be accessed online
3. Creating and networking digital / resource libraries for educational materials such as lectures, slides, video clippings etc. which can be accessed online as well as offline
4. Organizing prescheduled interactive lectures and practical sessions by prominent teachers through tele - education through national and international networks.
 - Developing unified high quality standards in health education across the country
 - Updating knowledge of health professionals by conducting online continued medical education/ special training programmes.
 - Evaluating quality of in-service health personnel by conducting online examinations
 - Training in-service health personnel by organizing localized interactive training courses
 - Enforcing regulations for tele-education applications by following existing guidelines of regulatory bodies like Medical Council of India, Medical Universities, Dental Council of India, Nursing Council , Pharmacy Council, various councils for alternate medical systems, other relevant bodies for Physiotherapy and other disciplines.

Research

Knowledge is both a key input for and output of health research. For increasing use of knowledge in medical research, both clinical research and basic research, following measures are proposed:

- Creating information culture by adopting recent advances in Information and Communication Technologies. Improving interaction between National and International researchers and stakeholders working in different subject areas by developing collaborative networks and alliances
- Creating an information system and a policy framework to facilitate Indian medical researchers abroad to return and join Indian medical research institutions.
- Enhancing research to policy through collaborations and exchange of information between researchers and health professionals ; between researchers and other stake holders involved in policy making (political leadership, planners and civil servants etc)
- Enhancing public-private partnership in health Preparing national information system of research funding by different funding agencies.
- Developing database of research resources such as manpower, equipment etc. available with different laboratories/medical / dental colleges/ universities etc.
- Developing disease database including clinical, epidemiological, genetic, biological and social parameters.
- Achieving high impact of research by effectively communicating research outcomes.
- Balancing between responsibility to share information for betterment of health of people and protecting intellectual property generated through research.
- Empowering health research institutions to use tools of Knowledge Management for improving quality research as per the guidelines of Medical Council/ Dental Council of India.
- Providing access to research data to other scientists and students for secondary analysis by taking care of ethical , copyright and IPR issues . Managing research priorities based on periodical in-depth analysis of existing research data.
- Creating a National Health Knowledge Repository for free access to all researchers.
- Encouraging the use of knowledge management for creation of different application groups and development of various disciplines like biomedical engineering.

Strategy for implementing Knowledge Management Policy

Broad strategy for implementing knowledge management policy for health is given below:

- There will be three important components/ tiers : policy framing, strategy planning and monitoring.
- An expert advisory group should be constituted under the chairmanship of the Secretary, Department of Health Research with following mandate:
 - ◆ To examine the policy document and modify it if necessary
 - ◆ To decide the priority areas
 - ◆ To classify the priority areas into short term, midterm and long term goals for Implementation
 - ◆ To constitute three technical sub committees in the areas Service Delivery, Education and Research to manage knowledge network for help with following mandate:
- To carry out feasibility study/ studies , pilot study/ studies, model projects and preparing proposal
- To define parameters to be included in feasibility study
- To liaison between the study group and other stakeholders of the proposed
- knowledge network to facilitate preparation of feasibility report
- To examine the feasibility study report and present it to the Secretary, Department of Health Research
- To devise a strategy for implementation along with other stake holders
- Monitor implementation of work

Funding of the different components of Knowledge Management Network

- i) The responsibility of different stakeholders in providing infrastructure, manpower and other resources needs to be defined by consultative process among centre, state, other public and private stakeholders.
- ii) While the network connectivity may be provided by central systems, department of information technology, UGC etc, the local supplementary support could be provided by State systems.
- iii) A dedicated system will be required for keeping it functional all the times. For this IT connectivity will have to be ensured along with funds allocated for this purpose.
- iv) A strategic plan for providing financial support for development of modules, appropriate software, professionals for data analysis on specific areas, mechanisms of review will have to be drawn for estimating the financial inputs.

Establishment of an Appropriate Authority

For developing and implementing a comprehensive plan for utilization of knowledge network for health service delivery, medical education and research, an Appropriate Authority under the Department of Health Research in the Ministry of Health and Family Welfare, Govt. of India may be desirable. Such an authority with committed resources will be responsible for strategic planning, for implementation and review of the progress from time to time. This Authority /Cell may establish units in the states for action at the local level.

Achievements

A draft document has been finalized after consultations at four major cities and getting opinion of different departments. It has been placed on the website for inviting the comments from various stakeholders for finalizing the policy.

National Health Research Policy (Draft)

The establishment of a Department of Health Research (DHR) in the Ministry of Health is recognition by the GOI of the key role that health research should play in the nation. The weakness of the publicly funded health structures and the research infrastructure is a key limiting factor in realizing the full benefits of this commitment to research. The fact that the almost 300 medical colleges in the country are not contributing of their best to health research is highlighted by the fact that in 2007, 96% of the research publications in India emanated from 9 medical colleges. Much of this published research is not on priority health concerns and the translational of key research findings into policy which could improve the health of the people is very limited and needs to be enhanced. Epidemiological know-how, surveillance technology and diagnostic services which are essential for determining health priorities are very poorly developed. There is also a compelling need to build multidisciplinary research blending physical, medical and social sciences. Besides, there is also an equal urgency to establish regulations, strict ethical norms and transparency, standardize methodology and international standards of research. Such capacity is necessary for undertaking operational research as also large-scale evaluation of diagnostics and trials of drugs, devices of both modern and traditional systems of medicine. It is in this context that the DHR has formulated a draft National Health Research Policy.

Vision of National Health Research Policy

To maximize the returns on investments in health research through creation of a health research system to prioritize, coordinate, facilitate conduct of effective and ethical health research and its translation into products, policies and programmes aimed at improving health especially of the vulnerable populations.

Objectives of the National Health Research Policy

The broad objectives of the National Health Research Policy are:

- i. Identify priorities for effective and ethical health research to enable the achievement of the objectives of NHP 2002, NRHM, Bharat Nirman and National Food security Act as well as global commitments such as MDG and IHR, ensuring that the results of health research are translated into action.

- ii. Foster inter-sectoral coordination in health research including all departments within the Government, Private Sector and the Academia to promote innovation and ensure effective translation to encourage/ accelerate indigenous production of diagnostics, vaccines, therapeutics, medical devices etc.
- iii. Focus on the marginalized, the vulnerable and the disadvantaged sections of society.
- iv. Strengthen national networks between research institutes, academia and service institutes, and encourage PPP.
- v. Put in place strategies and mechanisms for assessing the costeffectiveness and cost benefits of interventions for health.
- vi. Develop and manage human resources and infrastructure for health research and ensure that international collaborative research contributes to national health.

Prescription of the NHRP

1. Create a National Health Research System
2. Establish a National Health Research Management Forum
3. Operationalize a 10-point action programme

National Health Research System (NHRS)

In order to achieve intersectoral coordination and to make national priorities for health research a new architecture of national health research system is envisaged. Health research system is a concept that integrates and coordinates the objectives, structures, stakeholders, processes, cultures and outcomes of health research towards development of equity in health and in national health system. It is a system for planning, coordinating, monitoring and managing health research resources and activities, and for promoting research for effective and equitable national health development Health Research in the country would be developed into a National Health Research System (NHRS) wherein all research agencies, cutting across Ministries and sectors identify priority areas of research and coordinate with each other to avoid duplication, fragmentation, redundancy and gaps in knowledge, in order to enable the results of research to transform health as a major driving force for development.

Goals of the NHRS

- To generate and communicate knowledge that helps to form the national `health plan and guides its implementation, and thus contribute, directly or indirectly, to equitable health development in the country;
- To adapt and apply knowledge generated elsewhere to national health development; and
- To contribute to the global knowledge base on issues relevant to the Country

Functions of NHRS

The National Health Research System would be responsible for:

1. Developing National Health Research Plan

The DHR is responsible for the National Health Research Plan for a National Plan aligned with the Five Year Plans of GOI and its implementation and monitoring.

2. Set priorities

A Priority Research Agenda will be developed in tune with the National Programmes, and relevant to national and local needs.

3. Engage with Private Sector

The private sector, pharmaceutical industry, biotechnology and biomedical technology oriented Industries, private educational institutions, hospitals and nursing homes, research foundations and institutions, private practitioners, NGO's and CBO's working on a not-for-profit basis etc. are now major stakeholders in Health care research and delivery. The National Health Research System would recognise their important role in health research and shall foster their participation in the system as partners. These engagements have to be concurrent and intense rather than linear and loose.

4. Strengthen International Linkages

In the current global scenario International collaborative efforts are recognised as one of the factors in successful research because of the complementarity of technology transfer, capacity building and access to diseased populations. There are a large number of potential partners and in the choice of partners the priorities of the National Health Research Plan and national interest shall be paramount. Linkages with International Developmental partners and WHO and other UN Agencies shall be further developed and strengthened to ensure that India plays a legitimate role as an emerging economy.

5. Ensure Ethical Research

The Bill on Research on Human Subjects and establishment of the National Biomedical Research Authority therein along with the guidelines developed by other agencies shall regulate all research. The Health Research System shall review these Guidelines from time to time, and harmonise them with International Guidelines. Facilitation of training in ethical research shall be the responsibility of the DHR. A major achievement has been the establishment of a National Clinical Trial Registry and all clinical trials are mandated to be registered by the DCGI.

6. Ensure Targeted Financing

The National Health Research System shall be responsible for ensuring equity in resource mobilisation and allocation of public funds. It shall endeavor to ensure that the allocation/ expenditure on health research is at least 2% of the allocation / expenditure on health. International funds will also be mobilised in keeping with the priorities. The NHRS would track the resources available and

spent on research in the country and monitor its impact on health. Though a minimum of 2% of health expenditure has been achieved, this may be too small a figure considering that the allocation for health itself is meagre in relation to the population and health concerns of the country.

7. Monitor and Evaluate impact of health research.

To ensure that resources are used efficiently and in line with agreed priorities there is a need for continuous monitoring and evaluation. The health research system will develop explicit policies and procedures for reviewing proposals, and for monitoring and evaluating the output and impact of those that are funded. Indicators will be developed to monitor the development and effectiveness of the health research system. Indicators would also be defined for assessing health status, health system effectiveness, efficiency and affordability, in order to capture the contribution of research in reducing inequities. Direct indicators of National Development, would serve as indirect indicators of the efficacy of Health System research as a vehicle of development. Set mechanisms to ensure that best practices are encouraged, and practices are evidence based.

8. Partnership with State health system.

Encourage health research within States. Help set state level health research system by strengthening partnership between central and state systems.

9. Assess Health Research System

The health research system would need to be assessed periodically to provide evidence that it is functioning optimally.

The NHRS shall be managed by a National Health Research Management Forum (NHRMF).

The National Health Research Management Forum (NHRMF)

The National Health Research Policy envisages a System wherein all present and prospective players have their own space. However, an overarching National Health Research Management Forum is proposed, having representation of all key stakeholders, the DHR as its Secretariat, and the following functions / terms of reference:

- i) To advise on and evolve national health research policies and priorities and to evolve mechanisms and action plans for their implementation;
- ii) To develop a 5 year projection of the plans for health research and to prepare an annual National health research plan;
- iii) To do a mid-Plan appraisal for course correction, as needed
- iv) To promote the development of health research activities in the country;
- v) To review biomedical & health research management, and suggest strategies to overcome problems in implementation of policies;
- vi) To suggest mechanisms to nurture a scientific environment to attract talent and to develop human resources for biomedical and health research; and

- vii) To facilitate utilisation and dissemination of research results and advocacy for health research.

Structure of NHRMF

The NHRMF will be Chaired by the Minister of Health & Family Welfare and co-chaired by Minister of Science & Technology. The Minister(s) of State for Health would be the Vice-chairperson(s). The Secretariat shall be in the DHR and its Secretary shall be the Member-Secretary. All Secretaries of various

Departments in S&T would be the members, DGHS and 8-10 eminent scientists/public health experts (numbers flexible) as well selected representatives from State Governments would be the other members. These experts would also be the Chairmen of the various working groups which would be constituted to address the following areas:

1. Development and evaluation of interventions for promotion, restoration, maintenance and protection of health.
2. Human resource management and infrastructure development
3. Knowledge management
4. Encouragement to translational research and originality in basic science research, and innovations
5. Optimizing intra- and inter-sectoral networks, coordination and collaboration especially with private sector and industry.
6. Track current resource flow and future requirements to address priority areas of health research.
7. Establishment of priorities for health research.
8. Implementation of health research policy, planning, monitoring and evaluation.

Responsibilities of NHRMF

Stewardship

This would encompass a range of activities for the national health system intended to ensure quality leadership, productivity, strategic direction and coherent action. Sub-functions would include Strategic Vision, Policy Formulation, Priority Setting, Performance and Impact Assessmentⁱⁱ Promotion and Advocacy, and the setting of norms, standards and frameworks for the sound practice of research. Provide best practices for research management.

Financing

The essential functions of the System as regards finances would be to address issues related to resource generation, targeted allocation and judicious utilisation. On the basis of recommendations of the National Health Research Management Forum, funds would be allocated in ways that are consistent with national priorities. External

Partners would be apprised of these priorities, while a national capability to monitor where and how research funds are being spent, and the quantities involved, would be created and put in place. Ensure that funds are spent where the burden of disease is. Efforts would be made to invest at least 2% of national health expenditure in research and research capacity strengthening.

Knowledge Generation

The research system would generate knowledge relevant to the Indian health situation, appraise the measures available for dealing with health problems, and suggest the actions likely to produce the greatest improvement in health.

Utilisation and Management of Knowledge

The Research System fully endorses the principle that the research process does not end with Knowledge Generation, but includes the translation of results into policy or action, or absorption into the existing knowledge / technology base. For this to happen, links will be strengthened between researchers, policy makers, health and development workers, non-governmental organisations, communities, and media. Vertical and horizontal connectedness will be improved upon. More specifically, for better utilisation and management of knowledge, an information culture would be fostered, supported by enhanced use of information technologies currently and likely to be available. A synergy with Knowledge Management Policy would be made.

Capacity Development

A long-term approach to the development and maintenance of research capacity will be adopted. Efforts will be focussed on both the quantity and quality of skills available / needed, including research techniques, research priority setting, research management, use of research ('demand' side), policy and systems analysis, communications, development of partnerships including medical colleges and rural health research centres. A situation analysis done periodically would ensure a phased and realistic plan for constructive and sustained capacity development. Thus, both the 'Supply' and 'Demand' sides of the research system needs will be addressed. Encourage policy research.

The 10-point Action Programme -

1. Harmonize optimally National policies in a variety of areas (education, social sciences, population, agriculture, nutrition, science, etc) to facilitate intersectoral collaboration and partnership, so that maximum developmental returns can occur from health research.
2. Ensure true inter-sectorality of health research and harness the resources in areas such as social sciences, economics and traditional systems of medicine.
3. Facilitate priority setting to guide the direction of health research and prepare Five-year Plan and strategy documents
4. Encourage the development of fundamental and basic research in areas relevant to health to ensure that a national critical mass of scientists who can contribute the benefits of modern technology to health research is created.

5. Foster translational research to ensure that the products of basic research can be appropriately utilized in health systems and services.
6. Establish linkages between health research and national health programmes to identify key operational issues and facilitate the operationalization of evidence based programmes and to obtain feedback for the optimization of health research
7. Build and integrate capacity for research in National Health Programs, research institutions and in the private sector (profit and non-profit organizations) both in rural and urban research settings utilizing as far as possible areas of excellence already available in the country.
8. Ensure that the global knowledge base is available for national programmes, and that research is channelled in relevant directions without unnecessary duplication by the optimal use of information, communication and networking technology.
9. Manage global resources and transnational collaborations optimally to ensure that collaborative health research primarily facilitates the development of national health systems and services.
10. Generate the evidence-base for health systems and services, to be significant promoters of equity and contribute to national development so that health research becomes a poverty reduction tool.

Achievements

During 2010-11 a draft document was placed on DHR / ICMR website. Debates were held in four metropolitan cities and opinion of various departments was sought. Final draft policy has been put up on ICMR / DHR websites on February 28, 2011 for any comments before taking further steps.

Mapping of Health Research Institutes

1. Directory of Health Research Institutions in India

The Department of Health Research is planning to develop a databank having a Database Storage and Retrieval Software, which will cover all Indian Biomedical Research Institutions, such as: Academic Institutions, In-house R&D Units, National Laboratories, Research Institutes, Research Stations and Non-Commercial Medical Research Organizations including Medical Colleges. This 'Database of Health Research Institutions in India' will cover details of approximately 700 institutions, which are having valid research activities and are recognized by the peers. The main purpose to carry out this work is to provide a reference source to various Government Departments, R&D institutions, Policy makers, Researchers and others who may like to take the opportunity of initiating interaction with the institutions in various disciplines of medical and/or health research with a strong "Information Based Decisions".

The ongoing project entitled "**The Directory of Health Research Institutions in Indian**" funded by WHO, is for updating of earlier directory (2007 Ed.) and information have been collected as per WHO requirement. The work relating to this project is progressing and is going to be over within two months i.e. February 2011. Affiliation, Major subject area, Minor Subject area and services are new additional field in new directory. Finally the updated directory will provide the information of institute including Name of Institution, Standard Abbreviation, Affiliation, Remarks, Head of Institution, Establishment Year, Address, Phone no., Fax No., Email Address, Services, Type of Research, Major and Minor Subject Area. Various Searches carried out through Websites and other printed sources have indicated that the total number of institution is almost 700. However, the existing directory contains only 432 records. The same needs to be updated, with additional list of research institutions. There are approx 700 institutions spread over different states (including approx 150 Medical colleges carrying out R&D activities, out of a total of 300 recognized medical colleges). A stand alone software is also on the anvil for Database of the directory with the facility for updating on fixed time intervals, and bring out a printed copy along with a 'CD' (with embedded search and retrieval software). Efforts will be made to make an online version also.

2. Compendium of Health Research Institutions including Medical Colleges with Research Activities

The strong system of government support for Indian Medical & Health research has produced decades of discovery and innovation that have not only literally changed the way we live, but deepened our understanding of the human condition, of our health, and of our relationship to the society. This use of public resources is widely agreed to have yielded great social dividends for the citizens of our country and beyond. In many ways, the Health Research has unsurpassed among the array of federal agencies that support scientific research, providing 80% of the federal government's contribution towards biomedical research, that justifiably enjoys enormous public and congressional support. MHFW's success in its mission of science in pursuit of fundamental knowledge and the application of that knowledge to extending healthy life and reducing the burdens of illness and disability has been enormous. Governments' investment in biomedical research has helped produce remarkable results in terms of declining rates of disease, longer life expectancy, reduced infant mortality, and improved quality of life. The new Project entitled **"Compendium of Health Research Institutions including Medical Colleges with Research Activities"** has been conceived in continuation of the ongoing WHO project. This has got many additional parameters viz. information about institutional funding, quantum of funding, source of funding, status of different projects, sponsoring organizations for the projects, manpower etc.

The record of each institution would be provided with information about the full name, standard abbreviated name, latest change in name (if any), Address; Function/ Type of Institution; Source of funding and quantum; infrastructure: (Laboratory with type; animal houses); ethics committees; Major area of work/research; Number of projects undertaken in the last three years, - field of research, source of funding; Number of ongoing projects; Completed projects –last 3 years; Personnel (Overall-Regular, involved in the time bound contracts, emeritus scientists); and Publications-last 3 years. Wherever email/web address has been provided with will also be included. This will be achieved by:

1. collecting information about the institutions in India and collating them at one place.
2. creating a searchable database; on predefined fields and scope, using a suitable software for stand alone system and developing a "Databank of health research institutions" along with a master CD-ROM.
3. collecting information of all the Indian Medical/Health Research Institutions (including medical colleges with research activities) which will be finalized by the "Scientific Expert Group Committee" members.
4. personally visiting the institutions spread over different parts of the country for data capturing. As ICMR has got 31 HRRC's in different states, it is proposed that they can be involved for data collection from those institutions which falls within their geographical areas. Some institutions which could not be covered by the HRRC's, they may be covered by some of the ICMR's permanent institutes/regional centers. At every place some of the working staff will be

identified, proper training and orientation workshops will be organized for data collection. It is also proposed to give incentive to these participants. If there will be some institutes still remains to be covered, will be covered by the research staff appointed for the project.

5. collecting data from hard copies on pre-designed formatted input sheets. The fields will be decided in consultation with experts. Each field will be made searchable.
6. validating, editing and carrying out corrections before entering the data in the computer systems. Computer inputs will also be validated and checked, and a test run will be carried out.

The project is progressing.

Indian Council of Medical Research

Introduction

The Indian Council of Medical Research (ICMR) entered into its hundredth year in 2010. The centenary year was launched by Hon'ble Union Minister of Health & Family Welfare Shri Ghulam Nabi Azad at a function held at New Delhi on 15 November 2010. A number of activities such as scientific lectures, Workshops, exhibitions, etc. are planned besides publication of Centenary Document, Photo album, Monographs, Calendar and production of Video films, Coins, etc. on this occasion. It is one of the oldest medical research councils in the world. In 1911, officers of the then Indian Medical Services had the vision and foresight to create Indian Research Fund Association. Soon after Independence, it was rechristened as Indian Council of Medical Research.

It has blossomed into a vibrant network of 30 permanent Institutes/ Centres and over 70 field stations, employing over 5000 personnel including 750 scientists.

The ICMR has evolved over the years in line with changing health research needs, effectively addressing the new challenges that have emerged as a result of the economic, demographic, nutritional and epidemiological transition of the country. With the changing health challenges, the demands on ICMR are also increasing. The Mission of ICMR is to promote better health through research.

The Council has accepted a twin track approach to meet its objectives –intramural (through its Institutes) and extramural research (through grants-in-aid to projects in non-ICMR institutions).

The permanent Institutes of ICMR are mission-oriented discipline/disease-specific laboratories strategically located in different parts of the country. Extramural research is promoted basically to strengthen the biomedical expertise and infrastructure especially in medical colleges and the university system, aimed at developing and fostering a culture of research in academia. Currently, the ICMR spends about 25% of its budget on extramural research programme.

The research priorities of the Council coincide with health policy and priorities of the country. It works very closely with the national programmes, which have well designed targets for control, elimination and eradication of diseases. The ICMR is actively engaged in various aspects of research for control of communicable diseases (HIV/ AIDS, tuberculosis, malaria and others); infectious diseases targeted for elimination (kala-azar, lymphatic filariasis, leprosy) and those targeted for eradication (yaws,



The Hon'ble Union Minister of Health and Family Welfare, Government of India, Shri Ghulam Nabi Azad inaugurating the Centenary Celebrations of the ICMR on 15th November, 2010 by lighting the lamp at India Islamic Cultural Centre, New Delhi. From left to right – Minister of State for Health & Family Welfare, Shri. S. Gandhiselvan ; Union Minister of Health and Family Welfare, Shri Ghulam Nabi Azad and Dr V.M.Katoch, Secretary , Department of Health and Director-General, Indian Council of Medical Research, New Delhi.

poliomyelitis); non-communicable diseases (cardio vascular diseases, neurological disorders, metabolic diseases, cancers, injuries, etc.); and improving maternal and child health including nutrition;

The majority of the research activities of the Council are directed towards diseases that have significant links with poverty. It has a special focus on health of marginalized and under privileged section of society. It is responsive to issue of equity, gender, ethnicity, race and caste.

The ICMR has provided critical research support whenever the health needs of the country demanded rapid responses. With globalization, international collaborative research has also increased. The Council has played an important role in defining the limits of collaborative research and ensuring that such research is conducted in an ethically acceptable manner.

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Communicable Diseases

Intramural Research

TUBERCULOSIS RESEARCH CENTRE, CHENNAI

The Tuberculosis Research Centre conducts focused research targeting the control of two of country's biggest public health problems, tuberculosis (TB) and HIV.

Clinical studies

Clinical trial using moxifloxacin: An important research priority in TB is to shorten the treatment duration from the existing 6-8 months. A randomized controlled clinical trial to study the efficacy and safety of 3- and 4-month moxifloxacin containing regimens for treatment of patients with sputum positive pulmonary TB (PTB) is continuing in Chennai and Madurai. Preliminary results have shown that the proportion of patients who became sputum culture negative at two months of treatment was significantly higher in the moxifloxacin arm compared to the control arm.

Phase II clinical trial using TMC207: Development of new TB drugs is a research priority. TRC is participating for the first time in a phase II clinical trial to demonstrate the anti-bacterial activity of TMC207 when added for 24 weeks to a background regimen in participants with newly diagnosed sputum smear-positive pulmonary MDR-TB infection. If TMC207 is found to be efficacious, it would be a valuable addition to the existing drugs used in the management of MDR-TB patients.

Evaluation of chemotherapy regimens for TB in HIV-infected persons: A prospective randomized controlled clinical trial that compared the efficacy of a six months' intermittent regimen with nine months' regimen for treatment of TB among HIV-infected patients showed that extending the treatment duration from six to nine months did not significantly improve treatment outcome or survival at the end of treatment, but reduced bacteriological recurrences by half. Acquired Rifampicin Resistance (ARR) was a cause for concern among failures. This is the first report on ARR in patients treated with thrice-weekly rifampicin in the absence of antiretroviral treatment (ART).

Preventive therapy for TB in HIV-infected patients: A two-armed prospective randomized clinical trial on TB prophylaxis comparing a six-month regimen of isoniazid and ethambutol with 36 months of isoniazid found that the two regimens were equally efficacious in preventing active TB disease in HIV-infected patients. TB preventive therapy reduced the incidence of TB by 65-78% compared to historical data. Efficacy was more pronounced in patients with a CD4 count < 200 cells/mm³, irrespective of the regimen. Shorter duration regimens are likely to have a better adherence rate, are easier to implement and are associated with lower cost.

Clinical trial using once-daily antiretroviral regimens along with anti-TB treatment: A once-daily regimen of didanosine, lamivudine with either efavirenz or nevirapine along with standard anti-TB treatment in patients with HIV-TB showed higher failure rates and deaths in the nevirapine arm and confirmed the use of efavirenz - based regimen for HIV-TB patients on ATT.

Clinical trial comparing daily vs. intermittent 6 – month short course chemotherapy in patients with HIV and TB: This trial has been started with the aim to compare daily versus intermittent therapy of anti-TB treatment for a duration of 6 months to evaluate if daily administration of rifampicin could overcome the issue of ARR. The results will yield the best regimen that could be used for treatment of TB in HIV in the HAART era and will have a significant impact on both the TB and HIV control programmes.

HIV/AIDS Vaccine Trial

A DNA prime MVA boost Phase I HIV Vaccine trial was initiated during the year under review. This study was jointly conducted along with National AIDS Research Institute (NARI), Pune. A second group (6 vaccine: 2 placebo) received TBC-M4 at 0, 1 and 6 months. All the volunteers have received the scheduled injections and the study was completed. Analysis of the study data is in progress.

Programme related activities

Training: A total of 133 persons were trained for culture and drug susceptibility testing from 22 different national and international institutes.

Accreditation of laboratories: Nine laboratories have been re-accredited. The accreditation of eight IRLs/ Private Laboratories has started; among these RMRC, Jabalpur was accredited this year.

Laboratory studies

Bacteriology

Luciferase reporter phage assay for the detection of M. tuberculosis using phage lysin to decontaminate processed sputum specimens: Diagnostic luciferase reporter phage assay can be used for rapid detection of *M. tuberculosis* directly from processed sputum samples using phage lysin to control the overgrowth of normal flora.

Development and evaluation of rapid methods for TB diagnosis suitable for central laboratories/field centers: The LRP construct developed from Chennai temperate phage Che12 (phAETRC16) was capable of detection of viable tubercle bacilli for extended periods of incubation. Phage constructs (phAETRC21, phAETRC201, phAETRC202) were evaluated and tested for detection of active and dormant bacilli.

Screening of new compounds for development of potent anti tuberculous drugs: Using LRP – DST assay, extracts from plant products and actinomycetes strains from extreme environments have been screened for detection of anti-TB activity. (i) A crude yellow pigment produced from strain D25 was isolated from Thar desert soil showed promising activity. (ii) A novel actinomycete strain was isolated from the Rameshwaram coast and characterized. An accession number has been assigned to this novel streptomyces species (MTCC 5597). The antibiotic obtained from this strain has both anti-TB and anti-HIV activities. The details have been submitted for patenting through IPR section of ICMR.

HIV-TB laboratory

The HIV/AIDS laboratory is an internationally accredited laboratory equipped to perform all immunological and virological assays for diagnosis, monitoring and management of HIV-infected persons. This lab serves as a National Reference Laboratory for WHO for genotypic drug resistance testing for HIV and a Regional Reference Laboratory for NACO for viral load testing and diagnostic DNA-PCR for HIV infection.

Performance of an enzyme immunoassay for detection of anti-HIV antibodies in saliva: Assessed the performance of a commercial enzyme immunoassay kit HIV MicroLisa kit (designed for use in blood) on saliva samples. The test gave a good sensitivity and specificity and it has a potential to perform as a confirmatory test for use in epidemiological surveys or in clinical settings.

Emergence of drug resistant mutations after single dose nevirapine exposure in HIV-1 infected pregnant women in south India: Resistance to nevirapine (NVP) has been described with single dose preventive regimens in other populations. Mutations to non-nucleoside reverse transcriptase inhibitors were observed post-delivery in 33% of women who were treated with Sd-NVP. Our findings emphasize the need to implement more effective PPTCT regimens to minimize emergence of drug resistance.

Immunology

Identification of novel human T-cell antigens of *M. tuberculosis* by immunoproteomics: The *in silico* and *in vitro* immune response of novel Adk antigen was assessed in TB patients and healthy household contacts. The study data has shown that AdK may be a useful antigen to pursue for further protective studies in human TB.

Innate immunity in HIV infection: The role of NK cell receptors in HIV infection, particularly when co-infected with TB was studied. The effect of IL-15 + IL-12 on the NK receptors was also studied. Downregulation of iNKRs, upregulation of activating NKRs after IL-15 + IL-12 stimulation indicated an immunomodulatory effect on NK cells from HIV-infected individuals. The role of IL-15 + IL-12 as immunomodulator can be important in HIV infection.

Cytotoxic cell response in *M. tuberculosis* infection: Epitopes inducing cytolytic molecule positive T-cells, Th1 cytokines (TNF- α , IL-2) and chemokine RANTES positive T-cells and MCP-1 positive monocytes were identified. These peptides may further be explored in the south Indian population which would aid in the development of an epitope-based vaccine.

Role of Interferon gamma assay for latent TB in HIV infection: QFT-IT was more sensitive than TST in detecting active TB cases among HIV negative objects. QFT-IT performed better than TST in HIV-infected subjects and yielded high number of indeterminate results in advanced HIV cases.

Functional genomics of *M. tuberculosis*

Studies of serine/threonine kinase *PknE*: The mechanism by which serine threonine kinase, Pkn E reduced apoptosis was studied. This protein played an important role in the intracellular survival of *M. tuberculosis* and it reduced the apoptosis through

suppression of intrinsic mode. It also modulated the pro inflammatory cytokines and innate immune response. PknE can be used as an immunomodulator to arrest the survival of *M. tuberculosis*

Molecular epidemiology

The impact of HIV on recurrence of TB has been studied by comparing the genotypic pattern HIV/TB and HIV uninfected TB strains pre and post ATT treatment. Exogenous reinfection was higher in HIV-infected TB patients and endogenous reactivation was higher in HIV uninfected TB patients. The results show that good infectious control measures including management of HIV-infected persons in separate wards are needed to prevent nosocomial infections.

Toll-like receptor and TIRAP gene polymorphisms in PTB: The study findings suggest that the T allele of TIRAP gene 975 C/T polymorphism may be associated with susceptibility to PTB in south Indian population, and that a findings suggest that a combination of genetic markers may be useful to predetermine the development of TB.

Internalization of M. tuberculosis by non-phagocytic pleural mesothelial cells (Met-5A): This is the first report to demonstrate that pleural mesothelial cells have the ability to uptake *M. tuberculosis* but unable to support its growth. As a defense strategy, bacilli expressed the stress response proteins indicating efforts leading to latency. Overall, the present study highlights the probable role of pleural mesothelial cells in tuberculous immunity.

Clinical pharmacology

Factors influencing plasma nevirapine levels: a study in HIV-infected children on generic antiretroviral treatment in India: This multi-centric study in 94 HIV-infected children receiving generic NVP - based fixed dose combinations examined the influence of several factors on plasma NVP in children treated with generic antiretroviral drugs. A combination of factors (younger age, stunting, *CYP2B6* GG or GT genotype) could potentially result in sub-therapeutic NVP concentrations in some children. The study findings have important clinical implications and raise the issue of whether higher dose recommendations are required for malnourished children and those below three years.

Pharmacokinetics of anti-TB drugs in children with TB: The influence of age, nutritional status and HIV infection on the pharmacokinetics of first-line anti-TB drugs in children, who were receiving anti-TB treatment according to RNTCP guidelines, was studied. Preliminary findings indicate that children < 3 years had significantly lower levels of rifampicin, isoniazid and pyrazinamide compared to older children. Stunting was associated with lower blood levels. The study data suggests that dose recommendations for anti-TB treatment in children should take into consideration age and nutritional status.

Bioinformatics

Novel drug discovery: Attempts are being made to identify molecules that would aid in novel drug discovery. Inhibitors against 3-oxoacyl-[acyl-carrier-protein] synthase

(FabH) and pantothenate synthetase of *M. tuberculosis* have been identified. These molecules will be taken further for *in vitro* testing.

***M. tuberculosis* structural database (MtbSD):** A complete and integrated structure database for *M. tuberculosis* was developed, which has 857 3D structures for 328 mycobacterial gene products. It can be accessed online at <http://bmi.icmr.org.in/Mtbsd/MtbsD.php>. The database will be of profound value to the TB research community involved in modeling, docking and structure-based drug designing.

Structural proteomics and conservation of fold usage in the genome of M. tuberculosis: The conservation of the fold usage of proteins in *M. tuberculosis* was analyzed. Majority of the proteins of *M. tuberculosis* were found to belong to the α/β class of proteins and among other folds, TIM barrel fold was identified to be highly conserved even at very low sequence identity. Understanding the structural similarity of proteins will be useful in drug/target discovery.

Socio-behavioural studies

Alcohol use disorders (AUD) among TB patients: a study from Chennai, south India: Alcohol use disorders (AUD) among TB patients are associated with non adherence and poor treatment outcomes. This study was done to estimate prevalence of AUD among TB patients using the AUDIT scale and explore their perceptions on a feasible intervention programme. The qualitative findings of this study reflected the need for an intervention programme. This study has paved way for a larger study to test an intervention programme that could be introduced in the TB care delivery system.

NATIONAL JALMA INSTITUTE FOR LEPROSY AND OTHER MYCOBACTERIAL DISEASES, AGRA

LEPROSY

Study of post-elimination scenario of leprosy

To assess the post elimination leprosy and current integrated phase scenario in Uttar Pradesh, the institute is participating in an ICMR Task Force funded study in collaboration with The Leprosy Mission (TLM). The house-to-house survey initiated last year has been completed in 3 tehsils and selected clusters of Unnao district with the help of ASHAs and local health staff. A total of 92000 population was surveyed. 47 new cases were detected during the survey and put on treatment with the help of ASHAs whereas 23 cases were earlier on treatment. 2/70 (3%) had old deformities. This information will be used as a baseline for future comparison.

National Sample Survey to assess the disease burden in leprosy

The institute has been coordinating a survey in all the States and Union Territories of India based on a methodology standardized by NIMS, New Delhi and other specialists.

This study is being carried out as directed by Parliament and in coordination with the Central Leprosy Division, Govt. Of India and all the States and Union Territories. This study aims at assessing the prevalence of leprosy cases across the Country, ascertaining the deformity rate and also stigma of leprosy in the patient as well as community. During the year, training was imparted to 210 medical officers/DLOs, SLOs and ILEP validators who will be involved in the survey to be carried out in 99 selected districts using inverse sampling methodology. The data has been collected from several States, it is being electronically entered and will be analysed in the near future. The information likely to be available from this survey is expected to be useful to strengthen the National Leprosy Elimination Programme.

Evaluation of alternate regimens against leprosy

The institute has been evaluating various alternate anti-leprosy regimens earlier designed at this Institute and found to be effective in hospital based studies. These studies are progressing on leprosy cases detected in leprosy surveys in Model Rural Health Research Unit in Ghatampur. The regimens being assessed include uniform MDT of WHO, same as common regimen recommended by the Institute.

Mechanisms and precipitating factors for reversal reactions in leprosy

A study has been undertaken in collaboration with Foundation for Medical Research (FMR), Mumbai as a ICMR Task Force Funded Project. It was observed that live and metabolically active *M.leprae* were present in the lesions of type-I leprosy reaction patients. This was established by molecular (*in-situ* PCR, Real Time PCR and by immunohistochemistry) showing the presence of secretory protein of antigen 5 complex. These findings indicate the need of anti-leprosy treatment cover when managing these episodes with steroids.

Immunology of leprosy

Various studies on the mechanisms of T-cell responses, T-cell signalling, role of regulatory T-cells and mechanisms and role of NOD 2, TLR 2, soluble TLR 2 in mycobacterial diseases have progressed during this year. The data on NOD 2 polymorphism revealed a very low prevalence of those mutations in tuberculosis and leprosy cases which have been earlier reported to be associated with predisposition to mycobacterial diseases. These observations at variance with observations with other countries.

TUBERCULOSIS

Estimation of burden of tuberculosis

As a part of the research programmes funded by Central TB Division, Govt. Of India, the Institute is one of the Centres undertaking pulmonary tuberculosis survey in the districts of Banda and Kanpur Nagar. Using a well standardized common protocol, about 96000 defined population (belonging to rural as well as urban area) was surveyed. The result showed a prevalence of 37/10000 population in the area with

more cases in rural areas as compared to urban areas and higher incidence of the disease as the age advances. (Fig. 1)

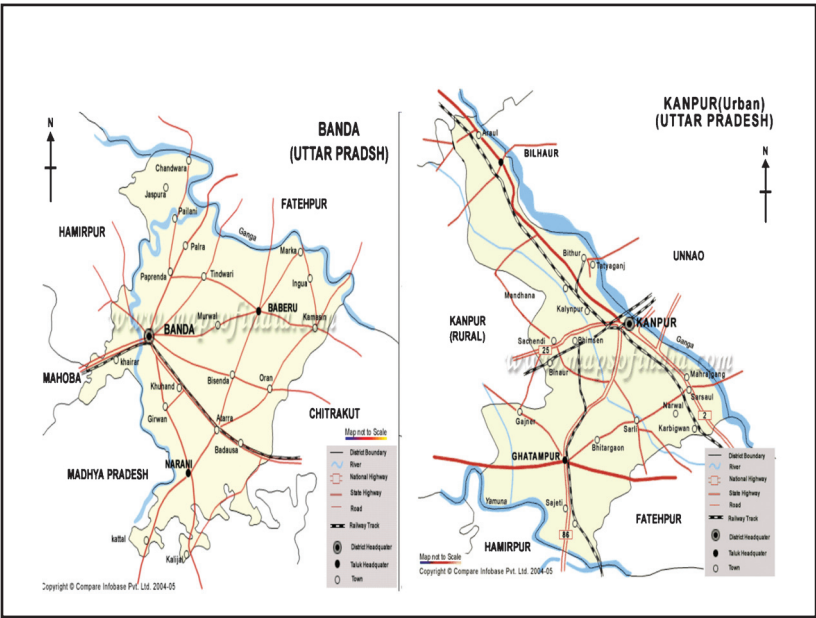


Fig. 1 showing the map of the two districts of Uttar Pradesh where prevalence studies were undertaken

Mechanisms of drug resistance in tuberculosis and mycobacterial diseases

During the year, studies on the molecular mechanisms of drug resistance by investigating the formation of biofilm as well as proteomic approach continued. Several proteins associated with streptomycin regimens have been identified in the proteomic studies. These are being investigated and docking analysis showed that one of the hypothetical protein on the cell surface could be a potential site for binding of the drug.(Fig. 2)

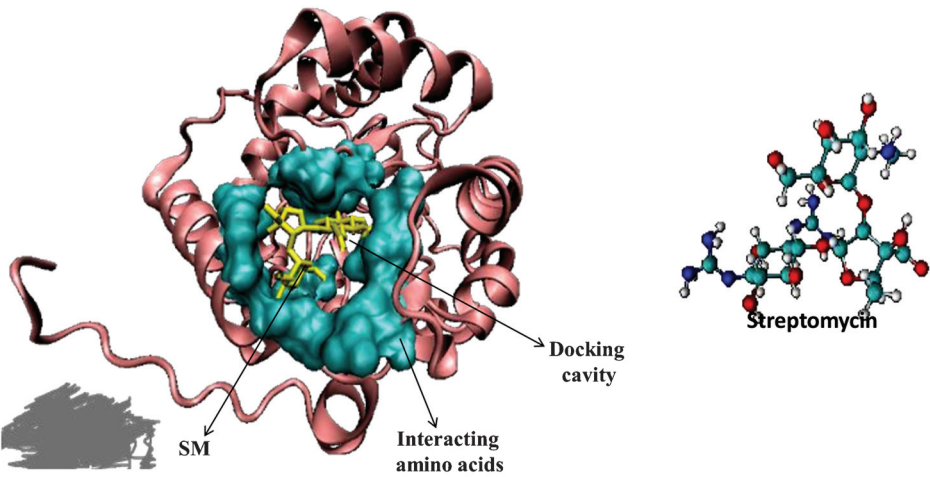


Fig. 2 Model of streptomycin docked with Rv3075c

Programmes of National Reference Laboratory (NRL) for tuberculosis

The Institute serves as one of the National Reference Lab for tuberculosis and is responsible for supporting the services in Uttar Pradesh, Uttarakhand, Himachal Pradesh and Assam. While the Institute is providing drug susceptibility testing support to these States, it has supported the efforts to accreditate the laboratories in Lucknow and Dehradun as intermediate leprosy laboratories so that they are able to take care of programme needs in these areas.

Determination of prevalence of drug resistance in Western and Bundelkhand regions of UP

The Institute has been carrying out a major study (funded by CTB, MOHFW through State TB Society) to determine the prevalence of drug resistance in TB in 35 districts of UP. During the year, the studies on drug resistance prevalence in Western UP and Bundelkhand Region were extended to 13 other districts of the State. So far 24 districts have been completed, others will be completed during 2011. The data will be compiled after completing all the districts in near future.

Patents

A patent was granted to a molecular test (PCR-RFLP) developed at the Institute. This test differentiates between *M.tb* and other mycobacteria that could be isolated from disease resembling tuberculosis or could be environmental contaminants.

NATIONAL INSTITUTE OF CHOLERA AND ENTERIC DISEASES, KOLKATA

Surveillance for Diarrhoeal Diseases

Hospital based surveillance to analyze the etiology of diarrhea [bacterial, parasitic and viral pathogens] was conducted on two random days per week by enrolling every fifth diarrheal patient admitted to the Infectious Diseases and Beliaghata General Hospital (IDH) and BC Roy Children Hospital (BCH), Kolkata. Comparative analysis of data generated in the previous year showed emerging trends in increased *V. cholerae* O1 infection among <2 years age group, resistance of *V. cholerae* O1 to tetracycline, rise of untypable *S. flexneri*, higher proportion of atypical EPEC and *G. lamblia*. Conventional microbiological assays failed to detect any known pathogen in approximately 30% of the diarrheal stool specimens. The number was substantially reduced when the same set of specimens were re-analyzed through newly developed real-time PCR assay that detected one or more pathogens in specimens that were earlier assigned 'no known pathogen'. The increased detection capability of the Real-Time-PCR assay revealed existence of very high degree of polymicrobial infections among hospitalized diarrhea patients in and around Kolkata. It's obvious that hospital based surveillance does not reflect the diarrhea situation in the community for its inherent limitations. As part of cholera vaccine

trial, NICED also has a surveillance system in place in the urban slums of Kolkata. Thus, this rural community-based surveillance system would be an important step in understanding the actual scenario related to diarrheal diseases in this part of the country.

Surveillance also revealed viral pathogens other than Rota virus to cause diarrhea. These are Astroviruses, Noroviruses, and Sapoviruses. Molecular characterization of Noroviruses isolated from children in Kolkata indicated its close relationship with strains reported from other countries that include Africa, Brazil, Italy, Japan and USA. Molecular characterization of human picobirna viruses (PBV) in children below 5 years of age, revealed that these strains were genetically related to PBV reported from Europe and Latin America. This raised questions regarding the possibility of zoonotic transmission of this virus.

Helicobacter pylori

A new trends on *Helicobacter pylori* infection and gastroesophageal reflux disease has been observed. The incidence of oesophageal adenocarcinoma which was very rare a few years back has been observed to increase recently. The decreasing incidence of *H. pylori* infection was concomitant with the increasing incidence of Barret's esophagus associated esophageal adenocarcinoma. So *H. pylori* association in GRED and Barret's esophagus was investigated. Analysis of clinical data collected from patients attending gastroenterology clinic in SSKM hospital, Kolkata followed by histoapthological analysis of the clinical specimens will be a value addition for understanding of *H. pylori* association in the disease process. Isolated *H. pylori* strains will be further studied by molecular genotyping to reveal correlation, if any, with *H. pylori* molecular types to the disease pathology.

Vibrio cholerae

Molecular basis of pathogenesis: Better understanding on the viable but non-culturable (VBNC) *V. cholerae* has been achieved. Detailed studies on *V. cholerae* O1 El tor variant strains (capable to produce cholera toxin of biotype classical) revealed its capability of higher toxin production as compared to the canonical El Tor strains. This could be a possible reason that recent cholera caused by these El Tor variants is more severe than the earlier ones. Detailed characterization studies on the CTX genetic element in achieved strains (period 1989 till date) showed emergence, progression and gradual replacement of the strains by best suited variants. Possible mechanism of emergence of different variants and their interrelationship has also been addressed.

Standardized Pulsed-field gel electrophoresis (PFGE) techniques has also been established for *V. cholerae*. This activity is under an umbrella of PulseNet Asia Pacific PFGE network activity through which images of the PFGE patterns are electronically shared for comparison of the target pathogen isolated from several sources of epidemiological interest.

During this period, *V. cholerae* hemolysin (HlyA), another potential virulence factor was characterized in detail. This study was carried out on a 65-kDa water-soluble pore-forming toxin that causes lysis of eukaryotic cells by destroying selective permeability of the plasma membrane bilayer. Mutational analysis helped in detecting three-dimensional structure of 65-kDa HlyA oligomer, using cryo-electron microscopy and single-particle methods (Fig. 1).

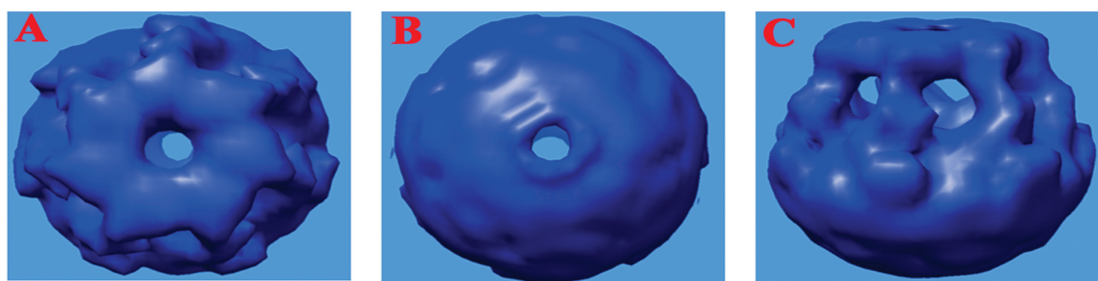


Fig. 1. Three-dimensional views of 65 kDa *Vibrio cholerae* hemolysin (HlyA) oligomer as derived by cryoelectron microscopy and single-particle analysis techniques. Proteolytic removal of the 132 residues from N-terminal region generates mature 65 kDa HlyA. HlyA transforms itself in biomembranes and synthetic lipid vesicles and forms a heptameric channel of internal diameter 1.5 nm. The image shows the top view of HlyA oligomer (A) with a ring-like structure at the top. View from bottom is presented in image B. with bowl-like structure. Side view of HlyA oligomer is presented in C.

X-ray crystallographic structure of the HlyA monomer has been fitted well with the oligomeric HlyA structure determined by EM which proved the correctness of the structure. An unique study on non-toxigenic *V. cholerae* strains have been initiated to detect and characterize virulence factors other than cholera toxin (CT). In an *in-vitro* rat intestinal model (Ussing's chamber) it was observed that these non-toxigenic *V. cholerae* strains showed enterotoxic responses. The enterotoxic factors were purified to homogeneity, two factors were identified and these are 35 kDa hemagglutinin protease (HAP) and 59 kDa novel serine protease.

Vaccine studies: Phase II and Phase III trials of a killed whole cell oral cholera vaccine has been completed and results are very promising. Based on this study, the new cholera vaccine was introduced in India in 2010. This vaccine will make a dramatic change in reducing the burden of cholera worldwide. This vaccine which is effective, cheap, safe, produced according to WHO and international norms, can be effectively implemented either preemptively in cholera prone areas or as reactionary measures for combating epidemics.

Rapid tests for cholera: Commercial kits that can be successfully used in outbreak scenario have been evaluated. Evaluation of a commercial immunochromatographic dipstick kit Crystal VC for rapid diagnosis of *V. cholerae* serotypes O1 and O139 directly from fecal specimens has been made. The study showed that sensitivity and specificity of the dipsticks was about 92 and 73% respectively which is very good in terms of its use in cholera outbreaks. (Fig.2)

Drug resistance in cholera: NICED maintains continuous monitoring on the changing pattern, if any, on drug sensitivity profiles of the enteropathogens over period of time. Continuous monitoring helped in detecting the emergence strains with multiple drug resistance phenotype. Currently, most of the recommended antibiotics/ drugs for the treatment of cholera are less effective. A very recent outbreak investigation of cholera conducted by the NICED team in Purba Midnapur showed 100% sensitivity of *V. cholerae* towards norfloxacin and azithromycin. A hospital based clinical study on efficacy of single dose azithromycin and standard dose of norfloxacin in the treatment of cholera among adults has been initiated and the study is ongoing at IDH hospital, Kolkata. The findings regarding the effect of the drugs on cholera will also be useful to combat the outbreak situations of cholera.

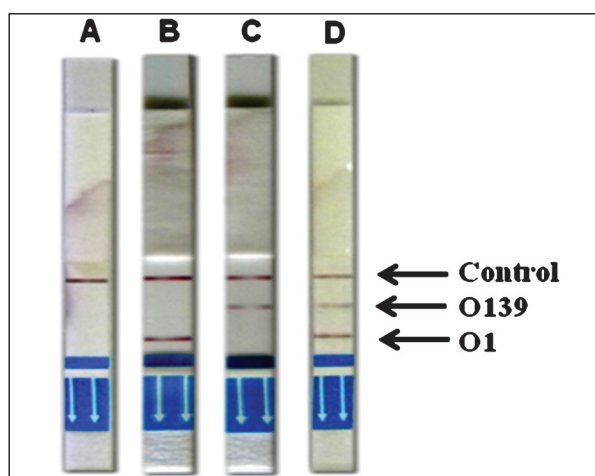


Fig. 2 Detection of *V. cholerae* O1 and O139 by Crystal VC dipsticks (Span Diagnostics, India). Control band to confirm validity of the test (A), appearance of two bands upper one is control and the other is specific to O139 *V. cholerae* (B), appearance of two bands upper one is control and the other is specific to O1 *V. cholerae* (C) and both the bands to detect presence of both O1 & O139 *V. cholerae* (D).

Shigella vaccine

Despite many years of extensive research to develop a *Shigella* vaccine, a practical vaccine is still not available. It was shown that oral administration of heat killed *Shigella flexneri* 2a can give 100% protection against homologous challenge. It has been observed that the 34 kDa outer membrane protein (OMP) played the key role in eliciting protective immune responses. The purified 34 kDa OMP was found to be cross-reactive and antigenically conserved among *Shigella* spp., and the epitope is surface exposed on the intact bacterium, which are the criteria of an optimal vaccine antigen and therefore deserves further study as potential subunit vaccine candidate.

Salmonella typhi

Identification and functional characterization of a novel adhesion protein of *S. typhi* and demonstration of its potential as a subunit vaccine against human salmonellosis have been addressed. This part of the study has been published journal with very high impact factor. A patent application has also been filed for newly characterize adhesion protein T2544 of *S. typhi*. Attempts were also made to identify and characterize aqueous extracts of three ethnomedicinal plants. Considerable anti typhoid and anti diarrheal activity was found. *In-vitro* and *in-vivo* validation of its activity has been carried out. Patent has been applied on the anti-typhoid activity of the plant extract. Studies were also extended to identify and characterize factor(s) responsible for carbapenem resistance in pathogenic bacteria that caused neonatal sepsis.

Rotavirus

As a virus depends on its host cell for replication and pathogenesis, it was hypothesized that the identification of host cellular proteins and virus encoded proteins, which facilitate virus replication and propagation by evading immune responses, will lead to better understanding of the mechanisms of pathogenesis. To understand functional significance and mechanism of rotavirus induced activation of PI3K/Akt signaling, rotavirus encoded proteins were studied. Nonstructural protein-1 (NSP1) was found to activate pro-survival pathways like PI3K/Akt and NFκB during initial stages of infection, to delay virus induced apoptosis. Furthermore studies with signaling pathway specific inhibitors significantly attenuated rotavirus growth and thereby confirming importance of cellular proteins during rotavirus infection. All these raised the possibility of targeting cellular chaperones for developing new anti-rotaviral strategies.

Influenza A H1N1

Surveillance and molecular characterization was carried out for influenza virus strains circulating in Eastern India together with laboratory diagnosis of pandemic H1N1 Influenza virus in suspected human cases during the avian influenza outbreak in Eastern India (Fig. 3).

The clinical samples were classified based on gender and duration of fever though no direct correlation was observed with influenza positivity. Maximum number of symptomatic patients were in the age group of 1-5 years. Very few adult cases were enrolled as few adults reported to hospital OPDs with flu like symptoms. The sample collection was maximum during May-July due to higher load of various viral infections in Kolkata during monsoon season. Out of 840 patients, 193 (22.9%) were positive by Real-Time PCR whereas of these 193 positives only 75 could be grown in culture (8.9%). Of 193 positives, 139 were positive for Influenza B, 52 for pH1N1 and 2 for H3N2. Influenza B was observed throughout 2010 with varying frequency, whereas pH1N1 circulated only in July. NICED continued to provide rapid diagnostics for the suspected cases on Novel H1N1 from Eastern and North Eastern States of India that was initiated in July 2009. A total of 3285 samples have been screened until Nov 2010 out of which, only 316 were positive for novel H1N1 and 98 were positive for seasonal flu (H3N2 /H1N1). In West Bengal, 4 deaths were reported in July 2010 but these patients had co-morbidities. In general most of the positive cases had mild symptoms.

HIV and AIDS

The studies include sex-trafficking and HIV infection in West Bengal, injecting drug use and genetic susceptibility to HIV in north-eastern states of India,

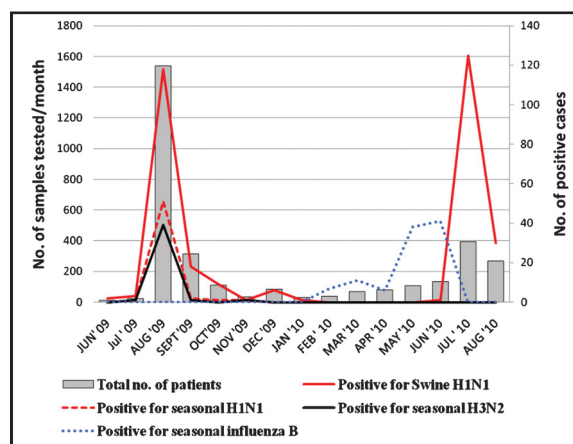


Fig. 3 Surveillance for pH1N1 strains in Eastern India

oncogenic Human Papilloma Virus infection and cervical cancer in sex workers of West Bengal, substance & sexual abuse among street children of Kolkata and genetic characterization of HIV among sex workers & IDUs. In 2008, NICED became a NACO regional Institute (Eastern region) to support and monitor HIV Sentinel Surveillance in West Bengal, Andamans and Nicobar, Chhattisgarh and Sikkim. Further, NICED was recognized as NIIHAR (Network of Indian Institutes for HIV/AIDS Research) by NACO.

HPV infections among the HIV positive patients from Kolkata were found to be more compared to HIV seronegative individuals. Increase in Recombinant HIV strains among the IDUs in Manipur has been observed and it's biological consequences are being studied.

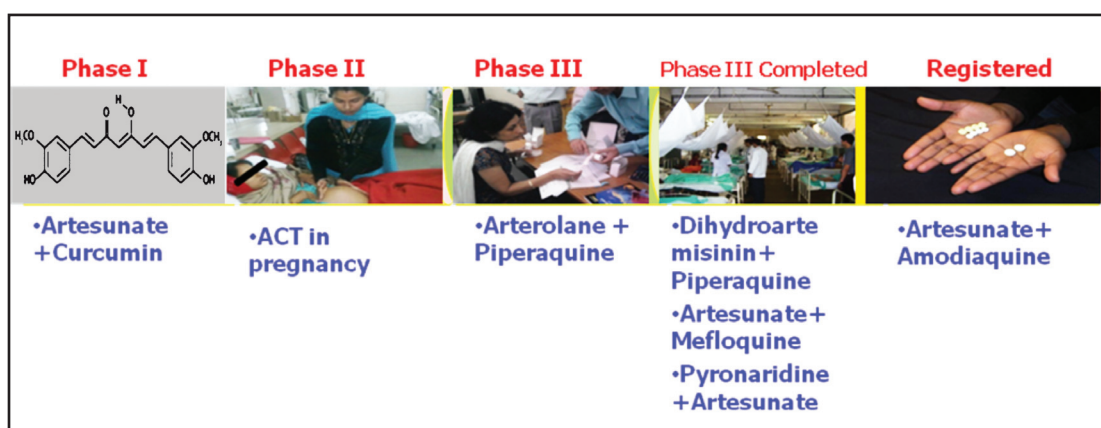
Sources of HIV-stigma are a) fear of transmission of HIV through non-invasive contact, b) shame and c) judgmental attitude including blame. Analysis of baseline data conducted by NICED revealed that educational status of the respondents in the general community was inversely associated with the 'fear of transmission of HIV through non-invasive contact'. While this finding provided a direction for future intervention development with a goal to allay such fears, addressing shame and judgment associated with HIV posed greater challenge as these attitudes were more in those who had correct knowledge about various modes of HIV transmission. Economically well-to-do status also did not help reduce 'shame' or 'judgment'. The scientist of NICED involved in development of HIV-stigma reduction intervention highlighted these issues in 2010 in various forums of policy makers and program planners. He also demonstrated that the intervention developed by him in collaboration with the Society for Positive Atmosphere and Related Support to HIV/AIDS (SPARSHA) to reduce HIV-stigma in the general community was effective in removing fears and reducing shame in the intervention arm compared to control arm. Make Art/Stop AIDS provided inputs for development of art-component of this intervention. The community based HIV stigma reduction intervention followed a cluster randomized design and thus through a community based experiment provided for the first time in the country a framework for future scale-up.

The tat gene of human immunodeficiency virus type-1 (HIV-1) is responsible for the initiation and elongation of viral transcription through the LTR (long terminal repeat) transactivation process. Our study included structural and functional analyses of the tat gene and LTR region of 35 injecting drug users (IDUs) from Manipur (a north-eastern state in India and a potential source of HIV-1 recombinants) in order to search for the recombinants and variation in the transactivation process if any due to recombination. Analysis showed prevalence of subtype C with few BC recombinants for the tat gene showing identical recombination breakpoints. Phylogenetic analysis of the LTR region of those IDU strains showed strong resemblance to Indian subtype C forming a completely separate cluster from the other global C LTR sequences. The TAR element (transactivator response region) in all the LTR sequences was fairly conserved. Further study of the transactivation rate of the C and BC tat for the Manipur C LTR showed almost equal transactivity in both the cases. This is the first report of characterization of tat gene and LTR region of HIV-1 samples among IDUs from north-eastern India.

NATIONAL INSTITUTE OF MALARIA RESEARCH, NEW DELHI

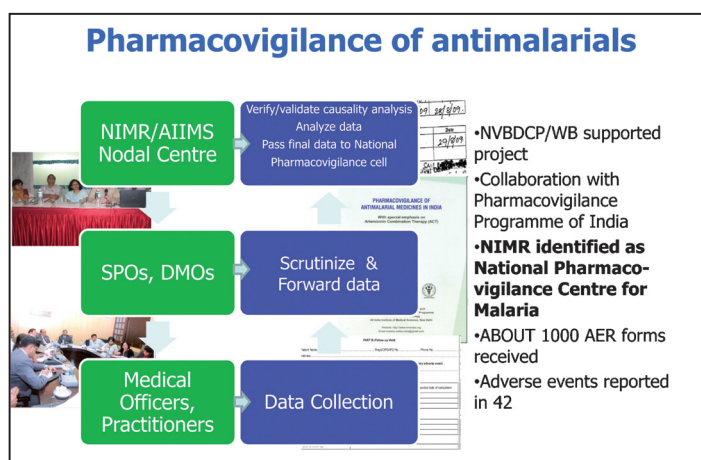
Clinical Research

The NIMR has developed necessary infrastructure for conducting clinical trials at eight different hospitals in malaria endemic areas of the country. The staff of the NIMR field units as well as the hospitals is trained in Good Clinical Practices. The combination artesunate+amodiaquine has been registered on the basis of results of phase III trial carried out by NIMR. Phase III trial has also been completed with dihydroartemisinin+ piperazine, artesunate+mefloquine, pyronaridine+artesunate. Currently, we are evaluating the combination of artemisinin analogue arterolane maleate with piperazine phosphate in phase III trial. A phase II/III trial for safe and effective antimalarial for malaria in pregnancy has been initiated. Combination of artesunate and curcumin is undergoing phase I trial.



Pharmacovigilance of antimalarials in India

Pharmacovigilance programme for antimalarial medicines in India was initiated with objectives "assessment of benefit, harm, effectiveness and risk of ACTs in treatment of malaria". In this programme, specially designed Adverse Event Reporting formats are filled up in patients on antimalarial therapy. Till date more than 1000 forms have been received. Adverse events in the form of nausea, vomiting, loss of appetite, pain in abdomen were recorded in 32 individuals.

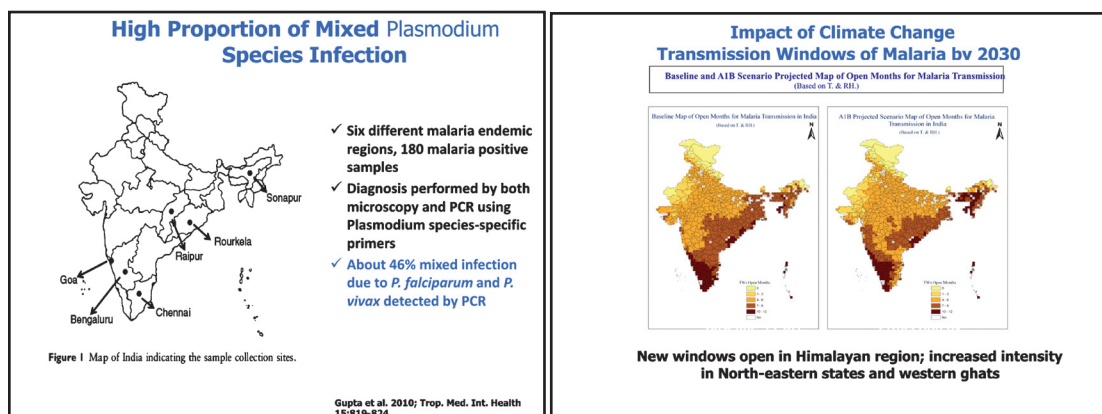


Quality Assurance of malaria rapid diagnostic tests (RDTs)

A study was initiated to assess the quality of RDTs procured and supplied by National Vector Borne Diseases Control Programme (NVBDCP) in July 2009. NVBDCP is the nodal centre and NIMR is National Referral Laboratory for this project. NIMR is preparing quality assurance panels of known parasitaemia from time to time. As a part of the pre-dispatch QA, RDTs were assessed to ensure their quality with known negative and positive samples before they were supplied to various states. Post-dispatch QA is being done to assess the quality of RDTs at periodical intervals with low positive panels and high positive panels. NIMR has been continuously receiving RDTs from Different States of the country. Till date, more than 1500 RDTs have been tested.

High proportion of mixed infection with Plasmodium species

In blood samples collected from southeastern part of India, very high proportion of mixed infection of *P. vivax* and *P. falciparum* to the tune of 46% was detected. The finding opens up avenues for understanding the competition between both species and adaptation to overcome the effect of antimalarials given for treatment.



Impact of climate change

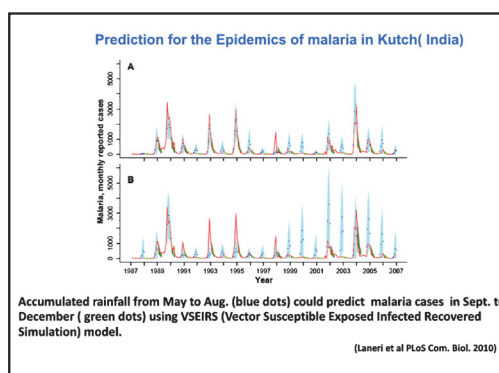
Enough evidence is available to link climate change and increase in vector borne diseases. At NIMR, impact assessment of climate change on malaria has been studied keeping in view the projected increase in temperature (T) and changes in relative humidity (RH) by the year 2030. Based on minimum required temperature and RH for ensuing transmission of malaria, transmission windows of malaria were determined for baseline as well as for 2030 using T and RH from PRECIS model developed by IITM, Pune. The findings indicate that in Himalayan region, new window are likely to open due to increased T. Intensity of malaria in Northeastern and western ghats is also projected in some pixels. Reduction is also projected in east coastal region which experiences heat waves. The role of other determinants like urbanization, agricultural practices, intervention and socioeconomic factors also need to be incorporated in the model for attributing the role of climate change alone in vector borne diseases.

Two generic research protocols contributed by NIMR, New Delhi and NICED, Kolkata on assessment of climate change impacts on vector borne diseases have been published by WHO SEARO.

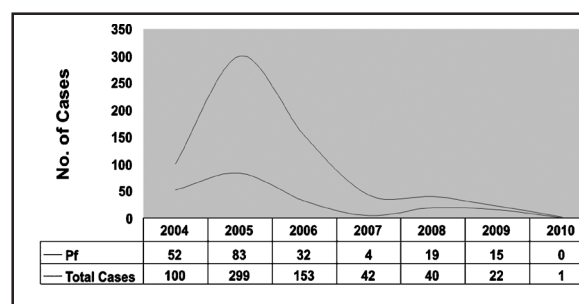


Rainfall as indicator for early warning of malaria

Rainfall has been associated with malaria in most part of the world. Even based on rainfall and other malaria and socioeconomic indicators, early warning of malaria was augmented long back in 1920 which continue till 1944. The technique lost its relevance due to changes in malariometric indices. Still peninsular India is epidemic prone and there is no early warning system (EWS) for malaria so that preparedness and response may be planned. Recently modeling of rainfall based EWS has been initiated in collaboration with Michigan University (USA). Results of Analysis reveal that accumulated rainfall from May to August could predict malaria cases in September to December months in studied area of Gujarat and Rajasthan.



Intervention (2004 – 2010)



Impact of interventions on malaria cases

Health Impact Assessment of Indira Sagar Dam and SSP Reservoir in Narmada Valley (Madhya Pradesh)

A retrospective study on Health Impact Assessment on Indira Sagar Dam and Resettlement and Rehabilitation Colonies (RR) in Sardar Sarover Project (SSP) reservoir funded by Narmada Valley Development Project, Bhopal (NVDA) was initiated in January, 2004 and accomplished in 2010. In India, this HIA project is the first longitudinal project which is operational for > 5 years and is a remarkable achievement.

Seven districts, viz. Khandwa and Dewas (Indira Sagar Project (ISP) & Omkareshwar Project (OSP), Khargone and Harda (ISP), Badwani, Dhar and Jhabua (SSP) consisting of 32 villages, 18 rehabilitation and resettlement (RR) centers and 5 command area villages and 6 Labour colonies were taken up in the study. Based on Entomological and epidemiological monitoring for all vector borne diseases (VBD) i.e. malaria, dengue, JE and filariasis, guidelines were provided to NVDA for implementation.

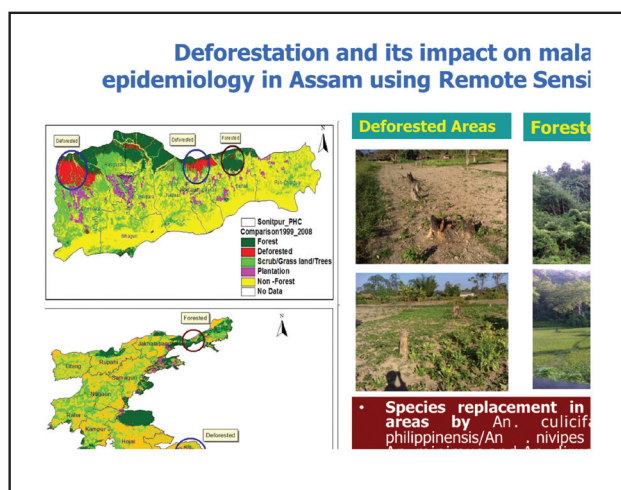
NVDA, State Health Department & Narmada Hydroelectric Development Corporation Ltd (NHDC) as per NIMR suggestions promptly implemented mitigating measures which resulted in drastic reduction of the vector density of malaria, dengue, chikungunya, JE and filariasis. Malaria cases reduced from 299 in 2005 to 1 case up to July 2010. Blood samples were also collected for testing Dengue, J.E. and filariasis but none was found positive. Vector species of Kala-azar was absent in this area.

NVDA has extended the funding of the project till 2014 to carry out the HIA Study, it would be progressively covering all 30 major dam areas in Narmada Valley Development Project and as per schedule the study will be continued till December 2014.

Impact of Deforestation on malaria epidemiology

A study was initiated in deforested and forested PHCs of Sonitpur and Nagaon districts of Assam using Remote Sensing and Geographical Information System (GIS) to assess the impact of deforestation on anopheline ecology and malaria epidemiology. Deforested and forested PHCs were identified after comparison of classified IRS-1D/ P6-LISS III remote sensing imageries for 1999 and 2008. Classification of IRS-P6/ LISS IV imageries (5 m resolution) of deforested PHCs revealed that the purpose of deforestation was habitation and agriculture activities. A major development seen in the deforested areas was the development of sub-stream network (channels) from the main streams for irrigation purpose.

Active fever surveys and state collected malaria epidemiological data revealed more number of malaria positive cases in deforested PHCs in comparison to forested



PHCs of both the districts. In deforested areas, disease transmission is being caused by two species namely *An. culicifacies* and *An. minimus* while in deep forested areas only *An. dirus* is involved.

Evaluation of insecticides for vector control

NIMR undertook evaluation of new insecticides for larval and adult mosquito vectors. Temephos and fenthion which are being used for larval control in different areas were re-evaluated and consequently fenthion has been withdrawn from the vector control program due to development of resistance. Mosquito repellent cream (Advanced Doods), Insecticide incorporated Plastic sheetings (Zero-fly) and long lasting insecticidal nets (Olyset net, Permanet 2, Icon Life and Duranet) were evaluated in different regions/eco-climatic zones in India for personal protection against mosquitoes.

Detection of *kdr* mutations (L1014F and L1014S) in *Anopheles culicifacies*

NIMR developed PCR-based assays for the detection of two major *kdr*-like mutations L1014F and L1014S, which has been reported to confer resistance against DDT and pyrethroids, in field population of *An. culicifacies*. For L1014F mutation an Amplification Refractory Mutation System (ARMS) and for L1014S a Primer Introduced Restriction Analysis PCR (PIRA-PCR) was developed which are highly specific.

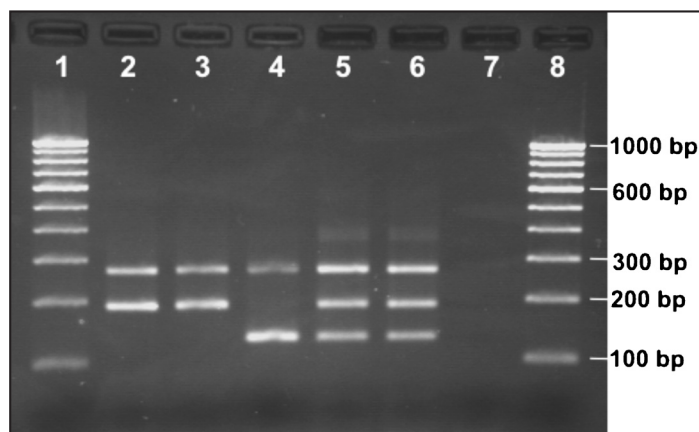


Figure : ARMS for L1014F detection: Lanes 1 & 8: 100 bp DNA ladder; lanes 2 & 3: homozygous wild; lane 4: homozygous L1014F; lanes 5 & 6: heterozygotes; lane 7: negative control



Events 2010

Informal Consultation on Standard Protocol Development for Estimating Malaria Disease Burden in SEA Region

Prof. Peter Agre, Nobel Laureate visits NIMR



Foundation Stone laying Ceremony of animal house facility

Global Exchange Lecture Course on Molecular and Evolutionary Genetics of Malaria



VECTOR CONTROL RESEARCH CENTRE, PUDUCHERRY

Lymphatic filariasis

Vascular Endothelial Growth Factor (VEGFR)-3, a tyrosine kinase receptor, signals the lymphangiogenesis by promoting lymphatic proliferation. Analysis of nucleotide sequence from patients of lymphoedema revealed the presence of a non-synonymous nucleotide variation (G->T) in the VEGFR-3 gene coding for this receptor, which will be helpful to differentiate Primary lymphoedema cases from secondary lymphedema cases. An AS-PCR assay has been developed based on this marker.

The Centre has been working on development of simple and less expensive xenomonitoring tools for *W. bancrofti* transmission. In this direction, an epitope (P2) for detecting infectivity has been identified and a prototype electrochemical sensor has been developed for detecting the infection. The infective stage (L3) specific RT-PCR assay, developed at the centre was optimized for field use and found to be highly specific and sensitive when large number of coded samples was tested. The assay is being evaluated in the field.

A real-time PCR assay has been developed to detect albendazole resistance in *W. bancrofti* from microfilaria carriers.

Studies on heterogeneous response of microfilaria carriers to DEC treatment have led to identification of three single nucleotide polymorphisms (SNPs) in the genes encoding enzymes in humans as biomarkers for the detection of non-responsiveness to DEC.

Structure based drug design (SBDD) for the development of a macrofilaricidal molecule was carried out using the filarial Glutathione – S - transferase (GST) as the target protein and substituted naphthoquinones as ligands. Out of 11 amino substituted 2-hydroxy-1, 4-naphthoquinones (lawsone) synthesized and screened during the year for macrofilaricidal activity against adult female *S. digitata* worms at 0.1mg/ml, three (VCRC/MFC-22, 37 & 38) have been identified as potential candidates as per WHO criteria for further studies.

A trial on alternative chemotherapeutic regimen (DEC with albendazole, DEC with doxycycline and sequential administration of albendazole) for clearance of filarial infection (*W. bancrofti*) showed difference in the level of reduction of mf count and antigen level between the arms (coded), after 90 days.

A lymphatic filariasis transmission risk map created for India based on geo-environmental risk model (GERM) has been validated through ground truth survey in 60 sites across the country. The model showed good agreement (92.3%) between predicted and observed values. This tool could detect the endemic status of LF in hitherto unknown areas (Fig. 1).

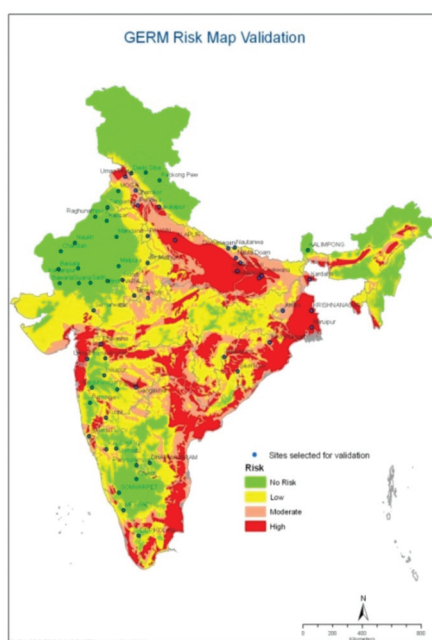


Fig 1. GERM Risk Map validation

A community based integrated vector management strategy, implemented as a supplementary measure to Mass Drug Administration at village level continued to show decline in the percentage of houses with positive vector breeding habitats and vector density.

Epidemiological evaluation carried out in villages for the long term impact of distribution of DEC medicated salt for one year as supplementary measure to Mass Drug Administration has shown that antigenemia prevalence is maintained below 1% with no recurrence after four years of intervention.

The interim results of the study on designing appropriate sampling protocol for assessing the impact of MDA for elimination of LF have shown that to achieve a power of 80%, at least 600 children (60 clusters of 10 children each) are to be tested for filarial antigenemia in an intervention unit.

Malaria

Studies on the feasibility of Integrated Vector Management strategy to control *An. fluviatilis* transmitted malaria among tribes in Koraput district of Orissa state has been initiated. A sample survey of 165 streams has shown that the construction of check dams across the streams under minor irrigation projects of the State has no impact on breeding status of malaria vector. A pilot trial is in progress in collaboration with the irrigation department to test whether construction of dams with sluice gate significantly reduces vector breeding in stream beds and malaria in the villages (Fig. 2).



Fig. 2. Construction of sluice gate for flushing of stream water – IVM to control malaria

Olyset Net and Interceptor were evaluated after 20 washes for residual activity against the malaria vector, *An. fluviatilis* in an experimental hut study under WHO Pesticide Scheme. The nets prevented entry of the vector mosquito into the huts by 73%-83% and the blood feeding rate was reduced by 80%-92%. The total mortality rate due to the use of nets ranged from 63 to 76%. There was no significant difference between the efficacies of the nets. These nets could be potential vector control options for malaria control.

Dengue/chikungunya/JE

Based on the knowledge generated on the bionomics of *Ae. albopictus*, the vector of chikungunya in rubber plantations, action plans for Integrated vector management for prevention of dengue / chikungunya have been developed for organized and un-organized sector of rubber plantations in Kottayam district (Fig. 3). The operational feasibility and impact of the strategy is evaluated for its replication.



Fig. 3. Launching of Integrated Vector Management Programme to prevent dengue/chikungunya in Kerala

To study the population diversity of JE vector(s) and its implication on the behavioural difference in JE prone areas, adult and larval collections of *Culex vishnui* subgroup were done in Warangal and Karimnagar districts of Andhra Pradesh and Gorakhpur district of Uttar Pradesh. DNA barcoding of 32 specimens of *Culex tritaeniorhynchus* collected earlier from Bellary, Mysore and Mandya indicated that the population belongs to a compact taxonomic clade.

Bio-control and chemical agents for vector control

Twenty five new bacterial isolates (VCRC B494-B518) exhibiting mosquitocidal activity (10 larvicidal and 15 pupicidal) have been identified for further studies from soil samples collected from desert and high altitude regions.

The stability of the mosquitocidal metabolite from the indigenously isolated *Bacillus subtilis* subsp. *subtilis* was tested under different abiotic conditions and the activity was found to be stable. The formulation is stable upon storage up to 3 months and safe to non-target organisms.

A solvent-extraction based down-stream process for the pupicidal metabolite of *Pseudomonas fluorescens* (VCRC B426) has been optimized that yielded maximum recovery of the metabolite from the culture broth.

Fly ash, a byproduct produced during the combustion of coal in thermal power plants was used as a carrier for the preparation of formulations (WDP) of the indigenous mosquitocidal bacterium, *Bacillus thuringiensis* var. *israelensis* (VCRC B17) (Fig. 4). The formulation resulted in 90% reduction of late instar larval and pupal stages by 24 and 48 hrs respectively in the field up to 6 days.



Fig. 4. Briquette and Granular formulation of Bti using fly ash

Silver nanoparticles have been synthesized using indigenously isolated microbial agent, *Bacillus thuringiensis* var. *israelensis* (VCRC B17) and conditions for optimizing the production of these nanoparticles are being standardized.

AnanotechnologybasedformulationofTemephos(VCRC/NT-4),anorganophosphorus mosquito larvicide has been developed (Fig. 5) and is being tested for its efficacy and safety.

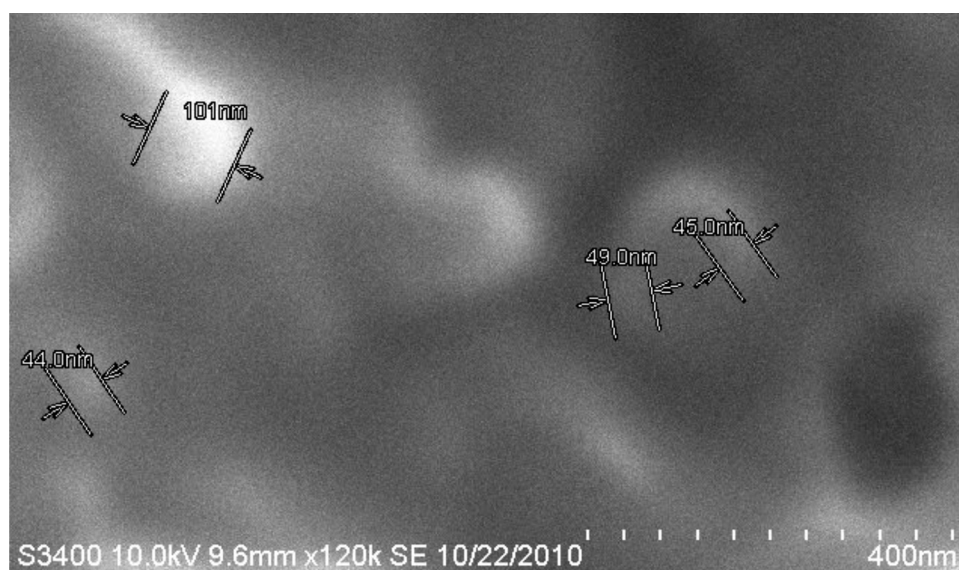


Fig. 5. Scanning Electron Microscopic analysis of nanoparticles of temephos, a mosquito larvicide

HRD activities

The 11th batch of students completed the one year Post Graduate Diploma course in Medical Entomology. Administrative and technical processes have been initiated to start a two year M.Sc., degree course in Public Health Entomology at VCRC under the Pondicherry University. Syllabus for the course has been prepared.

RAJENDRA MEMORIAL RESEARCH INSTITUTE OF MEDICAL SCIENCES, PATNA

Visceral leishmaniasis, commonly known as Kala-azar, is a vector borne disease and is mainly prevalent in Bihar, Jharkhand and West Bengal. Bihar alone contributes more than 90% of the Indian VL cases. RMRIMS, Patna has been conducting research on various aspects of the disease like epidemiology, diagnostic, treatment and control; as well as manpower development to the program people involved at the implementation level.

Programme related studies

Towards more cost effective Visceral leishmaniasis (VL) case detection and case management in endemic districts – Implementation strategies - PHASE-III: Three active case detection approaches viz. camp, index and incentive were compared with door to door survey in pre-identified intervention and control villages of saran districts. Out of 652 camp attendees 109 fever cases were screened through rK39 and 15 were found positive (14%) who were referred to PHC for treatment. Immediately following the camp approach household survey was conducted through the trained ASHA health workers. Out of 42,874 population covered through incentive approach, 114 suspected VL patients were referred and eventually 21 cases (18%) were found rk39 positive and treated with miltefosine at PHC level. No new VL cases could be detected in two rounds of Index case approach. Camp approach was found to be better with comparatively more new case yield. It was proposed to implement the camp approach by the Govt. machinery under supervision to validate the findings at the operational level.

Comparison of imprint smear microscopy and PCR application on biopsy from dermal lesions for diagnosis of Post kala azar dermal leishmaniasis cases in Bihar: After clinical examination for lesions' type, site and coalescence, biopsies from different skin lesions were collected aseptically from 80 PKDL cases for microscopic examination and PCR test. Leishmania parasite positivity by PCR and microscopy was found 95.6% and 91.3 % respectively in papulonodular lesions whereas in case of hypopigmented macular lesions, PCR was found to be more sensitive (92.5%) than microscopy (44.4%). The overall sensitivity of the PCR was found 24% higher than microscopy. Among the 20 treated PKDL cases, 2 were found positive by PCR after first course of treatment, but microscopically they were negative, possibly due to high sensitivity of PCR to detect even very low amount of parasitic DNA.

Remote Sensing and GIS: Tools for the prediction of epidemic for the intervention measures : A point data set was generated based on disease incidence report from 2000 to 2008. By calculating the X and Y co-ordinate of each point, mean centre and standard deviation of ellipse was drawn for each PHC. The results showed that the

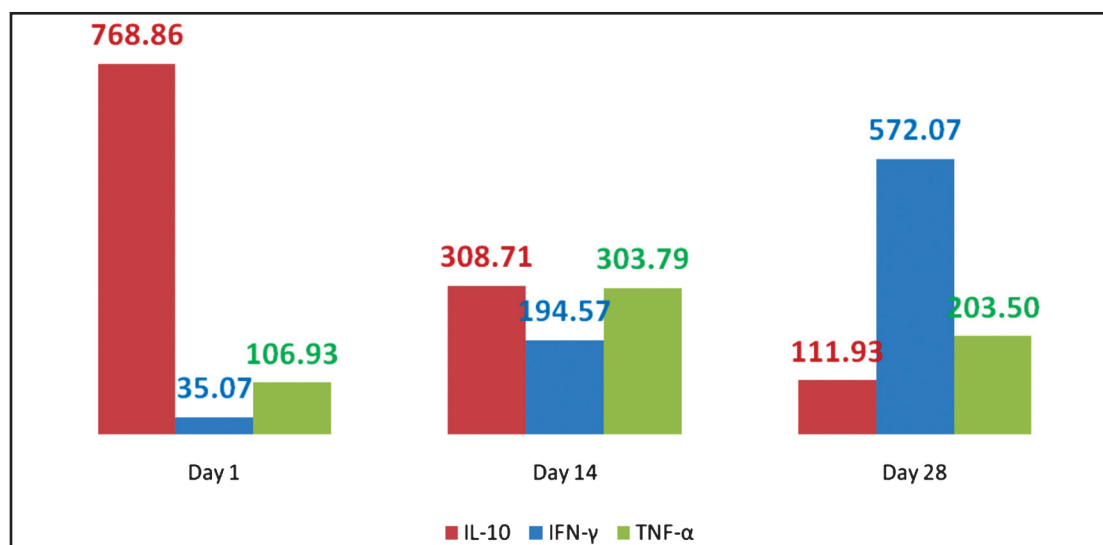
disease is more clustered in the western part of the study site. Soil adjusted Vegetation Index (SAVI) was calculated to measure the vegetation. The value of SAVI varied from -0.42 to 0.69 (Mean = 0.13; SD = \pm 0.32). Land use/ land cover characteristics were extracted from 60 sites (e.g. 2x2 km²) of Kala-azar endemic villages. Spatial auto-correlation between the affected villages was measured for 5 PHCs of the study site.

The study is in progress to estimate vector density through CDC light trap and man held aspirator technique at different environmental condition and study micro-climate and micro-habitat indicators for sandfly and geo-statistical analysis of the remaining PHCs.

Evaluation of the feasibility and usefulness of a monitoring and evaluation toolkit for VL vector control in national programmes (Phase IV): Monitoring and Evaluation (M&E) toolkit for IRS and early case detection has been developed and training was imparted to the concerned officials followed by two round follow up meeting cum workshop to discuss the issues. In between the 1st round training and follow up meeting, vector study was conducted in 4 selected districts. The shortfalls identified were insufficient infrastructure, manpower, technical knowhow. The suggestions evolved were fixed yearly schedule for IRS, uncomplicated and in-time funding, pre-spray training at PHC level, enhanced logistic support including PPE, transportation facility, camp system for DDT storage and stay of spray men, wage revision for spray men, more stress on IEC fund at PHC level, proper supervision and monitoring and delinking of personnel involved from other activities.

Clinical research

Safety and efficacy of zinc supplementation in treatment of Visceral Leishmaniasis (VL) in Bihar: A total of 27 parasitologically confirmed Zinc deficient VL cases meeting all the inclusion and exclusion criteria were randomized in test arm (n=16) and control arm (n=11). The patients under test arm were treated with amphotericin B in the dose of 1 mg/kg body weight for 15 infusions on alternate day along with zinc supplementation in the form of zinc sulphate tablets in the dose of 200 mg twice a day whereas the patients under control arm were treated with amphotericin



Immunological Profile of patients under test arm at different time points

B alone. In test arm all the patients were initially cured whereas in control arm one patient was found parasitologically positive at the end of treatment (initial cure rate 91%)

Efficacy and Safety of Infusion of Amphomul® (Amphotericin B Emulsion) as Compared to AmBisome in Patients of Visceral Leishmaniasis (Kala-azar) : Out of a total of 206 screened patients of suspected visceral leishmaniasis, 119 were randomized - 90 patients in the test group (Amphomul) and 29 in the control group (AmBisome). In the test group, 5 had initial treatment failure and 8 had relapse whereas in the control group no treatment failure or relapse occurred. All the 119 patients had undergone 30-days follow up whereas 108 have completed 6-months follow up. 114 patients had initial cure whereas 95 patients achieved final clinical cure up till now. No SAE has occurred till date whereas mild adverse events like rigor, fever etc occurred in a few patients.

Treatment Response of Kala-azar/ HIV co-infected patients with Ambisome and Anti Retroviral Therapy: A total of 55 patients (83.6% males, and 16.4% females, median age group 35 yrs.) were included in the study. Of these 61% were migrant labourers. The Kala-azar/ HIV co-infected patients included in this study were treated with AmBisome in the dose of 5 mg/kg body weight for 4 days followed by anti-retroviral therapy. Median CD4 cell count at the time of kala-azar diagnosis was 66 cells/ μ l (range - 38-112). Survival by one and two years after kala-azar treatment was estimated at 92%. None of the patients had initial treatment failure. Twenty seven (49.9%) had kala-azar relapse. A probability of KA relapse of 0%, 9.2% and 28.8% were found at 0.5, 1 and 2 years after KA treatment respectively. CD4 count less than 200 cells/ μ l at six month after ART initiation was predictive of subsequent relapse. The CD4 cell count at one and two years after ART initiation was 233 and 261 cells/ μ l respectively. No serious adverse events were observed during treatment.

Safety and efficacy of Liposomal Amphotericin B (Ambisome) in patients with Post Kala-azar Dermal leishmaniasis (PKDL): Altogether 46 parasitologically confirmed PKDL cases, meeting all the inclusion and exclusion criteria as per the study protocol, were enrolled in the study. Out of 46 PKDL cases, 42 had past history of VL. The enrolled patients were treated as per the protocol.

At the end of 1st course, 39 were found parasitologically negative but with the persistent skin lesions. Altogether 43 patients completed 2nd course and 25 had completed 3rd course of treatment. Out of 43 cases in 2nd course, 27 were found parasitologically negative but with less clinical severity. It was observed that even after parasitological cure, there were long lasting skin lesions though in the diminished form. The parasitologically negative patients with persistent skin lesions are under follow up to observe disappearance of lesions. No adverse side effect was observed, except in one case who developed Gullian-Barrie syndrome after 1st course of treatment.

Cholesterol involvement in Visceral Leishmaniasis: Initially peripheral blood samples were collected from 20 VL and 10 healthy controls for assessment of different biochemical parameters like total cholesterol, HDL-C, triglyceride, VLDL, LDL-C, Apolipoprotein A1 (Apo A1) and B (Apo B). It was observed that total cholesterol, HDL-C, LDL-C and Apolipoprotein A1 was down regulated in all the VL patients.

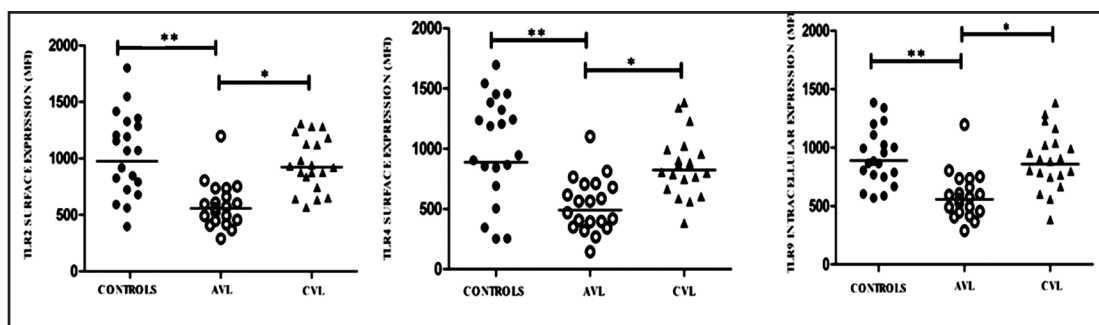
Triglyceride was found raised in VL patients and Apolipoprotein B was normal as to the healthy control before the start of the treatment. However, at the end of the treatment all the parameters returned to normal healthy control value except HDL-C and Apolipoprotein A1.

Basic research

Identification of Anemia as pathogenic factor in Visceral leishmaniasis: The hematological analysis of VL subjects revealed about 1.5 fold less erythrocytes number and 1.2 fold less Hb level in parasite-primed than non-primed samples of VL patients as compared to 1.1 fold for both erythrocyte and Hb level in healthy control. The heme level was 1.8 fold less in parasite- primed than non-primed erythrocytes of patients and 1.1 fold less in parasites primed than non-primed erythrocytes of healthy control whereas the non-heme iron level was found almost equal.

In vitro study on attachment and internalization of metacyclic promastigotes revealed that the sensitized macrophages with leishmania parasite were more capable in internalization of maximum level of Hb. It was observed that parasites require low heme content yet adequate supplies to gradually release for their growth and survival. The study findings reflect the cause of anemia gradually in patients.

GPI-anchored membrane proteins of *Leishmania donovani* mediated regulation of Toll Like Receptors and costimulatory molecules on antigen presenting cells and induction of cytokines: The GPI-anchored protein mediated regulation of cytokine synthesis was studied at the cytokine release levels by ELISA. Interestingly, it was observed that GPI-anchored proteins were able to produce enough amount of IFN- γ in-vitro in healthy controls but not in VL patients. TLR2 and TLR4 demonstrated reduced responsiveness on VL patients as stimulation with specific legends like LPS and Pam3Cys did not result in any significant production of cytokines.



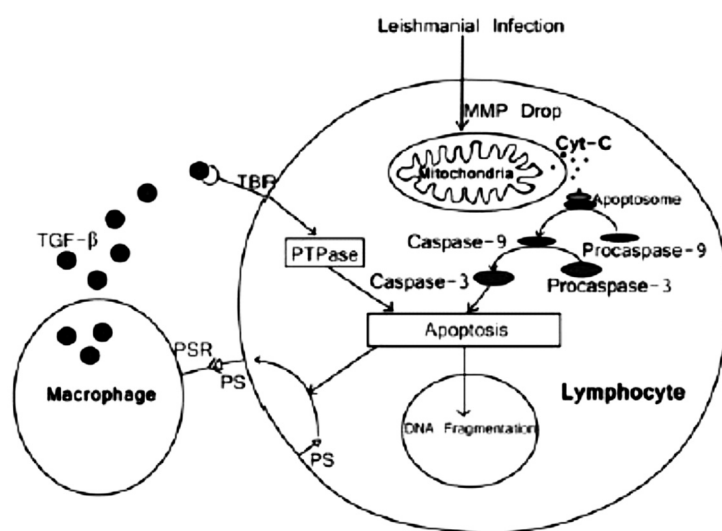
Human control APCs showed enhanced production of IFN- γ , TNF- α and IL-12 after stimulation with GPI-anchored proteins, but no significant change was found for production of IL-10. It was observed that the proteins were able to translocate NF- κ B, which denotes their potential role in pro-inflammatory cytokine production.

TLR expression status in VL patients before and after chemotherapy

Immunological changes in lymphocytes after leishmania infection: In mice model, the upregulation of TGF- β , T cell apoptosis and TGF- β induced PTPase activation were noticed. Additionally, it was found that TGF- β itself induces the PP2A activity.

TGF- β follows the SMAD independent pathway and phosphorylates the TGF- β activated kinase (TAK)-1 molecule. It was also observed that the enhanced PTPase activity dephosphorylates the ZAP-70, the key molecule involved in the TCR signaling. On the other hand, the high PP2A activity inhibits the survival signal by dephosphorylating the ERK-1/2. The use of sodium orthovanadate (PTPase inhibitor) and okadaic acid (PP2A inhibitor) confirms the findings that TGF- β induces both the phosphatases and impairs the cellular signaling and finally causes apoptosis because the inhibitors reduce the apoptosis and also rescue the cellular signaling. This probably suggests that the use of inhibitors may restore the cell-mediated immune function of the host and thus may help in parasite elimination. It was observed that TGF- β induces both phosphatases (PTPase and PP2A) and lymphocyte apoptosis via mitochondrial pathway.

*The hypothetical model of lymphocyte apoptosis during VL in *L.donovani*-infected hamsters*

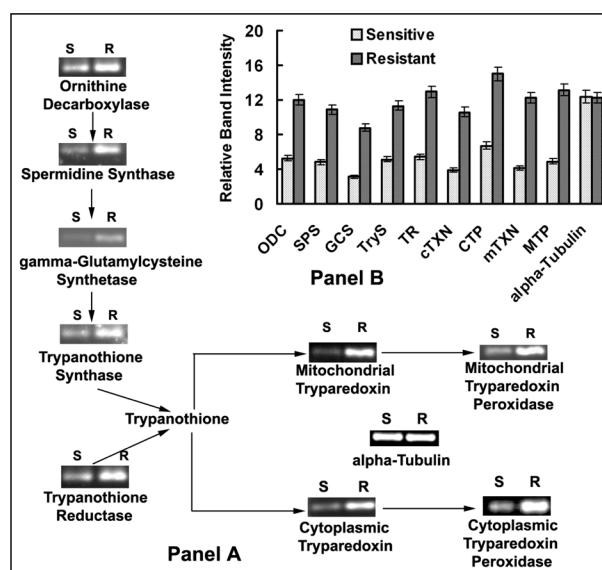


Mechanism of Amphotericin B Resistance in *Leishmania donovani* parasites:

Lower uptake and higher efflux rate of AmB was observed in resistant promastigotes compared to sensitive. Relative expression level of ABC Transporters (higher mRNA level of MDR1 and approximately similar mRNA level of PgPA) were assessed using semi quantitative RT-PCR. It was observed that there was higher accumulation of ROS in sensitive strain as compared to resistant and higher expression level of Thiol Metabolic Pathway genes involved in ROS detoxification in resistant promastigotes as compared to sensitive. The total intracellular reduced thiol content was found to be ~2 fold higher in resistant strain compared to sensitive. The emission anisotropy value of AmB-resistant *Leishmania* promastigotes was three times lower indicating a higher fluidity for the membrane of the resistant strain compared to sensitive. The AmB treated sensitive promastigotes demonstrated ~2.2 fold decrease in the intracellular K⁺ level indicating higher membrane depolarisation compared to sensitive. It was also observed that thiol metabolic pathway inhibitors (BSO and DFMO) reverses the resistant phenotype partially to sensitive which has been demonstrated by decreased intracellular thiol content ~1.4 fold and LD50 value ~1.8 fold for the resistant strain.

Association of HLA class I and class II Alleles in susceptibility to Visceral leishmaniasis in endemic and non endemic regions of Bihar:

To investigate genetic diversity by determining HLA class I and class II allelic distribution in VL cases blood samples, collected from VL patients, healthy contacts and unrelated healthy subjects from different endemic and non-endemic region of Bihar were subjected for DNA isolation. Alleles of HLA-A *02010101 and HLA-DRB1 *150201 were observed to be associated with protection against visceral leishmaniasis, while HLA-A *020601, *24020101 and HLA-DRB1 *150101 alleles were associated with susceptibility to visceral leishmaniasis.



Expression level of thiol metabolic pathway enzymes in Amb resistant and sensitive *L. donovani* using semi-quantitative RT-PCR.

Drug Development

Comparative molecular modeling of various important proteins of different Leishmania strains and ligand-protein interaction study of different anti-leishmanial drugs: Structural models of six different proteins of various *Leishmania* strains were developed and tested for its ligand protein interaction with diverse sets of ligands. In some cases structure of the protein is available from PDB, which was taken for this study to know the presence of interaction with already reported antileishmanial drug candidates and other predicted antileishmanial ligands. Some other proteins of which structural model has been constructed are Enolase, Serine Hydroxymethyltransferase (SHMT), HGPRT, pyrroline-5-carboxylate reductase. Near about nine hundred compounds or their analogues have been studied to know their ligand protein interactions with seven different important proteins (pyrroline-5-carboxylate reductase, actin, transcription initiation factor- like protein, major surface protease) of *Leishmania*.

Computer Aided Drug Design: Structure determination of Elongation Factor-1 α in *Leishmania donovani* by molecular modeling and NMR spectroscopy, targeting through QSAR and pharmacophore analysis: Computational models of Elongation Factor-1 alpha (EF1- α) have been constructed by using (template PDB id: 2b7C_A) the Yeast guanine nucleotide exchange factor eEF1B alpha K205A mutant in complex with eEF1A through MODELLER software 9v7 and Discovery Studio 2.1. Multiple alignment of amino acid sequences of EF1- α protein of different species showed close to each other ranging from 77-92 sequence identity score. A hairpin of 12 amino acids was modeled that was unique to the human EF1- α protein but in *Leishmania*, it was missing and so it had significant opportunity to design novel, small molecule inhibitors that bind specifically to the region.

The quality of the modelled protein was further validated and evaluated with Ramachandran's plot calculations using PROCHECK to obtain a stable structure. Stereo chemical evaluation of backbone Psi and Phi dihedral angles of modelled EF1- α protein was revealed in different percentages i.e. 89%, 38% and 3% residues falling within the most favoured regions, additionally allowed regions and generously allowed regions and few residues were in disallowed region of Ramachandran's plot respectively. The resulting model has the correct stereochemistry and good three-dimensional (3-D) structure compatibility. The 3-D structure of EF1- α protein has one chain, 20 β - sheets, and 8 alpha helices. Potential ligand binding sites (LBSs) in EF1- α protein have been identified using Pocket Finder program.

CENTRE FOR REASEARCH IN MEDICAL ENTOMOLOGY, MADURAI

Japanese encephalitis

CRME has continued studies to investigate the role of silent JE transmission in Thanjavur, a non-endemic zone, Tamil Nadu and its implication for the occurrence of impending JE outbreaks in future. Among various culicines, *Culex tritaeniorhynchus* was the predominant species constituting 85%, 65% & 85% in respective hyper, moderate and non- endemic areas. *Culex gelidus* was the second most dominant vector species in moderate and non-endemic areas. In the hyper endemic areas, *Cx. vishnui* was the second most dominant species, with an average per-man hour (PMH) density being highest in non-endemic area when compared to moderate and hyper-endemic areas. In moderate and non-endemic areas, the density of *Cx. vishnui* subgroup mosquito species reached a peak density in October and November each year whereas in hyper endemic areas it touched climax in January and March. Among anophelines, the mosquito *Anopheles subpictus* was a predominant species constituting 57%, 63% and 71% in hyper, moderate and non-endemic areas, respectively. The highest vector infection (% of +ve) of *Cx. vishnui* subgroup was 12.50, 7.41 in moderate and non-endemic areas, although no virus infection was found in the hyper-endemic area. During the course of studies on JEV in mosquitoes, two significant observations evolved: first, Thanjavur district showed continued infection by JEV in mosquitoes, and secondly, mosquitoes in Tirunelveli district began to show infection. This observation carries a high epidemiological significance since the presence of virus in mosquitoes presents a confirmed sign of virus activity in nature.

Lymphatic filariasis

Mass Drug Administration: Studies pertaining to lymphatic filariasis (LF) for determining the impact of mass drug administration (MDA) using diethylcarbamazine (DEC) with and without albendazole under filariasis elimination campaign on various filariometric indices, viz., microfilaraemia, antigenaemia, transmission, geohelminth infection etc. were continued in 18 villages of Tirukoilur taluk in Villupuram district (Tamil Nadu). During one year post MDA VI, the Per Man Hour vector density was lower in both the treatment arms (13.13 and 10.68 in DEC+ALB and DEC alone arms, respectively). After MDA VI the overall cumulative decline in microfilaraemia prevalence reached 86% in DEC+ALB arm and 80% in DEC alone arm. The overall reduction in antigenaemia was 75% and 38% in DEC+ALB and DEC alone arms,

respectively. Reductions in soil transmitted helminth prevalence and egg intensity at 3 weeks post-treatment period in DEC+ALB arm was similar to that observed for the previous MDAs demonstrating an impact on all the three helminths, while DEC alone showed effect only on the *Ascaris*. The above indices estimated during post-MDAs demonstrate the added advantage of addition of albendazole along with DEC in the LF elimination programme.

Vector control with MDA: To demonstrate large-scale operational feasibility and value of implementing 'time-limited' vector control (VC) to augment the effectiveness of MDA in lymphatic filariasis elimination programme, studies have been undertaken in 36 villages under 3 PHCs in Tirukoilur Block, Villupuram District, Tamil Nadu. Implementation of vector control activities (by using respectively expanded polystyrene beads, deltamethrin impregnated curtains and larvivorous fishes) in 24 villages was completed through active participation of the community supervised by local health personnel from the PHCs. Entomological monitoring for adult *Culex quinquefasciatus* showed that there was nil infection in the vectors dissected from the VC villages. In the MDA alone arm, the infection and infectivity rates were 0.48% and 0.18%, respectively. The insecticide persistence in the curtains was determined through the bioassay tests, and the overall mortality of exposed *Culex* on the impregnated curtain was 60% at 90 days post-impregnation. It is expected that in the long run this methodology will be cost effective for LF elimination if the population continued to work with self-sufficiency.

Dengue

The Centre has continued its studies in Kerala state which provides a model for dengue transmission by *Aedes albopictus*. About 65% of dengue cases in Kerala are reported from Thiruvananthapuram. A dengue vector study was initiated in the Thiruvananthapuram district showing potential breeding habitats observed like the cement tanks, plastic drums, coconut shells, mud pots and tyres from the peri-domestic habitats and the cement tanks, metal containers, and plastic containers from the indoor habitats. Larval indices gradually increased after the monsoon rain fall. *Aedes aegypti* was the only species found distributed in the coastal rural area (Vizhinjam), whereas *Aedes albopictus* and *Ae. vittatus* were found breeding together in the urban area (Medical College). Incidentally, *Ae. albopictus* was the only species found breeding in both the urban and rural areas. *Aedes aegypti* breeding was mainly observed in the cement tanks, plastic containers, metal containers, coconut shells, mud pots, tyres, plastic drums and flower pots, whereas *Aedes albopictus* breeding was recorded in the cement tanks, metal containers, coconut shells, mud pots, tyres, plastic containers, plastic drums, flower pots, plastic drums, flower pots, banana leaf axils and tree holes. Very few containers like metal containers, tyres and flower pots showed *Aedes vittatus* breeding. *Aedes albopictus* and *Ae. aegypti* were found breeding together in tyres, cement tanks, metal containers, flower pots, discarded containers, plastic containers and tree holes whereas *Ae. aegypti* and *Ae. vittatus* were found breeding together only in cement tanks in the outdoor landing collection conducted in urban and rural areas. This information would be useful for applying vector control measures.

NATIONAL INSTITUTE OF VIROLOGY, PUNE

Influenza

Pandemic H1N1 continued to be a concern in 2010. A positivity of 22 % for pandemic H1N1 and 2.3% for seasonal influenza was observed in 22,204 referred clinical samples from Maharashtra. In Kerala, 8 of 17 deaths in pregnant women due to pandemic H1N1 were attributed mainly to non-use of Oseltamivir. Serosurveys in Panchgani, Pune & Mumbai revealed widespread infections and subclinical / milder illnesses, mostly in children.

Surveillance of Influenza like illness (ILI) cases showed 21.8 % positivity for influenza in 706 samples Pandemic H1N1 predominating in 11.33% and influenza type B in 9.5%(Victoria lineage). Forty-four representative isolates were shipped to the collaborating centre at CDC, USA for vaccine strain selection. All 295 isolates, and 320 clinical specimens tested were sensitive to oseltamavir. Influenza disease burden in a rural community at Vadu, District Pune, was found to be 5.93/1000/year among patients hospitalized for defined medical causes, in a population of 91,223. In the urban slums in Pune, community surveillance, indicated moderate influenza transmission during monsoon months. Influenza viral etiology was detected in 20% ILI cases.

A single intramuscular 0.5 ml dose of pandemic H1N1 2009 vaccine administered to health care staff was found highly immunogenic in field use and antibody levels persisted for 6 months in most vaccinees.

Whole genome analysis of 24 pandemic H1N1 isolates and 45 HA gene analyses indicated that through Clade 7 predominated, Clade 6 was also in circulation. Role of host immune response and viral load in the differential outcome of pandemic H1N1 (2009) influenza virus infection in Indian patients was established. Studies on necropsy specimens from fatal cases of pandemic H1N1 infection from India showed evidence of several important pathological markers. These included diffuse alveolar damage, extensive cytopathic effect involving lower respiratory tract. Type II alveolar pneumocytes were identified as major targets for virus replication by ultrastructural studies.

Highly efficacious candidate recombinant protein vaccines for H5N1 and pH1N1 (2009) were developed showing complete protection of challenged mice. An ELISA for the detection of IgG-anti-HA antibodies was developed for pH1N1 (2009) virus.

Enteric viruses

The ongoing Multicentric Surveillance Programme for rotavirus disease and strains in children under 5 years of age highlighted the need for an expanded programme with additional centres. Characterization of group A rotavirus infections in animals identified human-animal reassortant and unusual rotavirus strains. Intragenotypic diversity was identified in VP4, VP6 and NSP4 genes of rotavirus strains circulating in adolescent and adult cases of gastroenteritis. Isolation and complete genome characterization of globally prevalent rotavirus genotype, G1P[8] of Indian origin was achieved. The ileum was identified as the most susceptible and supportive part of small intestine for perpetuation of rotavirus infection in mice.

Aichivirus genotype B was detected for the first time in patients with acute gastroenteritis from India. Association of multiple enterovirus serotypes was identified during the investigation of nation wide outbreaks of Hand, Foot and Mouth Disease in India. Coxsackie A-24V continued to circulate in different parts of India causing outbreaks of Acute Hemorrhagic Conjunctivitis.

Japanese encephalitis

Of the 73 JE cases from Gorakhpur, 43 were associated with genotype III and 30 with genotype I. Complete genome sequence analysis of three GI strains showed close relationship with other GI strains circulating in Japan and China. A total of 598 human clinical specimens that included 346 serum and 252 CSF samples from all over India were tested by JEV specific IgM ELISA; 12/ 252 (4.76%) CSF and 13/346 (3.75%) showed presence of JEV specific IgM antibodies. JE Seroprevalence studies in Goa revealed that there was increased seropositivity (25.8% in June 2009 VS.82.1% in October 2010) in children aged 1-15 years which could be attributed to vaccination in July 2009.

The assay developed for HSV specifically detects 37 genomic copies of HSV-1 or 2 from human clinical specimens. A WNV neutralization escape mutant was developed with reduced neuroinvasiveness. The mutant was immune-potent but showed reduced induction of TNF α , thereby providing a good candidate for attenuated vaccine development. The NIV-BBIL inactivated JE vaccine has entered phase I human clinical trial.

Dengue

In Pune city, it was observed that the percentage of confirmed dengue cases was much lower in 2010, (304/1397, 22%) compared to 2009, (1401/2047, 68%) with only 5% cases showing severe manifestations. All four serotypes were detected, DENV-2 and 3 being co-dominant. There was a DENV-2 outbreak in Raigad with 110 cases in June-July, with only two DHF cases.

A single tube DENV group specific Taqman based real time RT-PCR was developed and reagents were sent to five Institutes in India for evaluation. The test worked satisfactorily for DENV-1, 2 and 3 viruses. DENV-4 needed a higher CT value cut off.

Immuno-profiling of dengue patients in the context of disease pathogenesis revealed that the titre of DENV-specific neutralizing antibodies was significantly higher in patients with platelet count <50,000 compared to those with counts above 100,000. DENV replication in fibroblasts, showed that the Envelope protein interacts with kinesin – relevant to microtubule based anterograde trafficking.

Chikungunya

An outbreak of chikungunya-like illness with high morbidity and mortality in Tirunelveli Tamil Nadu was investigated in January 2010. High prevalence of CHIKV IgM antibody positivity (50%), clinical symptoms, virus isolation and presence of vector mosquitoes suggested CHIKV as the principal etiological agent. Dengue-specific IgM was detected in 10% serum samples. siRNAs developed against ns1 and E2 genes of CHIKV were shown to inhibit CHIK virus in vitro and in mice.

Hepatitis

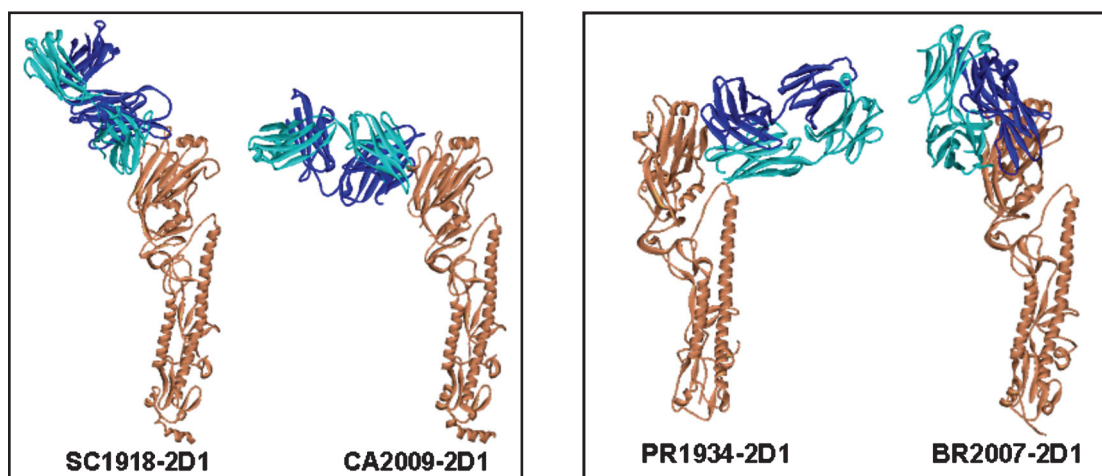
Hepatitis B outbreak with high mortality in Modasa, Gujarat was found to be associated with basal core promoter and pre-core mutants. Hepatitis E virus helicase domain protein was shown to have enzymatic functions as NTPase, helicase, and 5'-RNA-triphosphatase. Reduced levels of CCL4 and NKT cells were associated with fulminant hepatitis. A new hepatitis B virus genotype (I) was identified and shown to be prevalent in the primitive tribes of northeast India since 1963. Hepatitis E outbreaks in various districts of Maharashtra were investigated. Adults and adolescents were most affected. Experiments in rhesus monkeys showed that only ORF- 2 proteins was efficacious for hepatitis E and E+B combination candidate vaccines.

Measles

Measles lab was accredited as a WHO-SEARO Reference Measles Laboratory. Molecular epidemiology of Measles in North Eastern Region in India revealed circulation of D4 and D8 genotypes. Measles Aerosol Vaccine Program (MAVP) Clinical Trial – Phase II/III has been started.

Bioinformatics

Selection pressure analysis of HA genes of seasonal Influenza A (H3N2) viruses of the period 2004-2009 from different parts of India revealed positive selection within isolates from each season, indicative of local persistence of the virus and in-situ evolution. The molecular basis for the cross-reactivity of the 2009 H1N1 and the 1918 H1N1 pandemic viruses was understood by docking the crystal structure of an antibody, 2D1, derived from a survivor of the 1918 pandemic, to the structures of HA of the 2009 strain and seasonal influenza A/H1N1 vaccine strains.



SC1918-2D1 – Co-crystal structure (3LZF.pdb) of the antibody (Fab 2D1) and the HA protein of A/South Carolina/1/1918; **CA2009-2D1** - Antibody 2D1 docked to the A/California/04/2009 HA monomer (3LZG.pdb), recognizing antigenic site 'Sa'; **PR1934-2D1**- Docking positions of 2D1 antibody with HA protein monomer of A/Puerto Rico/8/1934 (1RU7.PDB);

BR2007-2D1: Docking positions of 2D1 antibody with modeled HA protein monomer of A/Brisbane/59/2007.

Bottom two docking positions are physically unrealistic orientations because under normal physiological conditions the interfacing residues on the antigen are embedded in the core of HA trimer. The HA proteins are shown in Orange color and 2D1 light and heavy chains are shown in cyan and blue respectively.

Selection pressure and molecular clock analysis of Dengue 1 viruses in India over the period 1962-2005 was studied. Drug binding site identification and docking of Dansylcadeverine in the Vesicular Stomatitis Virus glycoprotein suggested that the drug could prevent viral entry by membrane fusion inhibition.

Electron microscopy

High resolution electron tomography studies identified autophagy as a possibly novel cellular stress response to dengue virus infection in endothelial cells.

Microarray

Gene expression was studied in macrophage cell lines infected with H5N1 and H1N1 viruses. Multiple signaling cascades i.e. Jak-STAT, TGF-beta, MAPK and p53, activation of chemokines CXCL10 and CCL5 may all contribute to the 'cytokine storm' resulting in inflammation and tissue damage associated with highly pathogenic avian Influenza A (H5N1). High pathogenicity of pandemic (2009) H1N1 virus was found to be due to more efficient suppression of host innate immune responses compared to seasonal influenza H1N1 virus.

Arbovirus diagnostics

IgM ELISA kits were supplied to national programme for laboratory diagnosis of JE/DEN and CHIK in the Sentinel Surveillance Hospitals (SSHs). Total kits supplied during 2010 – JE = 158, Dengue = 1576 and Chikungunya = 572 (Total kits supplied = 2306). Additional dengue kits were supplied to SSHs in Delhi during Dengue outbreak that coincided with Common Wealth Games in the Capital. The mouse brain antigen has now been replaced with cell culture antigen for all the kits.

NIV Units

Bangalore: High level of dengue (45.4%) and moderate level of Chikungunya (19.2%) activity was documented in Karnataka state with 2694 samples being tested. The Polio and Measles Laboratories were re-accredited by WHO. A total of 8673 stool specimens were tested from 4336 AFP cases. No wild poliovirus was isolated in Karnataka and Kerala. Wild poliovirus P3 was detected in one case from Badaun, and one P2 VDPV case was detected from Shahajahanpur district of UP.

Of the 63 outbreaks investigated in Karnataka and Kerala, 41 were measles, 9 were Rubella and 8 were mixed outbreaks. Measles virus isolates, obtained from Kasaragod and Kozhikode districts of Kerala, in 2010 were genotype D8.

Gorakhpur: Provided diagnostic services for the AES cases occurring in the region. Geographic Information System (GIS) based Map Locator Platform was established to understand the risk factors for Japanese encephalitis/Acute Encephalitis Syndrome cases at Gorakhpur. A total of 874 acute encephalitis syndrome (AES) cases hospitalized in BRD Medical College Gorakhpur were investigated for Japanese encephalitis and Enterovirus infections. Seventy-three (8.35%) cases were diagnosed as JE while 11 (1.26%) cases were associated with EV infection.

Alappuzha, Kerala: Was designated as the regional centre for the study of influenza in Kerala. A total of 295 throat/ nasal samples were tested. Seven each were positive

for pH1N1 and Influenza type A. Total 1856 samples were received/collected during the period; 371 were positive for Dengue and 128 were positive for Chikungunya.

ENTEROVIRUS RESEARCH CENTRE, MUMBAI

Acute Flaccid Paralysis Surveillance

During 2010, a total of 13069 stool samples collected from 6576 AFP cases reported in Maharashtra, Madhya Pradesh, Chhattisgarh and Goa and 94 healthy contacts of AFP cases were tested for presence of polio and other enteroviruses by virus culture. Results of testing of 92% samples were reported to the polio eradication program within 14 days of sample receipt (99% results reported in 18 days). Non-polio enterovirus isolation rate was 25% for AFP cases. Polioviruses were isolated from 313 cases. Wild type 1 poliovirus was isolated from 4 AFP cases and two contacts reported in Malegaon (district Nasik) and 1 case in Beed in Maharashtra. These cases were reported between January and September 2010. Wild poliovirus was not detected in samples from MP, Chhattisgarh and Goa. Wild type 3 poliovirus was not isolated from any AFP case reported in these States.

A total of 42 AFP cases were confirmed as paralytic poliomyelitis due to wild poliovirus infection in 2010. Of these 18 were type 1 and 24 type 3 polioviruses. In Uttar Pradesh the last wild poliovirus type 1 isolate was reported in October 2009 and type 3 in April 2010. In Bihar wild type 1 poliovirus was isolated after a gap of 10 months (November 2009 till August 2010). These observations indicate significant progress towards polio eradication in UP and Bihar that had lagged behind for several years. Wild poliovirus type 1 and 3 transmission foci shifted out from UP and Bihar to Pakur (Jharkhand), Murshidabad (West Bengal) and Nasik (Maharashtra). However, these States had reached zero polio status in the past therefore it is likely that wild poliovirus transmission chains can be stopped effectively in these newly infected areas.

Molecular epidemiology of wild poliovirus

Complete VP1 sequences were used for phylogenetic analysis to understand virus transmission pathways. In 2010, all type 1 wild polioviruses, including those isolated in sewage samples in Delhi and Mumbai had genetic linkage with those isolated in Bihar in 2009. The extensive epidemic of polio 1 reported in 2010 in Tajikistan and neighboring countries (including Russia) was tracked to importation of poliovirus of genetic lineage found in western UP in 2009. No wild type 1 poliovirus was isolated in Bihar since November 2009. However, a focal outbreak of polio cases in Rautahat district in Nepal was linked to wild type 1 lineage in Bihar. The type 1 wild poliovirus was likely reintroduced in Champaran district, Bihar causing three cases of paralytic polio in August 2010.

Wild type 3 poliovirus genetic lineage from UP was isolated from polio cases in Pakur and Murshidabad districts in Jharkhand and West Bengal respectively. On the other hand, wild type 3 virus genetic lineage from Bihar was detected in sewage samples collected in Delhi during May- June 2010.

Molecular characterization of VDPVs

In 2009, vaccine derived polioviruses (VDPV) were isolated for the first time in India. Of the two type 1 VDPVs, one was isolated from an immunodeficient child (from Ghaziabad, UP) who suffered from acute flaccid paralysis (polio) and the other was reported in Assam as a case of AFP but was finally confirmed to be not polio. Of the 22 type 2 VDPV in 2009-10, three were reported in Bihar, 18 in Uttar Pradesh and 1 in Tamil Nadu. The type 2 VDPV case in Tamil Nadu was an immunodeficient girl child. In Bihar VDPVs were also isolated from healthy children during a special drive of sample collection. Complete genome sequencing of the type 2 VDPV isolates was accomplished. This has helped us to identify cVDPVs.

Majority (95%) (20/21 cases) of Type 2 VDPVs occurred in children below 3 years. 80% type 2 VDPV cases had not received type 2 containing OPV though all had received more than 7 doses of mOPV. 90% patients had residual weakness at 60 days post onset indicating that VDPVs were as neurovirulent as wild type poliovirus. Two high quality SIA rounds using tOPV stopped the VDPV outbreak. No new VDPV cases have been reported since February 2010.

VDPVs are defined as isolates showing $\geq 1\%$ nucleotide substitutions (10 changes and more) in VP1 region of poliovirus RNA as compared to Sabin vaccine viruses. Sequence analysis of a large number of type 2 vaccine-like isolates revealed that we had isolated strains that had less than 10 changes and that these strains evolved into VDPVs. Our observations were supported by studies in Nigeria. A change in the definition of type 2 VDPV has been accepted by the WHO. From January 2010, type 2 VDPV is defined as a Sabin-like isolate containing ≥ 6 nucleotide substitutions in VP1 region.

Environmental surveillance activities

Weekly sewage sample testing from F, G and M wards in Mumbai is being carried out since 2001. Wild poliovirus type 1 and type 3 was not isolated from any sample from F and G wards in 2010. Wild type 1 poliovirus was isolated from one sewage sample collected in November 2010 from M ward. VP1 sequencing indicated that the virus belonged to the transmission chain detected in Bihar in 2009.

In 2010, sewage sample testing was started in Delhi in collaboration with NPSP and NCDC. Wild type 1 polioviruses were isolated from sewage samples collected from May to October 2010 and type 3 from June to September 2010. The type 1 polioviruses were from Bihar transmission and type 3 from western Uttar Pradesh.

Population immunity against polioviruses after use of bivalent OPV (1+3)

Until 2010, mOPV 1 and mOPV 3 were used in supplementary immunization activities (SIA) in UP and Bihar. Attention was focused essentially on stopping transmission of type 1 wild poliovirus. b-OPV (1+3) was licensed in India in December 2009. By August 2010, bOPV was used in UP and Bihar in 3 to 4 SIA campaigns. Because of the minimum levels of wild poliovirus transmission in both the States, polio immunity in children in the age group of 6-7 months should be due to routine immunization (with tOPV) and b-OPV. Blood samples collected from a total of 1200 children in

the age group 6-7 months in high risk blocks in UP and Bihar (10 blocks each State and 60 samples per block) were tested for poliovirus antibodies. Antibodies to type 1 poliovirus were detected in 97% plus children and poliovirus type 3 antibodies in 76% children in all blocks. A large scale immunity gap was found for type 2 poliovirus indicating deficiencies in routine immunization coverage. It was concluded that b-OPV was suitable for maintaining high levels of population immunity in the high risk blocks.

Identification of reversion of poliovirus attenuation sites to wild type (assay development)

A multiplex SNP assay for detection of mutations causing reversion of attenuation of Sabin OPV strains to wild type has been developed. The assay is capable of detecting the six, three and two known attenuating sites in poliovirus 1, type 2 and type 3 Sabin vaccine origin strains respectively. The assay is useful for detection of reversion mutation in Sabin-like isolates from cases of vaccine associated poliomyelitis, VDPV and vaccinees.

Host cell response to Enterovirus infections

Expression of TLRs and cytoplasmic helicases in muscle (RD) and neuronal (SK-N-SH) cell lines infected with wild type 1 and Sabin 1 vaccine strain was investigated. It was found that neuronal cells express very low amounts of TLRs than muscle cells constitutively. Neuronal cell responded to Sabin 1 infection by inducing TLR 3 and TLR 7 and downstream signaling molecules leading to type 1 IFN production that restricted the virus in early stages of infection. Innate immune system receptors were not activated in neuronal cells at early stages of wild type 1 infection. The differences in signaling pathways may be exploited to study back mutation of Sabin attenuated vaccine viruses leading to increased neurovirulence.

HFMD outbreak investigations

Outbreaks of hand foot and mouth disease (HFMD) were reported in three States in three different geographical areas of India during 2009-10. The HFMD outbreak in Maharashtra (2009) was caused by CVA6, a virus not well known to cause HFMD. The outbreak in Wellington cantonment area in Tamil Nadu (2010) was due to CVA16. The outbreak in Agartala, Tripura (2010) was again due to CVA6. In 2006, the HFMD outbreak in Singapore was caused by EV71 (45.5% cases) and CVA6 (35.8% cases). In 2008, CVA6 caused HFMD was reported in Finland. Thus CVA6 is becoming an emerging cause of HFMD in recent years.

VIRUS UNIT, KOLKATA

Genetic variability of hepatitis B virus

Infection with hepatitis B virus (HBV) results in varying clinical outcomes, ranging from asymptomatic carriage, acute, fulminant hepatitis to chronic infection leading to liver cirrhosis and hepatocellular carcinoma (HCC). The clinical outcome of HB infection is influenced by host and viral factors. For better understanding the role of viral factors in the disease outcome during HBV infection, HBV genetic variability

associated with different clinical outcome of HBV infection in eastern India, was studied. The results revealed that Genotypes A and C were associated with higher rate of T1762/A1764 mutations than the most predominant genotype D. T1762/A1764 along with C1753 was common among cirrhosis and T1762/A1764 without C1753 was frequent among chronic liver disease cases. No significant association was found between A1896 point mutation and clinical status. Multivariate analysis revealed that T1762/A1764 double mutation, HBV/A, age above 25 years, C1753 and A1899 were critical factors for clinical advancement while age above 25 years and C1753 as significant predictor for cirrhosis in comparison with chronic liver disease.

HIV/HBV co-infection

Co-infection with HBV and HIV is common because of shared modes of transmission. Differences in HBV genotypes/subgenotypes, hepatitis B early antigen (HBeAg)-negative variants, and drug resistance mutations all seem to influence the clinical and therapeutic outcome in patients with chronic hepatitis B virus (HBV) infection. The information currently available on the virological features of HBV in HIV-coinfected patients is scarce. HBV genotypes were examined in HIV-infected patients with chronic HBV infection. HBV genotypic study was conducted on all the 89 samples that were registered in our lab. Presence of HBV DNA was checked by amplifying primers from the surface gene regions. A total of 54 HBsAg positive samples were found to have a detectable HBV DNA in the serum by sensitive nested PCR. There was no co-infection of HCV found among the study population. So far genotypes have been determined in 44 HBV-infected patients. Among them HBV/D was most common (32/44; 72.7%), followed by HBV/A (11/44; 25%) and HBV/C (1/44; 2.27%).

Cloning major genotype variants of hepatitis C virus

Hepatitis C virus (HCV) infects only human and chimpanzee. There are no small-animal models for HCV *in vivo* study but recently cell-culture models of HCV genotype 2a and 1b has developed only by applying reverse genetics. The major circulating HCV genotype variant in India is genotype 3 which has no reported representative strain. Thus, cloning of HCV genotype 3 as a representative strain is very important for future molecular study of HCV in India to determine a better therapeutic treatment against HCV for which an effective vaccine is not available. It was possible to amplify nearly the entire open reading frame and most part of the non-coding regions by long nested RT-PCR from a HCV genotype 3 strain isolated from Kolkata. The PCR amplified ~9.28kb HCV genome (nt44 – nt9330) was cloned in pGEM-T EASY vector and transformed in DH5α *E. coli* cells. Ampicillin resistant clones were selected and tested for HCV 5'UTR and NS5B region of HCV genome by PCR to screen HCV positive clones. PCR amplified 5'UTR and NS5B regions were sequenced and showed 99% and 96% homology to amplified HCV genome. The same HCV isolate genome in 12 overlapping fragments have been PCR amplified by nested PCR for sequencing and cloning of each fragment. The sequencing of most part of the HCV genome has been finished and this will give sequence of almost the whole HCV genome. DNA sequencing data shows the homology of the strain to HCV genotype 3a.

Herpes simplex virus infection

Among 247 samples from clinically confirmed STD cases from Medical College, Kolkata, 146 (59.1%) are sero-reactive to HSV-2 IgG and 37 (14.97%) to HSV-2 IgM antibody. While 24 (9.72%) are reactive to HSV-1 IgG and 9 (3.64%) are HSV-1 IgM antibody sero-reactive by Vironostika HSV-1 and HSV-2 IgG and IgM ELISA. On the other hand 62 (25.10%) samples are reactive to HIV-1 antibody by double ELISA and Tridot test. Further analysis revealed that 31 (12.55%) samples are reactive to both HIV-1 and HIV-2 IgG antibody. The 22 (8.9%) HIV-1 antibody positive patients also showed HSV-2 IgG antibody positivity; while 11 (4.45%) HSV-2 seropositive patients showed HIV-1 antibody positivity. Further study for antigen detection by immunofluorescence and PCR-based assay to quantify and typing is in progress.

Human cytomegalovirus infection

To determine the most suitable diagnostic approach towards detection of CMV infection and to determination the cut off value of the viral load responsible for the symptomatic expression and clinical manifestations of CMV infection a total 100 HIV patients showing signs of CMV infection were studied. Detection of CMV IgM via Elisa showed that samples positive for CMV was 49 (49%). Detection of CMV via pp65 antigenemia Assay revealed 78% were positive for pp65 Antigenemia Assay.

Surveillance for dengue fever in Eastern Kolkata

Hospital based in-patient suspected dengue surveillance was started in 2008 in ID & BG Hospital & B.C. Roy Children Hospital to study the epidemiology, clinical characteristics, and virologic characteristics of severe dengue in Kolkata. During two years period, a total of 5722 subjects were enrolled, among that 5353 patients presented with an acute fever of 0-7 days duration. During this period, a total of 5208 blood samples were collected. According to laboratory report, 5204 samples were processed for IgM and 315 (6.1%) samples were dengue positive. Every alternate febrile patient was enrolled for follow-up and attempt was made to collect convalescent sample within 14 -21 days from date of onset of fever. A total of 2437 convalescent samples were tested and 225 (9.2%) were dengue positive. For in-patient study, 642 suspected dengue patients were registered in the ID and B.C. Roy Children Hospital. All of those acute samples were tested and 126 (20%) were dengue positive for IgM test. Also convalescent samples of 537 were collected and all of those were tested for IgM. Out of 537 samples, 146 (27.2%) were dengue positive. Considering the data, crude incidence of dengue is 2.6% (95% CI: 2.58-2.62). Highest incidence is seen in age group 6-10 years. Multi serotype dengue viral strain were observed to be circulating in Kolkata with almost 46% were DEN.

MICROBIAL CONTAINMENT COMPLEX, PUNE

High Containment Lab & Virus Repository

Bats were investigated for their possible role as a source of emerging viral infections in Maharashtra and West Bengal. Two novel viruses were isolated from *Rousettus leschenaulti* bats of Maharashtra. Nipah virus was isolated from *Pteropus giganteus* from Siliguri, West Bengal. Intra-cytoplasmic Inclusions like Negri bodies were

detected in the neurons of brain of *Megaderma lyra*. Rickettsial inclusions were detected in lymphocytes of *Cynopterus sphinx* bat. A new cell line was developed from *Pipistrellus ceylonicus* bats and studied for its susceptibility to various groups of viruses. Domestic animals were investigated for their possible role as a source of zoonotic viruses by screening blood samples from slaughter houses for the presence of virus specific antibodies i.e antibodies against CCHF. Laboratory diagnosis was provided to various hospitals & Govt. agencies for Kyasanur Forest Disease, Murray Valley Encephalitis, Hanta, Buffalo pox, Ross River, Marburg, Ebola Reston and Sindbis viruses. Two training programs were conducted for working in BSL-3 laboratory.

Avian influenza

An unique AI H11N1 virus from a Eurasian Spoonbill and an H9N2 virus from backyard chicken were isolated during surveillance studies in Pune and in West-Bengal. AI surveillance in wild migratory, resident, domestic birds and in poultry in West Bengal (WB) and Pune (wet poultry markets) was continued. All samples were negative for AI H5N1 virus. However, AI H11N1, H4N6, H9N2 and NDV viruses were isolated from ducks and chickens from wet poultry markets in WB and Pune. AI H9N2 viruses were isolated from wet poultry markets and were observed to have pandemic potential as human infections have also been reported. Antibodies against H5N1 virus were detected in ducks in WB highlighting their role in the transmission of H5N1 viruses. Molecular characterization of the influenza A H5N1 viruses of the 2008-09 outbreaks in India revealed that all the viruses were highly pathogenic and belonged to clade 2.2 lineage.

H1N1 vaccine studies

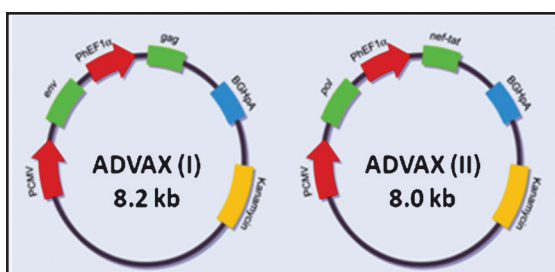
Pre-clinical evaluation of protective efficacy of the live attenuated (LAIV) and inactivated (IIV) pandemic influenza (H1N1) 2009 vaccines by mice challenge showed that two doses of LAIV and one as well as two doses of IIV rendered protection from the disease after challenge. Serum samples from the Phase II and Phase III clinical trials of pH1N1 LAIV were tested at the NIV. This work was in collaboration with the Serum Institute of India Limited.

NATIONAL AIDS RESEARCH INSTITUTE, PUNE

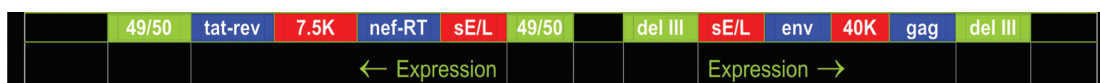
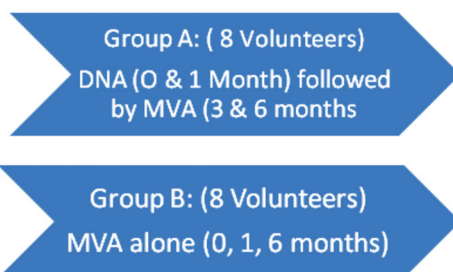
The research activities at National AIDS Research Institute focus around the themes of prevention of HIV and STIs, care and support for those infected with HIV and understanding the biology of HIV infection. In addition, the Institute takes up activities that are complementary to National AIDS Control Programme and capacity building.

Prevention of HIV infection

HIV Vaccine Trial POO1: Phase 1 vaccine trial of ADVAX (DNA Vaccine) and TBC-M4 (Modified Vaccinia Ankara Vaccine) was completed during the year with the last follow up visit scheduled in December 2010. There were no safety concerns. The immunogenicity assays have been performed. The data will be shortly decoded and additional immunogenicity assays will be performed.



DNA Vaccine (Advax 1 & 2)

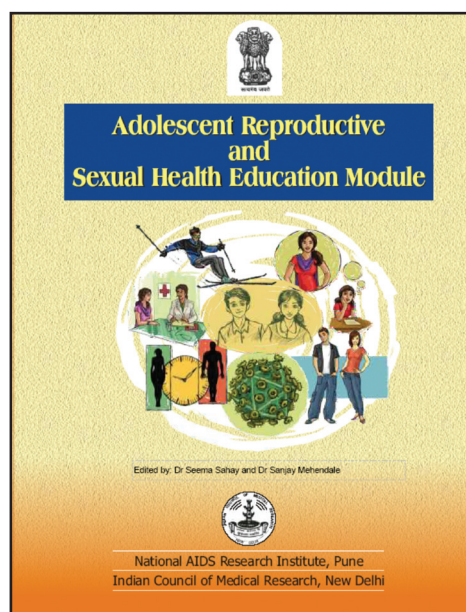


Modified Vaccinia Ankara (MVA) based vaccine

ART for prevention of HIV Transmission within HIV discordant couple setting: The ongoing clinical trial (**HPTN052**) on use of antiretroviral therapy for prevention of sexual transmission of HIV completed enrolling 175 couples who will be followed for 5 more years. The study will also evaluate the advantages of starting ART at CD4 cell counts > 350 cells/ μ L.

Community and Health care providers' perspective on male controlled biological options in India : This study aims at understanding community and health care providers' perspectives, concerns and prospective role in relation to male controlled biological options especially the circumcision (MC) in India in the context of HIV prevention and control program. Qualitative study was conducted with key stakeholders in health care delivery in context of male circumcision at five sites; Mumbai, Belgaum, Kolkata and Meerut. The data is being analysed.

Adolescent Reproductive and Sexual Health Education (ARSHE): A six chapter curriculum on Adolescent Reproductive and Sexual Health Education module has been developed to be shared with stakeholders. The curriculum has been developed as a result of a study among class IX and XI students from urban and rural Pune and consultation with teachers and parents.

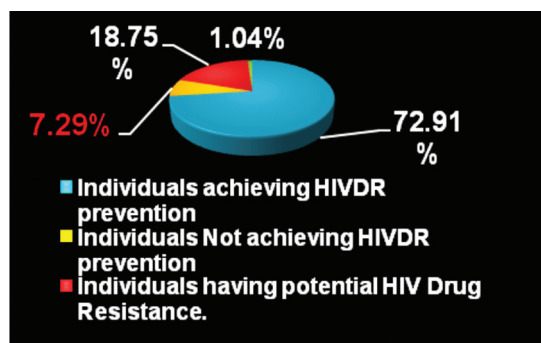


Social/sexual networks of married men having sex with men (MSM) in Mumbai: This study aims to identify social/sexual networks of married men having sex with men in Mumbai and find its association with sexual risk behavior, HIV infection, sexually transmitted infections such as syphilis, gonorrhea and Chlamydia and other antecedent determinants. Formative research was done among 20 married and 20 unmarried MSM in Mumbai. In its second phase, 265 participants have been enrolled in the study so far. Of the 140 participants whose testing is completed, HIV prevalence is 11.6% (26/225) for the whole sample; 9.8% (15/153) among unmarried and 15.3% (11/72) among married. . The interim analysis of the study

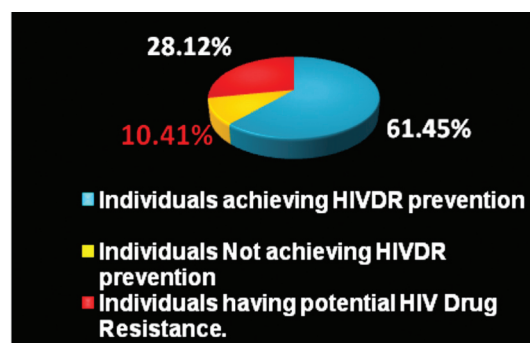
suggests that reaching this epidemiologically critical group with intervention is likely to pose immense challenges.

Care and support for HIV infected persons

While controlled clinical trials for ARV regimens among HIV infected persons is main activity in this area, potential anti-HIV activity in synthetic and natural products in *in vitro* assays, ARV drug resistance and psychosocial needs among HIV infected are the other important studies being carried out at the institute.



Chennai

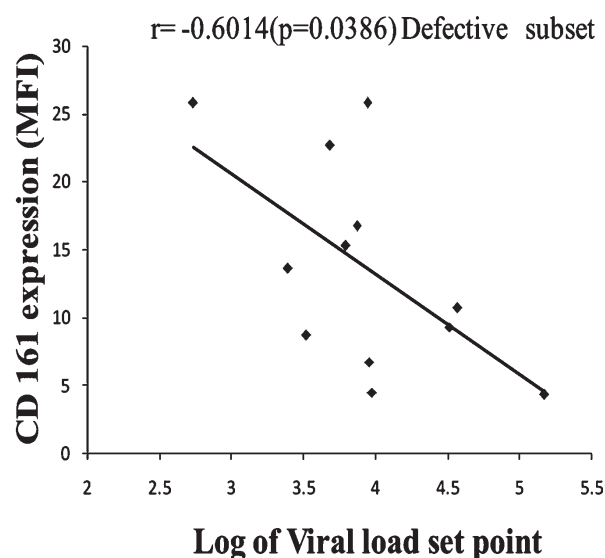


Mumbai

ARV Drug Resistance - Monitoring Survey: In the Monitoring Survey, at the end of one year of follow up after the initiation of anti-HIV therapy, the prevention of onset of HIV drug resistance (HIVDR) was studied at two ART cohorts, one in Mumbai and the other in Chennai. The 10% patients on ART in Mumbai showed drug resistance mutations, while 7% patients in Chennai showed drug resistance mutations. The results indicate that resistance levels are relatively low; however, there is need for increased adherence to treatment.

Screening for anti-HIV activity

***in vitro*:** The preclinical testing of indigenously developed drugs and new RT inhibitors, nucleoside and non nucleoside analogues was initiated. Using an internationally approved algorithm, 147 indigenous candidate products were screened using high throughput and confirmatory T cell systems that identified products with anti-HIV activity. Microbicide specific models for studying toxicity and HIV transfer using vaginal/rectal epithelial cells and cervical explants have been developed.

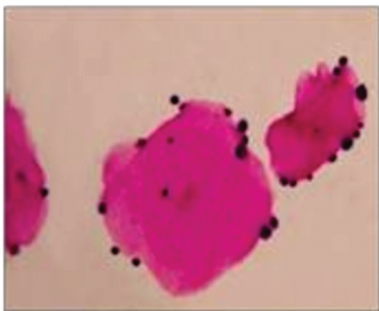


The national reference values for

absolute CD4 counts: An eight site multi-centric study for establishment of reference values of CD4+ T cells in adult healthy Indian population was completed. The normal values were between 381-1563 cells/ μ L (Mean: 852; median 822 cells/ μ L) for male and 447-1846 cells/ μ L (Mean: 995 and median 953 cells/ μ L) for female population.

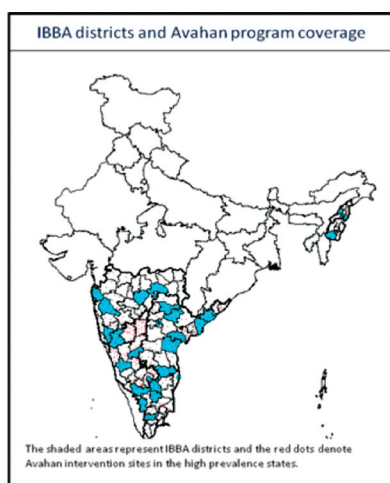
Biology of HIV infection

Immunologic and Virologic Factors in Early HIV infection: The immunopathogenesis of HIV infection is being studied in patients with recent infection. The HIV-specific CD8+ T cells in recent HIV infection secreting multiple cytokines appeared to be important in controlling viral multiplication. The natural killer cells in early HIV infection were functionally deficient that might be due to the reduced expression of proliferative marker CD161 on the immature/defective NK cells.



Adherence to buccal epithelial cells

Virulence Determinants in Candida species isolated from HIV infected persons: Virulence determinants of Candida species were studied among HIV positive and HIV negative subjects. Adherence to buccal epithelial cells, proteinase, phospholipase, phenotypic switching were detected as important virulence factors and were significantly produced more in HIV positive individuals.



Identification of vulnerabilities in HIV-1 envelope modulating virus neutralization: Complete functional HIV-1 clade C gp160 has been amplified from recently infected Indian patients sequentially over a period of 1 year. By constructing chimeric envelopes between neutralization resistant and sensitive envelope clones, distinct signatures were found that conferred enhanced virus sensitivity to plasma antibodies.

Integrated Behavioural and Biological Assessment Survey

Integrated Behavioural and Biological Assessment Survey was conducted in two rounds (2005-07 and 2009-10) in 29 districts in six high prevalence states to assess the impact of interventions implemented under "Avahan, AIDS India Initiative". The initial assessment reveals that the coverage under programme has increased bringing greater proportion of persons in risk groups coming under the programme. There is greater condom use with paid sexual partners; however, condom use with regular unpaid partners has not gone up. The prevalence of HIV and STIs was lower in the second round in most of the districts with few exceptions where there was increase.

Programme related activities

1. NARI functions as a regional Institute for HIV sentinel surveillance for Western India. Apart from monitoring and training NARI was instrumental in developing manuals for the surveys.

2. NARI functions as the Apex Laboratory for External Quality Assurance System (EQAS) for HIV testing in programme.
3. NARI is implementing EQAS for CD4 testing for NACO CD4 testing centres.
4. A controlled clinical trial to compare virologic and clinical response to Nevirapine containing regimen versus Effavirenz containing regimen in HIV/TB coinfecting persons.
5. Training of medical officers, counsellors, microbiologists and laboratory technicians.

NATIONAL INSTITUTE OF EPIDEMIOLOGY, CHENNAI

Disability status in Paucibacillary (PB) leprosy patients after release from treatment (RFT)

The study was done in PB leprosy patients having more than 5 years after release from treatment (RFT). Disability status was assessed using WHO guidelines 1980. Current disability status was compared with disability status after RFT. Out of 1385 RFT patients the crude incidence rate of disability in PB patients was 3.2%, Incidence of anaesthesia was 2.1% and visible deformity (Grade II & III) was 1.1%; recovery from anaesthesia was 79% and worsening from anaesthesia to visible deformity was 20.4%. The above results suggest that self care may help to prevent worsening of deformity.

Uniform MDT regimen for all leprosy patients

It is an ongoing multi-centric study having sites in India and China. During the year, 3230 and 166 patients were enrolled in India and China respectively. At present U-MDT appears to be promising with respect to clinical status of skin lesions.

Monitoring the compliance to the tobacco-free law in Tamil Nadu

A pilot study was conducted in Chennai and Vellore districts. 400 restaurants/ eateries in 20 wards in Chennai and 344 restaurants / eateries in 20 revenue villages and 27 wards in the urban municipal corporation limits of Vellore district were surveyed. Presence of signage indicating prohibition of smoking was 7.3% in Chennai, 2% in revenue villages and 1.8% in municipal corporation limits of Vellore. There is a need to strengthen the framework for ensuring implementation of smoke-free policies.

Public health training programme

During this year, there are 24 scholars in MAE and 30 in MPH program. 9 papers were published and 6 were accepted for publication. So far 88 and 12 scholars have graduated for MAE and MPH respectively (since inception).

Publications

In all 17 papers were published in peer-reviewed journals.

NATIONAL INSTITUTE OF MEDICAL STATISTICS, NEW DELHI

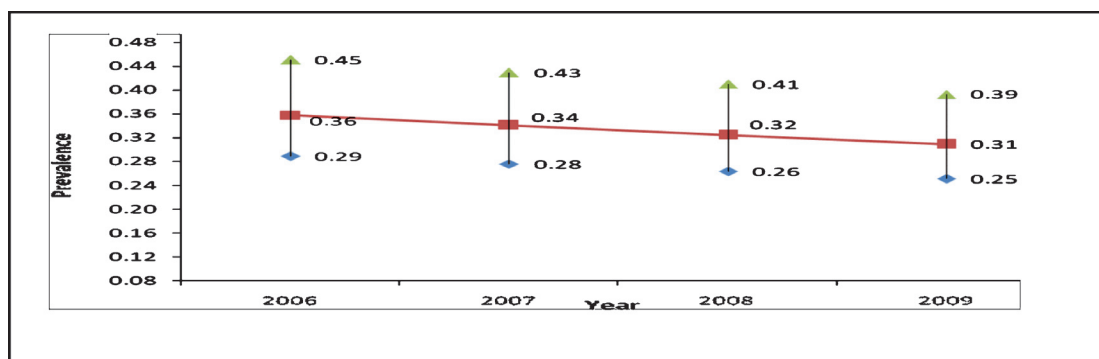
The National Institute of Medical Statistics has come up as a premier institute of biostatistical education and research covering the area of statistical research

methodology, survey methodology and programme evaluation, clinical trials, data repository and HIV/AIDS epidemiology. It undertakes and promotes research in statistical techniques and methodology in the field of health research. It provides statistical services and assistance to researchers in the field of health in the country. It exercises surveillance to ensure statistical adequacy and validity in the programme of the Ministry of Health & Family Welfare and other line departments. It provides capacity building by conducting training in health statistics to the young researchers.

Modelling estimation and projection of HIV/AIDS in India

NIMS acted as the nodal Institute for Monitoring & Evaluation of NACO's HIV Sentinel Surveillance (HSS) and Estimation of HIV Burden in the Country since 2003 in conjunction with the National Institute of Health & Family Welfare (NIHFW), AIIMS, WHO and UNAIDS. During the year 2010, estimates of adult HIV prevalence, people living with HIV/AIDS (PLHIV) and new HIV infections for the year 2008 and 2009 were provided by evolving improved methodology and updated epidemiological data from the latest rounds of HIV Sentinel Surveillance 2008-09 and other information on High Risk Groups for more accurate understanding of the Indian epidemic. The estimates were generated using Estimation Projection Package (EPP) and Spectrum Package. The methodology allows international comparison of the HIV estimates. The adult HIV prevalence (males and females together) in India in 2008 is estimated as 0.32% with uncertainty bounds 0.26%–0.41%, and 0.31% in 2009 with uncertainty bounds 0.25%–0.39%. About 2.44 million people were estimated as the people living with HIV within the uncertainty bounds of 1.97-3.09 millions in 2008. It was estimated 2.39 million with uncertainty bounds 1.93-3.04 millions in 2009. Among PLHIV, 61% were male and 39% were female; 4% were children below age 15 years, 83% were adults age 15–49 years and rest 13% were over 50 years. The four high prevalence states of South India (Andhra Pradesh – 0.5 million, Maharashtra – 0.42 million, Karnataka – 0.25 million, Tamil Nadu – 0.15 million) account for 55% of all HIV infections in the country. West Bengal, Gujarat, Bihar and Uttar Pradesh are estimated to have more than 0.1 million PLHA each and

Adult HIV prevalence trends from 2006 to 2009 in India.



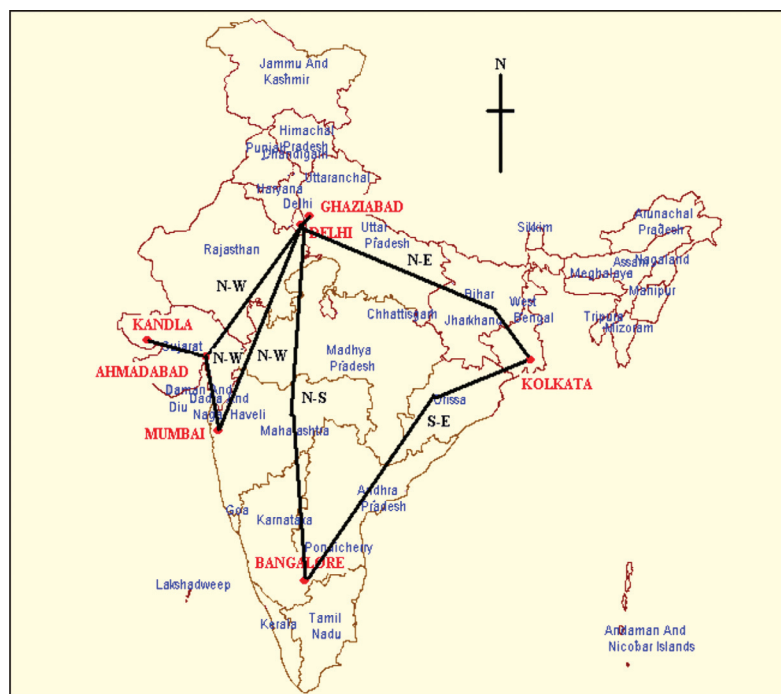
together account for another 22% of HIV infections in India. The states of Punjab, Orissa, Rajasthan & Madhya Pradesh have 50,000 – 10,000 HIV infections each and together account for another 12% of HIV infections. These states, in spite of low HIV prevalence, have large number of PLHA due to the large population size. The adult

HIV prevalence at national level has continued its steady decline from estimated level of 0.41% in 2000 through 0.36% in 2006 to 0.31% in 2009. All the high prevalence states show a declining trend in adult HIV prevalence. It is particularly reflected in Tamil Nadu where HIV prevalence has reached 0.33% in 2009. However, rising trends are noted in low prevalence states.

Analysis of epidemic projections revealed that the number of new annual HIV infections has declined by more than 50% during the last decade. This is one of the most important evidence on the impact of the various interventions under National AIDS Control Programme and scaled-up prevention strategies. It is estimated that India had approximately 1.2 lakh new HIV infections in 2009, as against 2.7 lakh in 2000.

While this trend is evident in most states, some low prevalence states have shown a slight increase in the number of new infections over the past two years, which underscores the need for the programme to focus more on these states with low prevalence, but high vulnerability. Of the 1.2 lakh estimated new infections in 2009, the six high prevalence states account for only 39% of the cases, while the states of Orissa, Bihar, West Bengal, Uttar Pradesh, Rajasthan, Madhya Pradesh and Gujarat account for 41% of new infections.

Integrated Behavioural and Biological Assessment along National Highways (IBBA-NH)



Routes

The four route corridors were selected as they covered almost 90% of the long distance truck drivers in India.

NE: North-East (Route joining the cities of Ghaziabad-Delhi-Kolkata)

NS: North-South (Route joining the cities of Ghaziabad-Delhi-Bangalore)

NW: North-West (Route joining the cities of Ghaziabad-Delhi-Ahmedabad-Kandla-Mumbai)

SE: South-East (Route joining the cities of Bangalore-Kolkata)

Note: IBBA-NH Round-2 did not cover TSL at Kandla

The Bill & Melinda Gates Foundation (BMGF) created the India AIDS Initiative, later called Avahan in 2004, to curtail the spread of HIV in India. Avahan programme implemented in 75 districts in six high prevalence states among high risk population

FSW, MSM, IDU and Truckers in India. Integrated Behavioral and Biological Assessment on National Highways (IBBA-NH) in 2007(R-1) and 2009 (R-2) was undertaken to assess the outcomes and impact of the interventions under the Avahan project. The details of routes and transshipment locations in Round-1 and Round-2 are shown in map below.

In the survey, the long distance truck drivers (LDTD) reported to have their first sex at the age of 18-20 years; only 3% of the truck drivers reported that they never had sex with any partner. About half of them ever had sex with paid female partner (PFP) and one-quarter in past 12 months. Over the intervention period, the consistent condom use increased for paid as well as non-paid female partners; the syphilis prevalence decreased which was the most prominent STI among them; and the HIV prevalence remained either lower or same. The HIV prevalence among young LDTD aged <30 years, working as truck driver for < 8 years, educated with <10 years of schooling, has not increased between the two surveys across the route categories. The utilization of Khushi clinic services was a visible service outlet.

Infant and child mortality in India: Time trend and associated factors derived from three rounds of the National Family Health Survey

A time series structure analysis is carried out by applying the autoregressive integrated moving averages (ARIMA) model to the IMR and U5MR to forecast beyond the series up to 2015 (MDG target year) for India and major states using data from the India's Sample Registration System (SRS), 1978-2008.

The analysis shows that without further intervention, India will not be able to achieve the set target of an U5MR of <39 by 2015 (Fig. 1). However, among major states,

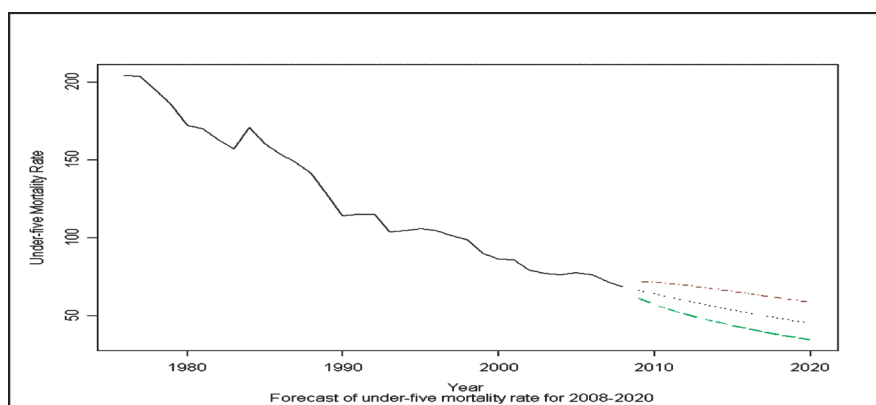


Fig.1: Forecast under-five mortality rates, India, 2008-2020

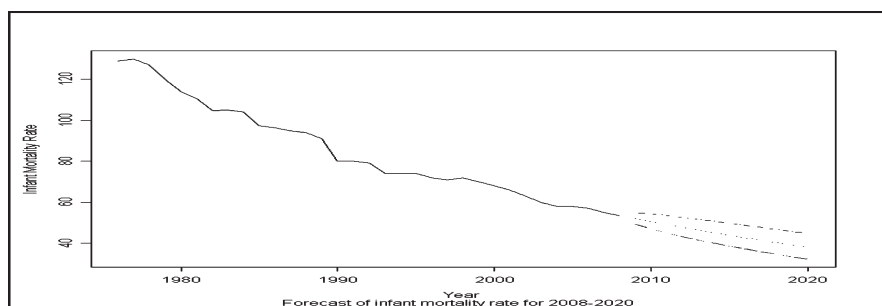


Fig.2: Forecast infant mortality rates, India, 2008-2020

six states namely Kerala and Tamil Nadu in South, Maharashtra in West, Punjab and Himachal Pradesh in North and West Bengal in East will be able to achieve the reduction of the U5MR below 39 by 2015.

In the Eleventh Five Year Plan (2007-12) India set goal, which states that Infant Mortality Rate is to be reduced to 28/1000 live births by 2012. Further, infant mortality rate was projected up to 2016 using ARIMA method for India and major states as shown in the Figure b. Based on the projection India will not able to reduce infant mortality 28 per 1000 live birth by year 2012, among major states Kerela and Tamil Nadu will be reduce IMR and other two states Maharashtra and West Bengal will closer to the national target 28 per 1000 live births by 2012.

An analytical study of malnutrition among women and children in India: Need for action

Analyzed last two rounds of the National Family Health Survey, 1998-99 (NFHS-2) and 2005-06 (NFHS-3) for the level and trend of the prevalence of under-nutrition (underweight, stunting and wasting) among children <2 years in the state of Uttar Pradesh. The low status of women in UP is the primary cause of adversely influencing birth weight as well as nutrition and health care of children. There is a need to focus on improving the status of adolescent girls and women using a life cycle approach for addressing under-nutrition. Efforts for improving infant and young child feeding practices need to be combined with actions which improve the health, education and social status of women. The reduction of child malnutrition will depend not only on the provision of food supplements to children but also the care and support of pre-pregnant and pregnant women.

NIMS worked on the development/maintenance of the **Clinical Trial Registry – India (CTRI)** (www.ctri.in) with the support of Department of Science and Technology (DST), WHO and the ICMR. The number of trial received by 31 Dec'2010 is 2072 of which 1500 have been registered.

REGIONAL MEDICAL RESEARCH CENTRE, BHUBANESWAR

Lymphatic filariasis

Pathobiology : To generate evidence on lymphatic abnormality if any in *W bancrofti* infected children that can become forerunner for adult disease expression and to look for possible reversal with MDA drugs, a study has been initiated. The results can be utilized in the current national programme as an advocacy tool for enhancing drug consumption in children during MDA. In the ongoing study 31 microfilaremic children between 5 to 18 years of age without overt clinical filarial manifestation were subjected to lymphoscintigraphy. Amongst them 50% of children demonstrated delay in lymph flow (Fig 1) and in two cases adult parasite was visualized (filarial dance sign) by ultrasonography. The study revealed distortion of lymphatic channel and delay in lymph flow in the limbs where adult parasite was also visualized. Collateral lymphatic channels were

observed in a 12 year child with normal lymphatic flow indicating successful compensation. It is planned to enroll 100 subjects with 6th monthly follow up for two years look for reversal of pathology.

Higher dose of albendazole in combination with DEC: The ongoing Mass Drug Administrations (MDA) programme across the country to eliminate LF shows low compliance rate as one of the major hurdles for the success of the programme. The current MDA programme uses DEC (300mg) with Albendazole (400mg) to eliminate filariasis within 5-6 years. While DEC is known to be a powerful microfilaricide, Albendazole is believed to have sterilizing effect on adult worms that possibly suppress the resurgence of Mf. No effective regimen is available that can kill an adult worm. Hence effort has been made to identify a more effective MDA regimen by increasing the dose of Albendazole (800mg against 400mg) or rhythm (annual/ bi-annual) used in MDA through a randomized open clinical trial. The comparative efficacy of the four arms((S1: DEC(300mg) +Alb(400) annual, S2: DEC(300mg) + Alb(400) biannual,

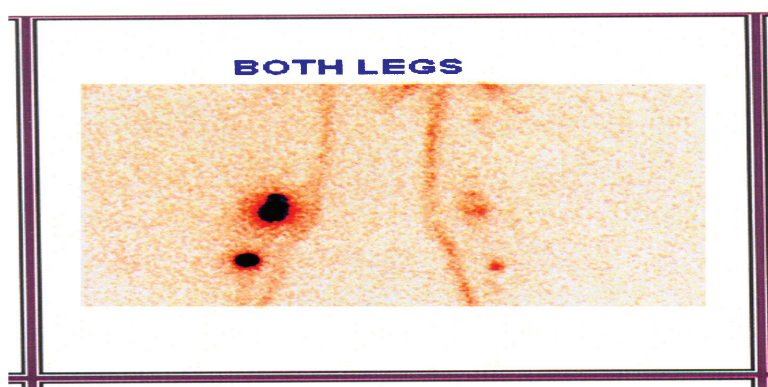


Fig1: Lymphoscintigraphy in an asymptomatic children showing less lymphatic flow on right leg with right popliteal node enlargement.

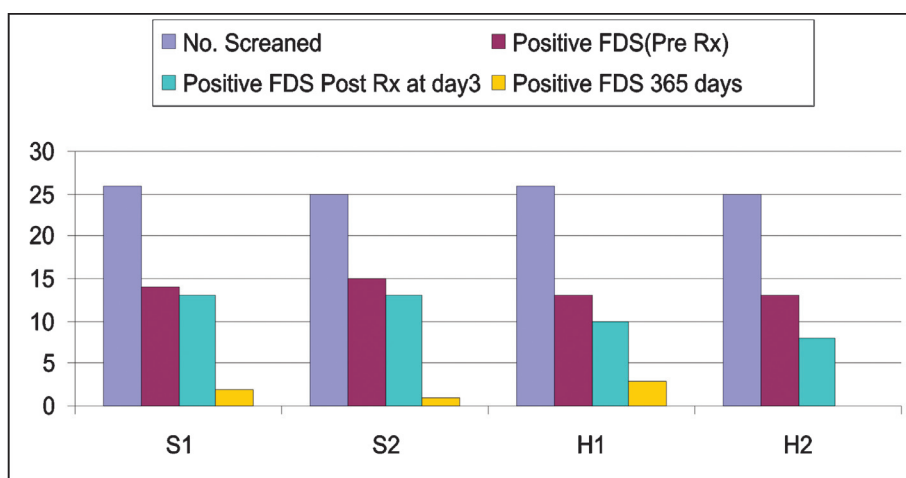


Fig 2: Mf reduction in 6th & 12th months after treatment with DEC plus Albendazole (S1: DEC(300mg) +Alb(400) annual, S2: DEC(300mg) + Alb(400) biannual, H1: DEC(300mg)+Alb(800) Annual, H2: DEC(300mg)+ Alb(800) Biannual)



Photograph of a patient taking DEC + Albendazole in the hospital



Photograph of distribution of DEC in the field

H1: DEC(300mg)+Alb(800) Annual, H2: DEC(300mg)+ Alb(800) Biannual) is being studied, recruiting 104 microfilarimics. The group receiving 800mg of Albendazole with DEC (300mg), given biannually achieved higher clearance of Mf at twelve month post drug. Disappearance of adult worm evidenced by filarial dance sign by ultrasonogram immediately (48 hrs) after drugs was higher with 800mg Albendazole (30%) against 400mg Albendazole (10%) (Fig.2). Hence the interim results indicated higher efficacy of high dose Albendazole. The study is planned to complete follow up of the subjects for two years for final interpretation and recommendation to the programme.

Efficacy of low dose DEC: In another approach this centre looks for the comparative efficacy and tolerability of uniform low dose DEC (100mg) versus standard dose of DEC (300mg) used in the current programme. This study is based on the hypothesis that lowering the dose of DEC can reduced the side reaction while maintaining it's Mf clearance property. The current programme uses DEC in three dosages i.e, 100,200 & 300mg in 2-5, 6-14 & above 14 yrs age groups respectively; the drug being distributed by volunteers from the community. Thus both the community and the drug distributor face difficulty in taking the prescribed number of tablets. This is added over the problem of fear of side reaction that limits compliance. A open community based field trial is being undertaken in three endemic villages with annual mass administration of DEC that mimics the MDA programme except that the

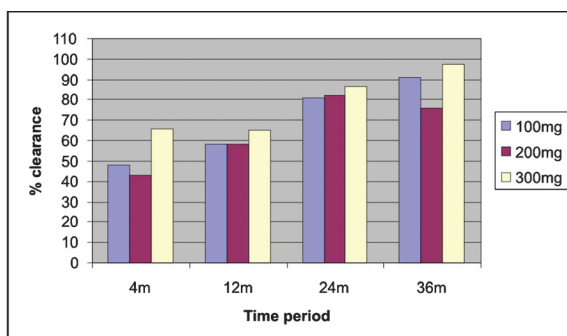


Fig 3 : % of Mf clearance at different time

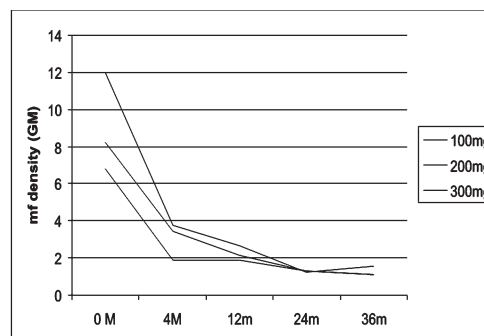


Fig 4: Mf count at different time

population in the villages either receive 100,200 or 300mg DEC irrespective of age after randomization at village level. Four annual rounds have been instituted in the three respective villages which shows significantly lower frequency and intensity of side reaction with lower (100mg) dose DEC. The microfilaria clearance evaluated at 4th, 12th, 24th & 36th months indicates comparable efficacy of 100mg with 300mg dose Fig. 3 & 4). Xeno monitoring of vector populations showed > 70% reduction in infectivity rate and infective larval load in the vector Cx quinquefasciatus in the three dosage sites. The study will evaluate effect of five rounds of MDA before recommendation to the programme.

Maternal-fetal transmission: Although host genetic polymorphism and other environmental factor(s) may influence susceptibility to infection and disease, filarial infection acquired through maternal origin has been considered a risk factor for increased susceptibility. Study conducted at the Centre indicates that filarial specific IgG1, IgG2 and IgG4 antibodies were significantly elevated in cord blood from infected mothers than uninfected mothers (Fig. 5). Comparison of the percentages

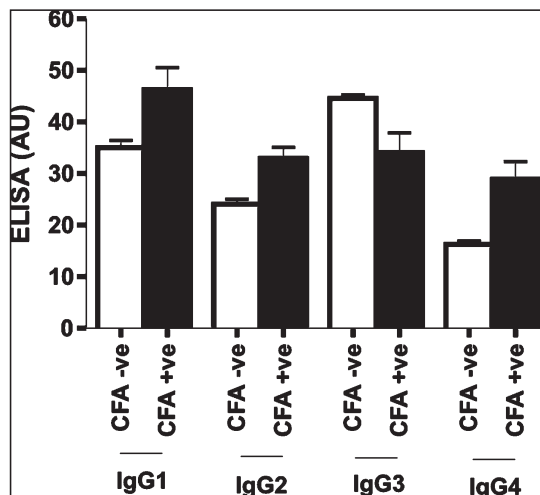


Fig.5. Filarial specific IgG subclass responses in cord sera of infected and uninfected mothers

of CD4+ cells expressing CD25 in paired maternal and cord samples from filarial infected and uninfected groups shows significantly higher T regulatory (CD4+ and CD25+ cells in cord blood samples of filarial infected mothers compared to cord blood samples of uninfected mothers. These findings provide evidence for influence of maternal infection on the development of subsequent anti filarial immunity in offspring. Significantly low levels of IgM antibodies to Actin and LPS in microfilaria carriers (known to be immunologically hyporesponsive) compared to patients with chronic filarial disease and endemic normals (immunologically hyper responsive) raises the possibility of poly reactive property of these antibodies

Malaria

Malaria is a leading cause of mortality and morbidity in the state of Orissa. To support the National Programme of Malaria Control GIS based micro planning in high endemic areas of Orissa has been prepared from the data obtained from house

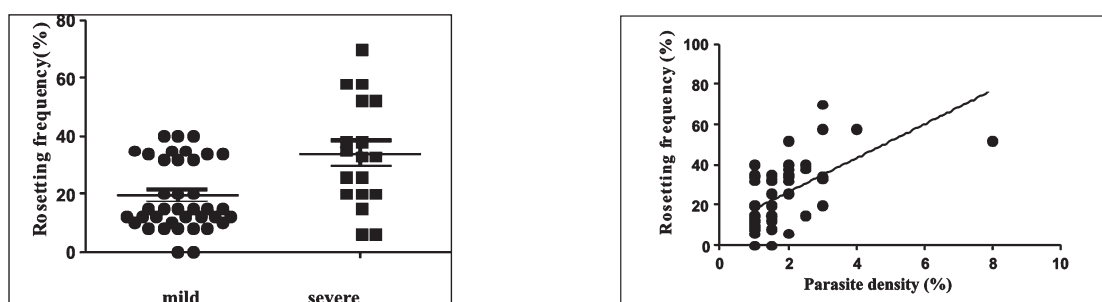


Fig.6. Significant association of rosetting frequency with severe malaria and its positive correlation with parasite density.

to house survey in Papadahandi block of Nawarangpur, Ghatagaon of Keonjhar and Banpur of Khurda district. In a recent survey conducted in 5 districts of Orissa during rainy season, *P. malariae* infection was detected by PCR assay; the prevalence being

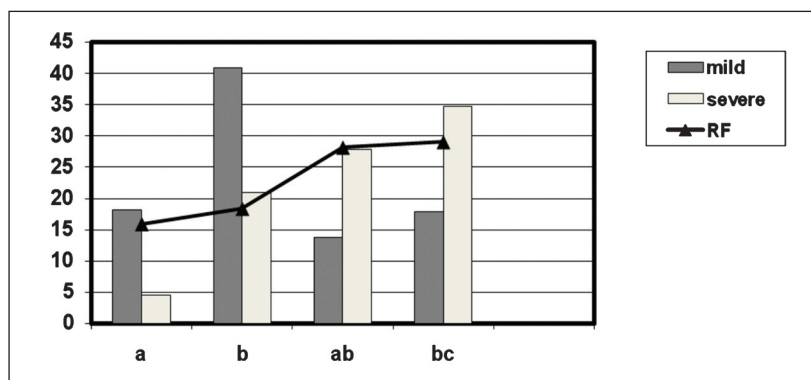


Fig 7 : Mean rosetting frequency distribution amongst genetic variants of DBL 1- α and percentage distribution of DBL 1- α FR variants.

as high as 44.6% and majority of them are mixed with *P. falciparum*. The factors contributing to the pathogenesis of cerebral complications in malaria are not precisely known. A recent study indicates that the parasite population can be stratified based on their association with severity of clinical expression. While analyzing the extent of duffy-binding-like (DBL) gene diversity and rosetting potential of the parasite population associated with severe malaria, a significant association between high parasite density (Fig 6) and severe malaria and “b” variants of FR region of DBL α (Fig 7) with high frequency of rosetting was observed. This indicates that rosetting plays a significant role in the development of severe malaria in this endemic region.

Anopheles sibling species: Anopheles mosquitoes are invariably species complexes. Each sibling species may vary its own distribution and biology and may vary in response to insecticide and capacity to transmit malaria. For the first time the presence of **A** and **D** sibling species of *An. culicifacies* and role of *A. subpictus* (previously non vector) as an incriminating vector for malaria has been reported from this Centre from Orissa. By RAPD and ISSR analysis reveals 25 different types of RAPD and 15 different types of ISSR banding patterns among the *An. annularis* of Orissa and the neighboring state of Jharkhand.

Diarrhoeal diseases

The State of Orissa experiences diarrhoeal outbreaks frequently that accounts for high morbidity and mortality. A large outbreak of cholera was reported in Kasipur, Bisamcuttack and Kalyansinghpur blocks of Rayagada district during the period (Sept.2010) under report. The causative organism was El Tor variant of *V. cholerae* having similar antibiogram profile of 2007 epidemic. Timely diagnosis of rectal swab and environmental water samples and reporting helped the Health Dept of the State to take quick action.

Anaemia in pregnancy

Despite the national anaemia control program for pregnant women, effects of large scale daily iron supplementation is disappointing due to poor compliance,

cost, side effects, and lack of education about the importance of iron in pregnancy. Pregnancy is too short a period to reduce existing anemia, when women do not seek prenatal care until 2-3rd trimester. Adolescence is considered the best time to intervene in order to assist in physical and mental development, and to prevent later maternal anemia. A cluster randomized efficacy trial has been designed to assess

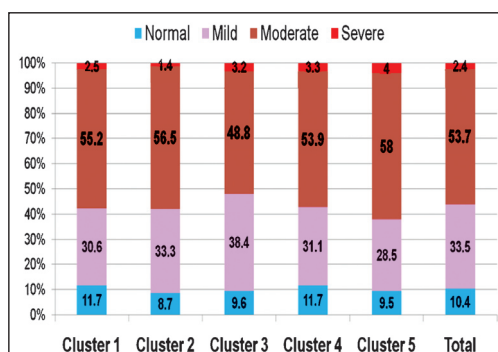


Fig 8a: Cluster-wise anaemia prevalence

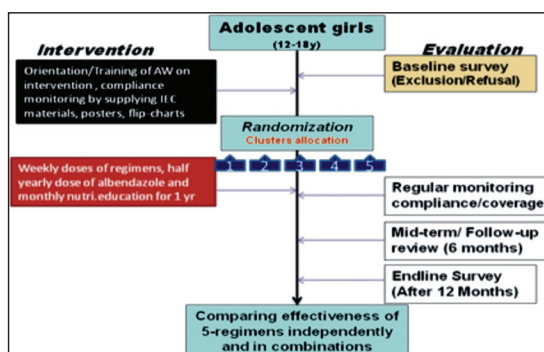


Fig 8b: Flow diagram of intervention

the effectiveness of combined 5-arm regimens of iron-folic acid, vitamin B₁₂, deworming supplementation, and nutrition education in controlling iron deficiency anemia among tribal adolescent girls (12-18y) in Serango sector of Gajapati district. Base line survey among 994 adolescent girls reveals that anemia is prevalent among 90% (hemoglobin <12g/dl) of the samples, of which 36% had hypoferritinemia and 20% had acute infection tested by C-reactive protein. Among them Iron deficiency was detected in 51% of the sample, vitamin A (serum retinol <20 µg/dl) deficiency in 30%, vitamin A (serum retinol <20 µg/dl) deficiency in 32%, folic acid (<6ng/ml) deficiency in 33%, and vitamin B12 (<200pg/ml) deficiency in 30% of the sample. Five clusters were randomized to respective regimen arms, with 150 girls in each cluster and intervention is going on for one year with weekly supplementation. A three-level monitoring system (self independent card, Anganwadi Workers and investigators) put in to the system to assess the compliance, coverage and impact of the programme.

Dengue

There was no previous record of dengue outbreak in the state of Orissa barring few sporadic case records. An outbreak of suspected dengue was reported for the first time in Orissa from Malkangiri district that borders Chatishgarh and Andra Pradesh. Epidemiological investigation confirmed dengue IgM antibody from both symptomatic individuals and asymptomatic house hold contact. House hold clustering of cases and vector abundance indicated indigenous transmission. *Aedes albopictus* was found to be the dominant vector mostly found in peridomestic locations. Immediate reporting and recommendation for control measures to the health authorities enabled public health action to contain spread.

Influenza A H1N1

The centre served as the referral diagnostic facility for investigation of H1N1 influenza cases in the region. The centre used to issue the diagnostic report on

the same day of receiving the samples from different hospitals of the state, which helped treatment and chemo prophylactic action. Out of 484 swab samples tested 118 were confirmed for H1N1. The cases were recorded from twenty one out of thirty district of the state and the epidemic curve has shown peak during the month of August 2010 (Fig.9). As requested by the Government of Orissa a malaria epidemic survey was also conducted in Nilagiri block of Balasore district, where the slide positivity rate was 54.5% and all were *P falciparum*. Two mosquito vector species *A culicifacies* and *A annularis* were present and sporozoites were detected in both the species.

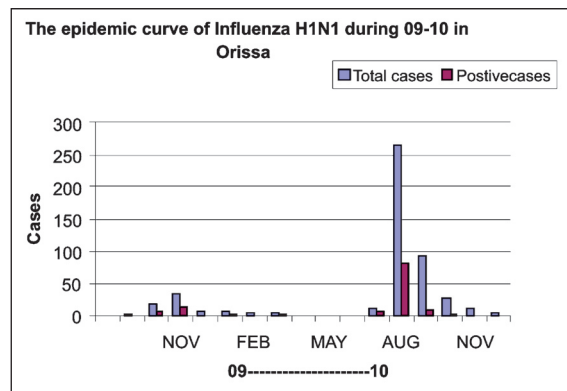


Fig 9: The epidemic curve of Influenza H1N1 cases in Orissa.

REGIONAL MEDICAL RESEARCH CENTRE FOR TRIBALS, JABALPUR

Haemoglobinopathies

Protection provided by haemoglobinopathies in uncomplicated and severe *Plasmodium falciparum* malaria: Haemoglobinopathies and malaria are public health problem in central India and haemoglobinopathies are stated to have been evolved as it provides protection against malaria. A prospective study is undertaken in highly malarious predominantly *Plasmodium falciparum* infected area in Dindori district to observe the protective effect of common haemoglobinopathies. The inhabitants of these villages are primitive Baiga tribe. This is the first community based longitudinal study carried out in India.

In a year a total of 2,681 blood slides were collected from individuals having fever or history of fever in the last week preceding the surveillance date. Slide positivity rate for malaria (SPR) was 36.9 and proportion of *P.falciparum* malaria (Pf%) was 74.3%. A total of 1016 persons were examined for red cell genetic polymorphism and were also monitored for malarial infection. Interim analysis indicates that there were 150 (14.8%) persons with sickle cell trait (HbAS), 27 (2.6%) persons with β -thalassaemia trait, 22 (2.1%) with G6PD deficient and 31(3%) were with raised level (>2%) of foetal haemoglobin (HbF). Only 670 samples could be analysed for α -thalassaemia type II. Of this, only 18.2% of population had all four alpha genes. About 50.5% population had two gene deletion.

Persons with polymorphic traits of HbAS, G6PD deficiency, β -thalassaemia trait and α -thalassaemia have significantly lower level ($p < 0.0001$) of *P.falciparum* parasite count than the normal person suggesting that the malarial infection in these persons is of milder type. Protective phenomenon is observed for all red cell markers studied. The study is in progress.

Communicable diseases

Malaria

Epidemic investigation of *Plasmodium falciparum* malaria in forest villages of Central India: Rapid fever surveys were carried out door to door in Dindori and Balaghat districts of Madhya Pradesh to investigate the epidemic on the request of Tribal Welfare Department of Govt. of Madhya Pradesh to assess the burden to contain the disease. and The inhabitants of these villages are Baiga primitive tribe.

Dindori district: The study was carried out in 44 Baiga villages of 3 community health centres (CHC) in Dindori district. Both *Plasmodium vivax* 4.3% (169/3955) and *Plasmodium falciparum* 32% (1256/3955) were prevalent in all age groups with preponderance of *P. falciparum* (88%). Slide positivity rate (SPR) was lowest in adults (age above 14 years) as compared to other age groups ($P < 0.0001$). Highest SPR was recorded in children (1 to 4 years) and a similar trend was observed in distribution of *P. falciparum* cases ($P < 0.0001$). The lowest prevalence of *P. vivax* was observed in adults and age group 1 to 4 years showed highest prevalence ($P < 0.0001$). A total of 539 *An. culicifacies* and 88 *An. fluviatilis* were collected by hand catch and pyrethrum spray catches. Out of these specimens, one *An. culicifacies* and two *An. fluviatilis* were tested positive for *P. falciparum* circumsporozoite antigen. Further analysis revealed that positive specimen of *An. culicifacies* was collected from cattle shed represent sibling species C while two positive specimens of *An. fluviatilis* collected from human dwelling represent species S (Fig. 1).

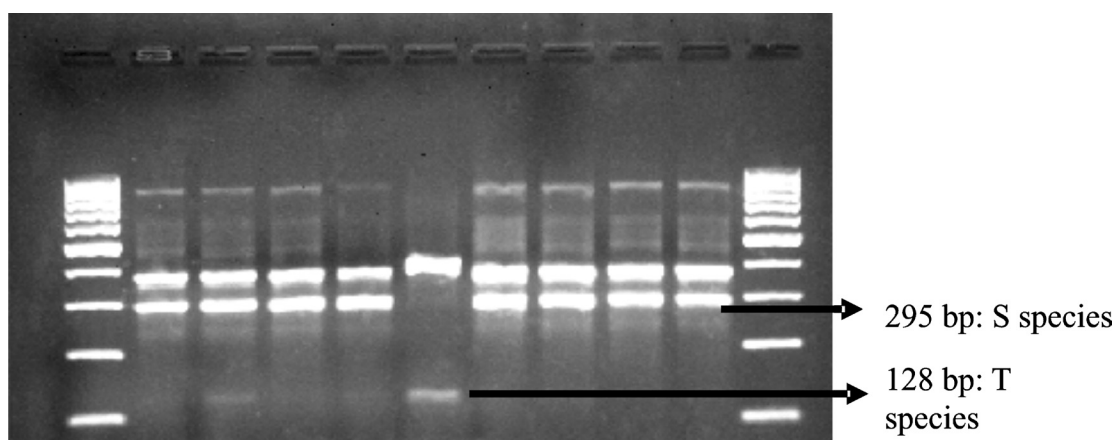


Fig. 1: Polymerase chain reaction assay for differentiation of members of *An. fluviatilis* complex.

Balaghat district: Point prevalence surveys in 20 villages of Birsa and Baihar CHCs in Balaghat district revealed a very high prevalence of malaria in both infants (>25% with 64% Pf) and older children (>30% with >85% Pf) as compared to adults (>11% with 90% Pf). Children between 1-14 yrs have significantly more malaria and *P. falciparum* as compared to other age groups ($p < 0.00001$). Spleen rate among children (2-9 yrs) was 60% (166/275). *An. culicifacies* was incriminated as vector for both malaria parasites.

Comparative evaluation of commercially available rapid diagnostic tests (malaria Pf/Pv Kit) vs. traditional and molecular techniques for malaria: This study was conducted in 10 villages of Bajag Community Health Centre of district Dindori

and 10 villages of Satanwada Primary Health Centre, District Shivpuri. Five rapid diagnostic tests (RDT) evaluated were selected on the basis of two main criteria, i.e. tests detecting both *P. falciparum* and non-falciparum infections and available commercially. The objective was to produce data to guide the national programme in procurement decision of RDTs.



The overall sensitivity and specificity of First Response for malaria was 96 and 59%, Parascreen 93 and 64%, Malascan 90 and 60%, Falcivax 88 and 65% and by ParaHIT Total 66 and 77% respectively (Table 1). The RDTs sensitivity according to parasitaemia revealed that the First Response was most sensitive for diagnosis of *P. falciparum* (96%) and *P. vivax* (87%) as compared to other 4 RDTs especially for levels of parasitaemia above 200 parasite/ μ l.

Exposure of all RDTs to high temperature i.e. 35°C, 45° & 60°C and low temperature (-10°C) did not result in any loss of sensitivity for both *P. falciparum* and *P. vivax*. There were no false positive/ false negative test results, however, there was some reduction in test line-intensity at high temperature. First response clearly has an advantage over other RDTs. The Para screen represented a good alternative. All other RDTs were relatively less sensitive to both *P. falciparum* and non falciparum infections (Fig.2).

Preparation of a field site for malaria vaccine trial in and around Jabalpur: This study was undertaken in Bargi and Sihora Community Health Centres (CHCs) of district Jabalpur. Among different components of the study, the objective of the immunoepidemiological component was to evaluate longitudinal immune response in population which is naturally exposed to malaria in an endemic region of central India to know the development and maintenance of the immunity in different age groups.

There was an age-wise increase in antigen specific IgG level. Seropositivity with 7 Pf and 6 Pv antigens were compared between groups. Results were significant between groups in case of 7 Pf stage-specific and 6 Pv stage-specific antibodies. The adults who developed naturally acquired immunity to both types of malaria had high antibody levels to CSP, MSP1, MSP2 and AMA1 for PF and MSP1, MSP2, AMA1 for PV. Gametocyte antigens showed lower response. Antibodies detected against peptides regarded as an indicator of exposure and increase of antibody with age illustrates the continuous exposure and development of humoral immunity to malaria in the study population.

Blood samples collected from pregnant women were checked for antibodies. Seroprevalence was more in parasite positive cases. Significant differences ($P < 0.05$) have been observed between pregnant women of primigravidae compared to secundigravidae and multigravidae for Pfmsp1, Pfama1, Pfg27, Pvcsp, Pvmsp1, Pvg25.

The infants' umbilical cord blood and mothers' placental blood (92 paired samples) were tested for antimalarial antibodies to both Pf and Pv antigens to determine the possible effects of maternal antimalarial IgG antibodies on protection against placental infection and infection in infants. Species and stage-specific antibody responses were found to be almost similar in cord and placental blood ($P>0.05$).

To understand immune-correlates of cerebral pathogenesis, cytokine markers were evaluated. A group of healthy controls (HC), mild malaria (MM), cerebral malaria (CM) and noncerebral severe malaria (SM) cases were tested for proinflammatory and anti-inflammatory cytokines, chemokines and growth factors. SM group showed highest circulatory levels of IP-10. No difference was observed in IL-10 mediated antiinflammation among studied group. IL-12 levels were negatively associated with falciparum malaria severity that could also be related to parasite burden. Fatal CM have significantly lower levels of VEGF, IL-4 and IL-12 than nonfatal CM, which showed lower angiogenesis repair capacity, suppression of erythropoiesis and weak TH2 response.

Genetic polymorphism analysis of merozoite surface protein-1(*m*sp1) gene of *Plasmodium falciparum*: The merozoite surface is structurally complex. It is most abundant protein on surface of the invasive blood stage of malaria parasites and is a leading candidate for a vaccine against *Plasmodium falciparum*. Comparison of available sequences revealed that MSP-1 divided into 17 blocks which were either variable, conserved or semi conserved. The main aim of study was to determine the genetic polymorphism of vaccine candidate antigens Merozoite surface protein 1 (MSP1).

The 555 bp polymorphic region of block 2, merozoite surface protein 1 gene were amplified and sequenced. A total of 103 *P. falciparum* infected blood samples were used for the amplification and sequencing of merozoite surface protein 1, block 2 from baigachak area of Dindori district. Out of these 58 samples were sequenced and analyzed for MSP 1 gene. The overall allelic prevalence was recorded which

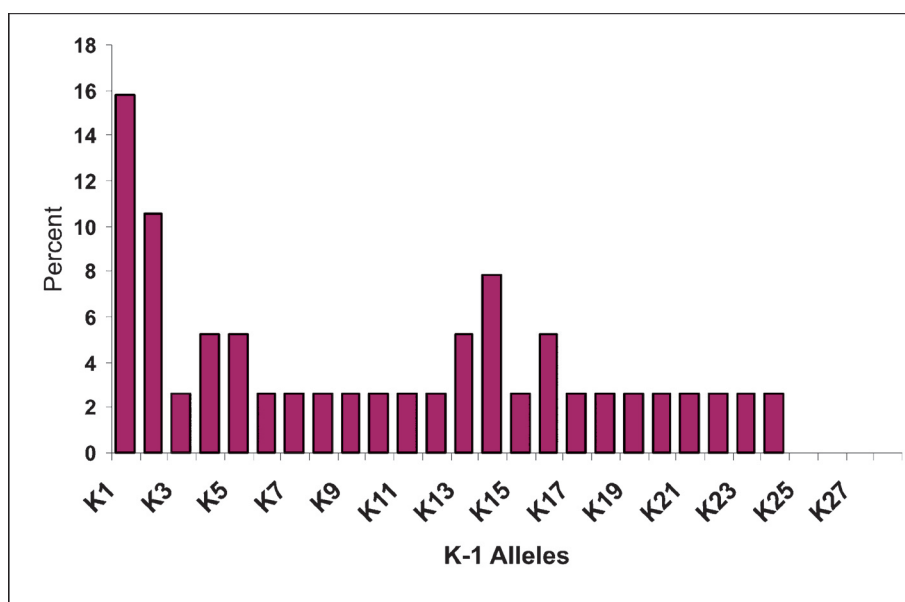


Fig 3. K-1 Allelic Family (2005)

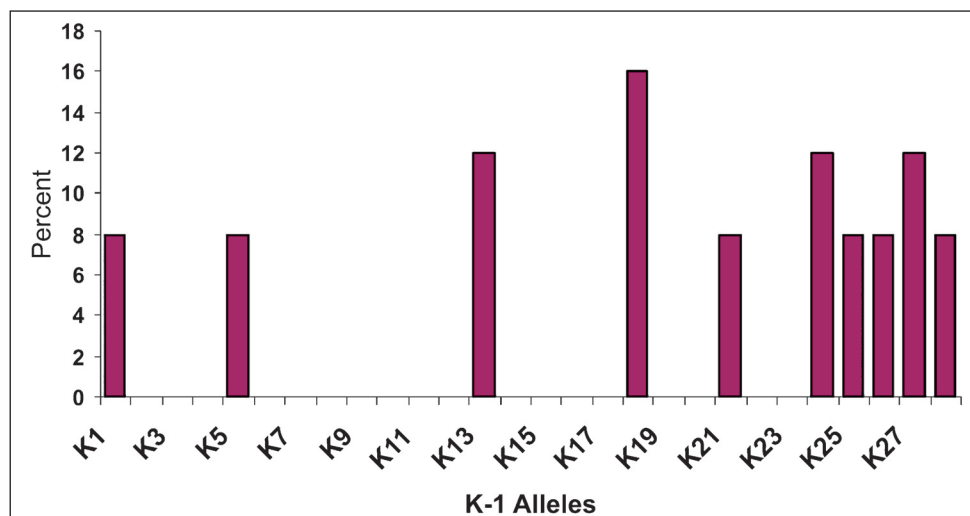


Fig.4. K-1 Allelic Family (2009)

was higher in K1 (43 %) followed by MAD20 (31 %) and RO33 (26%). In the block 2 of MSP1, the nucleotide and the deduced amino acid sequence were found to be highly polymorphic among the isolates. A total 10 types of variants were found in the K1 type alleles. MAD20 type of allelic had limited 6 variants as compared to the K1 type alleles. The RO33 showed almost semi conserved pattern showing only three variants. The amino acid sequence alignment when compared with 2005 showed many new variants and disappearance of 2005 variants particularly in K1 allelic family (Fig. 3&4).

Lymphatic filariasis

In Madhya Pradesh 11 districts are endemic for filariasis. Mass drug administration was carried out once in a year since 2005. Prior to the fifth round of MDA (April 2010), a cross sectional microfilaria survey was carried out in three districts to ascertain the mf rate. The survey was carried out with the target to collect at least 100 blood slides from each selected villages. Thick blood smear was prepared taking about 40 microlitre of blood by finger prick method.

Overall 1737 blood smears were collected. One hundred thirty seven slides were positive for microfilaria (Mf rate 7.9%). Mf rate was significantly higher among males (8.9%) than female (6.7%) ($Z=2.05$, $p<0.05$). Overall mf rate significantly increases with the increase in the age upto the age group of 30-35 years then declines ($X^2=28.4$, $p<0.0015$). However, in females age wise difference is not significant ($X^2=9.6$ df 10 $p>0.4$). Despite 5 round of MDA no significant reduction in mf rate in Ajay Garh tehsil is recorded. There is an urgent need to strengthen IEC programme for better utilization of health services.

Pulmonary tuberculosis

Jabalpur is one of the sentinel sites of prevalence study of Central TB Division. A cross sectional survey was conducted among the urban as well as rural population of Jabalpur district of Madhya Pradesh. The eligible persons ≥ 15 years were screened for symptom inquiry after registering the entire population in the selected cluster. Sputum samples were collected and processed for microscopy and culture by

standard methodology.

Of the total 99595 eligible individuals, 95141 (95.5%) were screened for chest symptoms and 7931 (8.3%) were found symptomatic. Sputum was collected from 7456 (94.0%) symptomatic individuals who were eligible for sputum collection. A total of 221 cases (smear/culture positive) have been identified and were referred to the nearest DOTS centre for anti-TB treatment as per the RNTCP guidelines.

Drug susceptibility testing (DST) has also been undertaken and is being done by proportion method for first line drugs namely streptomycin(S), Isoniazide(H), rifampicin(R) and ethambutol(E). This is the only laboratory in Madhya Pradesh where drug susceptibility can be tested. It has been completed for 158 isolates. Of these, 24 (15.1%) isolates had mono drug resistance (S=12, H=11, R=1). One isolate was multidrug resistant i.e. resistant to H & R. Twelve (7.6%) isolates were resistant to two drugs. Of the twelve, 9 isolates were resistant to S & H, 2 to R & E and 1 was resistant to H & E. One isolate was found resistant to S, H & E.

Swine flu (H1N1P)

In view of global pandemic of swine flu, a testing facility for swine flu (H1N1P) diagnosis laboratory was established at this centre and the testing started in the end of October 2009. Using WHO protocol for real time RT PCR, till March 2010, 497 samples were tested. Out of those tested 95 were positive for H1N1 P virus. Maximum samples were received in the month of January (200 nos.). Adults in the age group of 18-60 were relatively most affected (Fig.5).

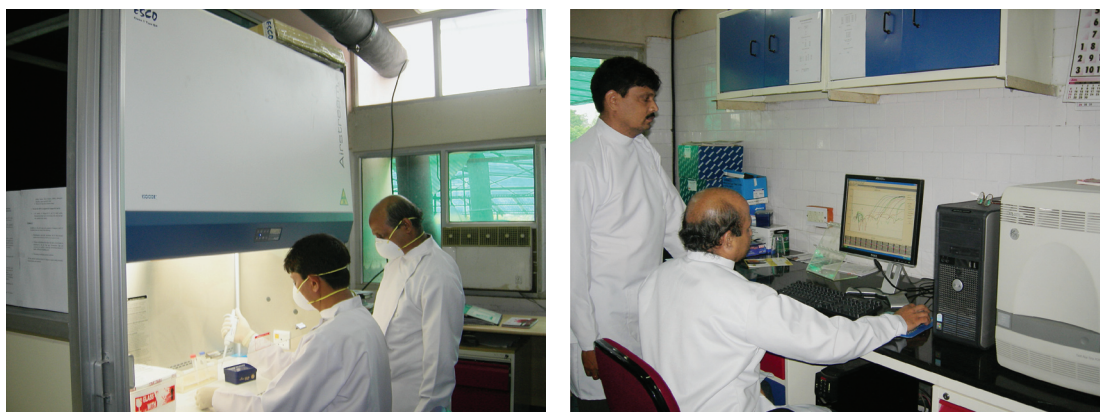


Fig. 5. H1N1P testing in the laboratory

There was not much difference in infection to male and female. City of Indore was most affected with 52 cases followed by Jabalpur (20) and Bhopal (12). Fifty-three seasonal flu (only influenza A) cases were also detected during this investigation.

Health and nutritional profiles

Fluorosis

A cross sectional study was carried out in 10 villages of Seoni district to assess the severity and magnitude of the fluoride problem and to initiate intervention and study its impact. A total of 5437 individuals of different ages from 10 selected

villages were surveyed for collection of baseline data. Dental fluorosis was observed among 1032 (18.9%) individuals from study villages. Genuvalgum or knock knee was seen among 509 (9.3%) individuals (Fig.6) and skeletal fluorosis was observed among 395 (7.2%) individuals. A total of 2923 individuals (53.76%) were suffering from different form of non skeletal fluorosis like loss of appetite (11.6%), gas in stomach (13.4%), pain in stomach (16.7), chronic diarrhoea (6.2%) and chronic constipation (5.8%) among studied population. Intervention programme is in progress.



Fig. 6 . Male with severe knock knee

Health and nutritional profile of Baiga and Sahariya tribes

The main objective of the study was to assess health and nutritional status of different primitive tribes of Madhya Pradesh. Cross sectional study was carried out in 22 sampled villages of Baihar Tehsil in Balaghat district and 23 sampled villages of the three blocks - Bajag, Karanjia and Samnapur in Dindori district. Similarly study was carried out in 26 Sahariyas dominated villages of Datia district.

Baigas

Balaghat District: Acute respiratory infection (25.6%) was the most common morbidity followed by fever due to malaria (22.4%) and scabies (9.3%) among the preschool children. Malaria was also seen in 15% of the adult population which was very high. The commonest intestinal parasitic infestations seen among school children were round worm (16.9%) and hook worm (16.1%), followed by dwarf tape worm (*H. nana*) 5.6% and pin worm (*E. vermicularis*) 2.4%.

The mean anthropometric measurements i.e. height, weight of Baiga tribe was lower as compared to the respective values for other tribal children of M.P. as well as NCHS standards. Cereals formed the bulk of Baiga diet. Consumption of protective foods such as pulses, flesh food, milk, fruits, oil and fats were grossly inadequate. None of the children up to 6 year exhibited signs of Kwashiorkor, while the prevalence of Marasmus was 1.6%. The prevalence of Bitot's spot (4.7%), conjunctival xerosis a sign of vitamin-A deficiency was 9.8% and Angular stomatitis was 3.1%. Overall the utilization of health services was poor.

Considering high malaria prevalence National Malaria control programme needs to be strengthen and special intervention programmes are required to control malaria.

Dindori District: Overall malaria was the most common morbidity (21.4%) in all age groups. It varied from 14% among infants to 31% among school going children. This was followed by acute respiratory infection (6.6%) and dysentery (1.5%). Among non pregnant non lactating (NPNL) women pelvic inflammatory disease (PID) was the most common morbidity (12.3%). In pre-school children acute respiratory tract infection was most common morbidity (15.6%) followed by diarrhea (3.4%), while conjunctival xerosis and bitot's spot was 5.9% & 1.4% respectively.

Cereals formed the bulk of Baigas diet while millets (Maize & Vergu) also consumed in the form of 'Pej'. Mean intake of food stuffs was below the recommended dietary allowances (RDA). Consumption of qualitative foods was grossly inadequate. The intake of all the nutrients except calcium was below the recommended levels which was likely to be due to intake of *Cassia tora* (chakoda leaves) which is one of the rich source of calcium. Among 369 male and 433 female adults, 46.9% males and 54.1% of females had chronic energy deficiency (BMI < 18.5). Considering high malaria prevalence National Malaria Control Programme needs to be strengthen and special intervention programmes are required to control malaria.

Sahariyas

Datia District: Malaria (11.9%) was the commonest morbidity among Saharias of Datia district followed by upper respiratory infection 11.5% and scabies 6%. Out of 237 preschool children 35.3% were wasted, 52.6% were stunted and 67.9% underweight. The stunting and underweight was more in boys than in girls whereas the wasting was more in girls than boys. Night blindness was reported by 14% followed by conjunctival xerosis (6.5%), Bitots spots (6.2%) and corneal xerosis (3.2%). The prevalence of anemia was 40% and females were more anemic than males. The pre-school children and adolescents were relatively more anaemic than the other age groups. A total of 126 stool samples were examined of which 47% were positive for various parasites. The most common parasitic infection was dwarf tape worm (*Hymenolepis nana*) 28.8% followed by Hook worm (*Ankylostoma duodenale*) 20.3%, Round worm (*Ascaris lumbricoides*) 18.6%, *Entamoeba histolytica* 15.3%, and Thread worm (*Enterobius vermicularis*) 11.9%. The information will be useful for the planners and policy makers working in the area for the development of the Sahariyas.

Reproductive health

Behaviour and vulnerability to reproductive morbidity among Sahariya tribal youths: The primitive tribes are vulnerable population with scanty information on their behavioural dimensions of reproductive morbidity. The present study is an attempt in this direction with an objective to understand the social risk factors and behavioural dimensions of reproductive and sexual health among the Sahariya tribal youth (15-24 years). The study shows that there exists lot of misconception and wrong practices related to various aspects of reproductive and sexual health. HIV/AIDS was heard by 45% (315/702) of the respondents. Avoidance of multiple sex partners and use of condom reduces the chance of HIV infection is known to 68% (215/315) and 55% (174/315) of the respondents respectively.

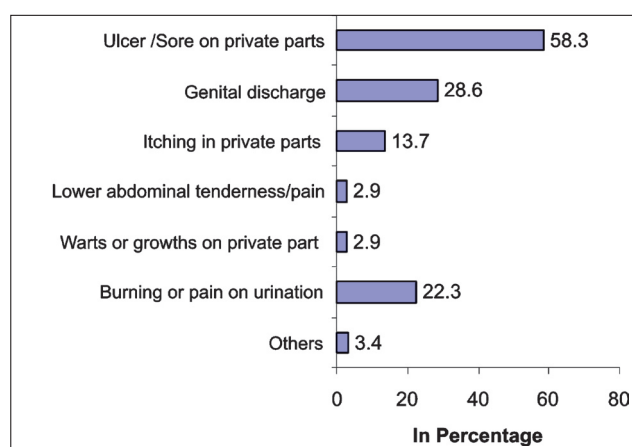


Fig. 7. Awareness of symptoms of STIs (N=175)

There were many misconceptions about the transmission mechanism of HIV infection among the respondents. Apart from HIV, other STI were heard by 25% (175/702) of the respondents and they mentioned their knowledge on various symptoms (Fig. 7). Around 17% of the total respondents (118/702) reported to have suffered during three months preceding the survey. Very few among them availed some treatment mostly from private practitioners for the symptoms reported. Need has been felt to sensitize the tribal youth on the awareness and right practices related to reproductive and sexual health and reduce the unmet need of the government health services. There is also a need to strengthen the government health delivery system at grass root level. The study is in progress.

Utilization of maternal health care services among Baigas: A cross-sectional community based household survey being carried out among Baiga primitive tribe in Dindori district of M.P. to examine the knowledge, perception and utilization of health services among the Baiga tribe. So far 498 ever married women (15-49 years) are interviewed from 24 selected villages. The study is based on a sample of 380 women who experienced maternity during last five years. Majority of the women received first antenatal checkup during second trimester of their pregnancy (43%) mainly due to lack of awareness. Consumption of IFA tablets and T.T. immunizations was reported by 68% and 76.3% women respectively. Delivery at home is the usual practice and only 8% deliveries were conducted at health Institutions. The mean age at delivery of first birth was 19 years. About 84% home deliveries were assisted by untrained health personnel while that by ANM/LHV was 7.9%. This is important to note that about two-third ever married women were not aware of maternal health services while one-third women were aware but could not utilize the services due to poverty, inaccessibility, etc. The study is under progress.

Newborn care among Bhil tribes of Dhar district: A cross-sectional survey was carried out in 60 Primary Sampling Units to study the socio-cultural practices related to newborn care and study the prevalence of early childhood morbidities (reported symptoms) and the treatment seeking behaviour among Bhils of Dhar district. Overall 1049 RDWs out of 1047 selected households were successfully interviewed.

The coverage of antenatal services in the study population is almost at par with state average. About 89% women received at least one ANC during their last pregnancy, however, only 48.6% of them received the recommend three or more ANC's. Moreover, only 13% women received the recommended 90+ IFA tablets, and only 10% of them consumed the minimum required IFA tablets. About 64% of deliveries took place at some health centre and most of these deliveries were conducted at Government health facilities (Fig.8). Only 41% women reported that they received any postpartum check-up.

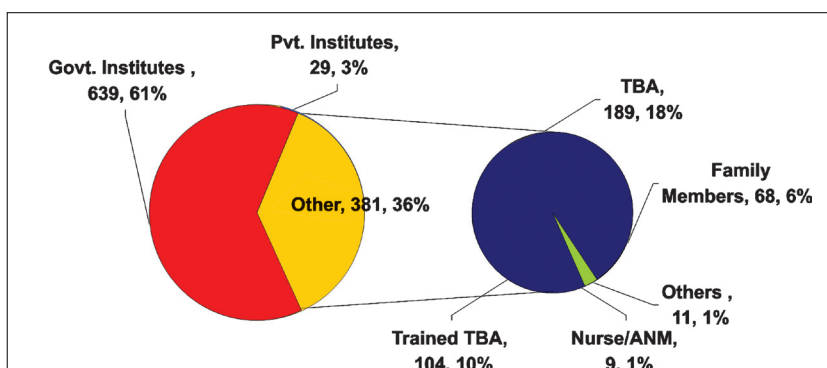


Fig.8. Place of delivery and persons conducted home deliveries

Only 59% women feed colostrums to their babies and only 33% women put their baby to breast first time within 24 hours. The practice of offering pre-lacteals to babies is very common. Among the commonly reported health problems of newborn, fever (14.6%) and diarrhea (8.8%) mostly reported in the study population and most of them availed treatment. Though the utilization of maternal and child health services has improved among the tribes, however, there is need to improve the quality of services. Overall the study reflects that there is imperative need for promotion of healthy newborn care practices among Bhil community.

REGIONAL MEDICAL RESEARCH CENTRE, PORT BLAIR

Investigation of outbreaks

Malaria in Billiground, Middle Andaman: An outbreak of malaria was suspected in Billiground and nearby areas in August – September 2010. On the request of the Director of Health Services, a team from the Centre was deputed to Billiground to carry out investigation of the suspected outbreak with the objectives of confirming the outbreak, identifying causes of the outbreak and also to suggest measures for control of the outbreak and prevent future outbreaks in the area. Analysis of epidemiological information indicated an outbreak of malaria during August-September 2010. In view of the abundance of *An. barbirostris*, this mosquito species may perhaps have a role in the transmission of malaria.

Chikungunya fever in Rangat Middle Andaman: A sudden upsurge of fever cases suspected of chikungunya was observed in Rangat in July-August 2010. We investigated the outbreak to confirm the diagnosis, existence of an outbreak and to identify the causes of the outbreak. Serological tests performed on acute blood samples indicated the outbreak was due to CHIKV infection. This is the first observation of chikungunya fever in Rangat. Sequence analysis is in progress to characterize the virus.

Hand foot Mouth Disease (HFMD) cases in a primary school in Port Blair: A cluster of students from a primary school in Port Blair and their family contacts suffered oral ulcers and vesicular lesions on palms and soles of feet during August 2010. Hand Foot and Mouth Disease was suspected based on the clinical picture. We investigated this cluster of cases to confirm the diagnosis of HFMD, identify and characterize the etiological agent. A total 29 suspected cases of HFMD were included in the study and throat swabs were collected from all of them. All the 29 children had vesicular eruptions. Fourteen (48.3%) had fever, nine (31.0%) had macula-papular rashes and one each (3.4%) had running nose and cervical lymphadenopathy. The clinical feature observed among the children is characteristic and classically consists of a combination of exanthem and enanthem. Papulo-vesicular lesions were present over the hand, feet, buttocks, knee and oral mucosa. We standardized the RT-PCR conditions for detection of 400 bp NCR region, which is common to all the enterovirus family. So far 18 samples have been processed by RT PCR analysis and six samples were positive a 400 bp NCR region. HFMD was not earlier reported in these islands and less common on the mainland. This is the first observation on the occurrence of HFMD from these islands, which is rarely reported on the mainland.

Leptospirosis in Sindhudurg, Raigad and Ratnagiri districts, Maharashtra: A suspected outbreak of leptospirosis occurred in Sindhudurg and Raigad districts of Maharashtra State during November 2010. Several hundreds of people were affected and 52 patients died. On the request of the Director General of Health Services, Govt. of Maharashtra, a team from the Centre was deputed to the affected districts of Maharashtra to investigate the outbreaks. The data from month-wise occurrence of leptospirosis in Sindhudurg district showed a sharp increase in the number in November 2010 thus confirming the existence of the outbreak. Several isolates of leptospires have been obtained. The commonest infecting serogroup as per MAT titres appear to be *Pyrogenes* followed by *Hebdomedis*, *Pomona*, *Canicola* and *Icterohaemorrhagiae*. *Hebdomedis*, which is an unusual pattern indicating a unique transmission cycle in the islands. Several isolates of leptospires have been obtained from human patients and animals. Characterization of these isolates and analysis of clinical and epidemiological data is in progress.

Leptospirosis

Development of DNA Vaccine for Leptospirosis: In respect to protection strategy, few vaccines were prepared either from inactivated whole bacterial cells or sub-unit proteins elicit serovar specific immunity for short duration being used for vaccination of animals in some countries. However, the efficacies of none of these vaccines are not up to the acceptable level. Thus, there is a need for the development of a more effective vaccine that not only elicits immunity across the heterologous serovars but also induces long-lasting immunological memory for both humans and animals. So we proposed a novel consensus-based approach to vaccine development, employing a DNA vaccine approach that can provide more highly cross-reactive cellular and humoral immunity against Leptospires. The gene of interest LipL45 and DNAj were sequenced and the nucleotide sequences were analyzed. Similar pattern of expression for DNAj (42kDa) and LipL45 (45kDa) against rabbit hyper immune sera as well as patient serum samples was observed. It was evidenced that DNAj was expressed in eukaryotic and prokaryotic system and LipL45 was in eukaryotic expression system. Further the purified protein will be used to rise anti – leptospiral DNAj and the DNAj and LipL45 construct will be used for immunization with BALB/C mice. The cellular immune response and humoral immune response will be studied for the efficacy of this DNA vaccine. The challenging and immune protective studies in guinea pigs and hamsters are in progress.

Development of ELISA for the diagnosis of Leptospirosis using recombinant lipL32: There may be some virulence markers associated with the infection. These markers are most probably proteins and they play a major role in virulence and pathogenicity. Identification of such markers could probably aid in the early diagnosis of leptospirosis. In this context, the family of outer membrane proteins is highly immunogenic in nature due to immediate host immune response. The leptospiral lipoprotein 32 (LipL32) is apparently expressed in both acute and convalescent phase of infection and conserved among all the pathogenic serovars. The gene coding for the protein has been cloned and the protein expressed. The purified recombinant protein was used to develop both IgM and IgG ELISA. These ELISA tests were evaluated using a total of 890 known positive and 109 negative serum samples. IgM ELISA showed a sensitivity of 89.3% and a specificity of 89.2% whereas the IgG ELISA had a sensitivity

of 93.4% and a specificity of 90.9%. Further evaluation of these tests is in progress.

Identification, characterization and role of proteinases during the pathogenesis of Leptospirosis: During infection and invasion the bacteria cross the physical barriers and later it encounter with the host defence mechanism. These processes may involve proteolytic degradation of the host tissue biomatrix. Studies were initiated to understand whether leptospires express their own matrix degrading enzymes. We could identify different type of proteinases having molecular weight 83.65 kDa, 66.42 kDa, 47.51 kDa and 46 kDa. The 83.65 kDa and 66.42 kDa are more resistant to higher temperatures. A 47.51 kDa is a metalloproteinase is found associated with the outer membrane of *Leptospira*. This 47.51 kDa gelatinase appears to be important in the pathogenesis of the disease as most of the pathogenic serovars expressed high level of the enzyme.

Identification of differentially regulated proteins during the host pathogen interaction of leptospirosis and establishment of a proteome database: Bioinformatics approach has showed that, the genome encodes Chromosome-I with 265 to 367 genes and 235 to 367 coded proteins and Chromosome-II with 2980 to 4401 genes and 2645 to 4360 coded proteins distributed among serovars with sequenced genome. The protein expressed is an indicative of the functional level of genome. So the knowledge about the proteins expressed by the pathogen at various conditions of its interaction with host and environment is very important to know its strategies on survival and pathogenesis. A number of differentially expressed protein spots in the pathogenic and non pathogenic serovars by 2D gel electrophoresis were identified. The significant difference of the protein among the *Leptospira* serovars may be studied for the reason of virulence of the pathogenic and non pathogenic organism. The temperature and osmolarity induced protein profile also needs to be studied in detail.

Chikungunya

Clinico pathological study of arthropathy and acute flaccid paralysis following chikungunya virus infection: A detailed study on clinic-pathological aspects of chikungunya infection, particularly with regards to chronic arthritis following infection and acute flaccid paralysis is in progress. Last year we had reported the findings of MRI imaging studies in patients with chronic arthritis. The studies had shown that the arthritis in chikungunya is inflammatory erosive in nature and that it resembles rheumatoid arthritis. This year further in vivo and in vitro studies were carried out. These studies include Cytokine profile of different groups of patients such as those with acute chikungunya fever, those who had recovered completely from the disease without chronic sequelae, those with chronic arthritis following chikungunya infection and controls and Cytokine production by peripheral blood mononuclear cells (PBMC) from patients with post-CHIKV arthritis, acute patients and recovered patients after stimulation with CHIKV.

Animal model studies on the role of macrophages in the pathogenesis of chikungunya fever

Six cytokines viz. IL1-Ra, IL-6, IL-8, MIP-1a, MIP-1b and MCP1 had higher levels in patients with chronic arthropathy following CHIKV infection as compared to controls and recovered patients and these appears to have a role in the pathogenesis of chronic arthropathy after CHIKV infection. The cytokine and chemokine response

observed in chronic CHIKV arthritis patients has many features common with that of Rheumatoid Arthritis (RA) and Epidemic Poly Arthritis (EPA). Perhaps the evolving intervention strategies targeting cytokine and chemokine pathways in RA and EPA such as IL-6 and IL-8 blockage might be applicable for chronic CHIKV arthritis as well.

When stimulated with CHIKV, expression of IL1RA and IL6 by PBMC from chronic patients was much higher than that from recovered patients thus corroborating the results of in vivo cytokine profile studies. The expression of IL8, MIP1A, MIP1B and MCP1 were also enhanced in patients with chronic arthropathy though statistical significance could not be demonstrated. MIP-1a and MCP-1 has been identified as the most prevalent chemokines in collagen-induced arthritis models and these have been postulated to play an important role in bone resorption. Inhibition of these chemokines using antibodies have been shown to improve of artificially induced arthritis in rats, which opens up further avenues for research on chronic post CHIKV arthritis treatment modalities.

Gross and histopathology of various organs and cytokine profiles were assessed in three groups of mice viz. macrophage depleted ones challenged with CHIKV, normal mice challenged with CHIKV and unchallenged normal mice. Macrophage depleted mice did not show any signs of illness or any gross or histopathological changes in organs. However, various lesions were observed in liver, spleen, brain and lungs of non-macrophage-depleted mice challenged with CHIKV indicating the role of macrophages in the pathogenesis of chikungunya fever. Studies on cytokine profile of these animals indicated that six cytokines viz. IL-1 β , MCP-1, IL-10, TNF- α , IFN- γ and IL-2 might be playing a role in the pathogenesis of chikungunya fever.

Dengue

Emergence of multiple Dengue serotypes in Port Blair: During the months between June-August 2010 several suspected Dengue, Dengue Haemorrhagic Fever and Dengue Shock Syndrome cases were detected in South Andaman. We undertook studies to identify the circulating sero types; which caused the Dengue Hemorrhagic fever/Dengue Shock Syndrome. The NCBI nucleotide blast of the dengue virus and phylogenetic analysis confirms the presence of circulation of dengue serotype-1 and dengue serotype -2 in South Andaman. Five samples showed positive results for RT PCR of which 2 samples were Dengue serotype 2 virus and 3 samples were Dengue serotype 1. These findings have great public health importance as DHF and DSS have not been reported from Andaman and Nicobar Islands earlier.

Hepatitis B

Serological and Molecular studies on Hepatitis B infection among the Nicobarese of Car Nicobar 10 years after inception of the Universal Hepatitis B Vaccination: Hepatitis B is highly endemic among the Nicobarese Tribes of Andaman and Nicobar Islands. When universal vaccination is introduced in a community with high endemicity where widespread transmission of infection usually occurs, the chances of emergence of mutant strains could be high. The Nicobarese community of Car Nicobar faces such a situation. In view of this, it was considered important to

study the existence of infection with mutant strains of HBV among the community both among persons who are vaccinated and have developed protective levels of antibody against non-mutant strains as well as among those are not vaccinated. Therefore, a study was initiated in Car Nicobar. One person, among the vaccinated individuals had demonstrable levels of anti-HBsAg antibody response, is positive in PCR for HBV DNA, indicating the presence of infection with a surface mutant strain of HBV. The preliminary findings will have implications on the ongoing programme of universal immunization against hepatitis B in Nicobar District.

Diarrhoeal diseases

Molecular Characterization of *Shigella sonnei* Isolated from A & N Islands and its Significance in the Epidemiology of Shigellosis: Hospital based surveillance in Andaman Islands has identified shigellosis as a major cause of childhood diarrhoea in the Islands. Rapidly increasing prevalence and widening the spectrum of antimicrobial drug resistance among *Shigellae* have been major problems. Generation of data on the mechanism of acquisition of drug resistance among *Shigella sonnei* would not only help us understand the epidemiology of *S. sonnei* diarrhoea in the islands, but would also help us identify the routes of acquisition of resistance to these drugs. In view of this a study was initiated. Presence of three to ten plasmids were noticed in *S. sonnei* isolates so far used in the study. All fluoroquinolone-resistant strains had a uniform mutation in GyrA at position 83 (replacement of serine with leucine), and the majority of strains had a second mutation at position 87, with replacement of aspartic acid with glycine, asparagine or tyrosine. Non-functional point mutations were detected in *gyrB* region also. All the fluoroquinolone-resistant strains had a single mutation in ParC at position 52 (replacement of serine with isoleucine) and some of them had two mutations in ParE at positions 438 resulting in replacement of Aspartic acid with Glycine and at 458 resulting in replacement of Serine with Alanine. Eight strains of *S. dysenteriae*, *S. sonnei* and *S. flexneri* showed the presence of *aac* (6')-Ib-cr and three *qnrB*. Two strains had both. None of the isolates were positive for *qnrA*, *qnrC*, *qnrS* and *qepA* genes.

Microbiological, clinical and epidemiological study of childhood diarrhoeas in tribals and settlers of Andaman & Nicobar Islands: Bacteriological surveillance of childhood diarrhoeas in Andaman Islands started in 1994 when RMRC initiated collection, isolation, identification and characterization of enteric pathogens from stool samples obtained from paediatric patients admitted to the G.B.Pant Hospital, the only referral hospital in Port Blair. After the Tsunami in December 2004, the number of isolates decreased may be due to revamped sanitation system, public health measures and awareness among the common people. A total of 262 children with diarrhoea admitted to three hospitals in Port Blair were included in the study during the reporting period. All the isolates showed a wide range of drug resistance which is a case of concern. All the isolates were resistant to tetracycline, nalidixic acid, cephalexin, co-trimoxazole, ampicillin, nitrofurantoin, carbenicillin and tetracycline. In addition, resistance to gentamicin (57%), ciprofloxacin (67%), amikacin (71%) and azithromycin (71%) was also observed. Multiplex PCR revealed that all the isolates harboured virulent genes *ctxA*, *tcpA*, *toxR*, *toxS*, *toxRS*, *VPI*, *toxT*, *ace*, *zot* and *tcpP*. Such resistance could be the result of spontaneous mutation in *V. cholerae* or transfer of resistance from other co-inhabiting microbes. However, this

needs further confirmation as no vibrio isolates have been obtained during the inter-epidemic period.

Non-communicable diseases

Assessment of risk factors of chronic non-communicable diseases among the population of Andaman and Nicobar Islands: In Andaman and Nicobar Islands, analysis of the death registry data of one year showed that more than 30% of deaths were due to chronic diseases. A preliminary study on hypertension and obesity conducted among the Nicobarese, the largest tribal community of the islands showed high prevalence of hypertension among them. The study was a cross-sectional sample survey for estimating the prevalence of eight risk factors following WHO STEPS protocol for non-communicable disease surveillance. Complete data including physical and biochemical measurements was collected from 2,911 individuals. The standardized ratio of overweight/obesity in the whole of survey participants was about 30%. Overweight/obesity among Nicobarese is comparable to urban Indians, while the urban participants had slightly lower prevalence of overweight/obesity as compared to national figures for urban people. In the case rural people it is the opposite with the prevalence among the survey participants in Andaman and Nicobar higher than national average. A major observation of concern that has emerged from the analysis of the data is the high risk profile of the Nicobarese. They have extremely high prevalence of tobacco use, high prevalence of alcohol consumption and heavy drinking, very low fruit consumption, a prevalence of obesity/overweight comparable to urban Indian populations, very high prevalence of hypertension and high prevalence of low HDL cholesterol levels. Findings warrant intervention measures.

Extramural Research in Communicable Diseases

Highlights of some major projects completed

- After exploring variety of whole and purified filarial antigens, the investigators at Jamnalal Bajaj Tropical Disease Research Centre, Mahatma Gandhi Institute of Medical Sciences, Sewagram and Centre for Biotechnology, Anna University, Chennai have been able to identify some of the candidate *B. malayi* filarial antigens of diagnostic use (such as Bm mf S2 and Bm mf ES4). The filarial diagnostic tools developed using recombinant antigens were evaluated in different centres, using coded groups of filarial cases. The study revealed that rWb14 is more sensitive than Wb paramyosin to detect filarial antibodies in microfilaraemic cases. External validation of the rWb14 based IgG4 antibody assay was carried out at RMRC, Dibrugarh. The assay gave 97.7% sensitivity to detect mf carriers with 90% specificity. The positive and negative predictive values of the assay were 89.6% and 97.8% respectively. The study concludes that rWb14 antigen based IgG4 antibody assay provides a useful tool to detect infected cases for the prompt initiation of anti-filarial therapy and for the surveillance of elimination programme.
- Geographic Information System (GIS) technology allows study and examination of remotely sensed land elements that relate to vector abundance and therefore transmission risks. Therefore, filariasis risk maps for both endemic and non endemic blocks have been developed in a study conducted by RMRC, Bhubaneswar. Significant differences were observed in soil pH, land use, land cover pattern and vector density between endemic and non endemic blocks. Continuous monitoring these maps will help in assessing the spread of filariasis to non endemic areas as well as impact of the intervention measure in endemic areas, which will help the government to take measures against transmission/ control of filariasis.
- Delimitation of transmission risk areas is an essential step, and hence a geo-environmental risk model (GERM) on GIS platform was attempted for determining potential areas of transmission of lymphatic filariasis, based on which a map for filariasis transmission has been created in India in a successfully concluded TF study by VCRC, Pondicherry. The model has been validated through a 'ground truth study', which gave a sensitivity of 100%. Ground truth survey results showed that the model predicts all the true non-risk areas (based on ICT survey) perfectly. The GERM model developed on GIS platform is useful for LF spatial delimitation purpose on a macro scale. Further, the risk map developed will be useful for the National LF Elimination programme for prioritizing the areas for intervention.
- A study on comparative evaluation of PCR primers in diagnosis of VL and PKDL was carried out at Banaras Hindu University, Varanasi, which was provided successful diagnosis VL of 87.2% sensitivity using patient's whole-

blood with BHUL18S primer and 86.7% sensitivity with BHUSSU primer. None of 250 nonendemic controls were positive and thus, specificity in this group was 100% using both primers. The study concludes that with Indian strains and isolates of *L. donovani*, the PCR assay developed at BHU is sensitive enough to detect 18S rRNA gene in an amount equivalent to a single parasite or less in a one million human cell environment. High sensitivity of PCR in relatively non-invasive peripheral blood opens up the possibility of its deployment in field for the routine diagnosis of VL, and it is possible to eliminate the risky method of splenic aspiration.

- Although *Campylobacter jejuni* is the microorganism most commonly implicated in the development of Guillain Baare Syndrome, an autoimmune disorder of the peripheral nervous system, studies demonstrating the mechanism of disease development and its progression after *C. jejuni* infection are least understood, probably due to lack of an animal model. In a study concluded at SGPGIMS, Lucknow, an animal (chicken) model for the disease following *C. jejuni* infection was developed. Immunopathogenesis of *C. jejuni* associated GBS and the role of Th1 and Th2 immune response with disease pathology was studied in this model. The study provided an evidence for a relation between disease activity and IL-1 β , IL-2, IFN- γ , IL-6 and TNF- α . Elevation of TGF- β 2, IL-4 and IL-10 has been related to recovery from the disease, suggesting that Th1 response is likely to contribute to the immune-mediated nerve tissue damage in *C. jejuni* associated GBS and the Th2 immune response helps in the recovery from symptoms. This experimental inoculation with *C. jejuni* in chickens may provide a new model for understanding the pathogenesis and immune response during the different stages of disease.
- Indiscriminate use of beta-lactam antibiotics has resulted in emergence of AmpC β -lactamases. Considering the lack of comprehensive studies from India, a study was undertaken at Vallabhbhai Patel Chest Institute, Delhi to evaluate and compare various phenotypic methods for the detection of AmpC β -lactamases in clinical isolates of *Klebsiella* spp. and *Escherichia coli*, and to detect and characterize AmpC β lactamases produced by these isolates by analytical isoelectric focusing (IEF) and polymerase chain reaction (PCR) as well as by sequencing of *ampC* genes. The study showed that extra number of AmpC producing isolates could be identified by including isolates resistant to cefoxitin as well as those which are intermediate resistant as screen positive. The results showed that all the AmpC positive isolates of *E. coli* as well as *Klebsiella* spp. to be susceptible to imipenem. This is the first report from India, which has characterized AmpC β -lactamases by PCR and nucleotide sequencing. The study concluded that carbapenems, which include imipenem, ertapenem and meropenem, should be the drugs of choice for treating patients suffering from infections caused by AmpC producing isolates.
- To understand how *L. monocytogenes* switches from a saprophyte to a pathogen, in a study carried out at University of Mysore, investigators have

studied the transcription of its thiol genes. An unbiased transcriptomic study in a listerial species was conducted, which depicted the whole genome transcriptional landscape of *L. monocytogenes* in diverse growth conditions that mainly includes biofilm model system. The results indicated that the thiol disulfide redox metabolism is considered to be the central metabolic network which plays a crucial role in all living systems. It provides a general strategy for donating and accepting electrons and has a molecular mechanism for controlling protein function. It functions to maintain the formation of deoxyribonucleotides for DNA synthesis and for protection of cells against ROS and toxic compounds. Moreover, the study provided evidence that bacterial transcription is more complex than previously anticipated and urges the investigations at a single bacterial level. Such studies will help in understanding the unclear phenotypes insertion mutagenesis.

- Fimbrial proteins are difficult to be purified from wildtype strains of pathogenic *E. coli*. The project complete at Centre for DNA Fingerprinting and Diagnostics, Hyderabad has over-expressed and purified these proteins in presence of their natural chaperone. These subunits can have further potential to be used for raising antibodies to check the intervention in adherence and biofilm formation by pathogenic *E.coli*. These proteins can also be checked for their antigenicity in patients for scoring for potential vaccine candidates.
- Food borne infections due to non-typhoidal *Salmonella* (NTS) serovars are a major concern worldwide. Therefore, genetic level discriminatory (RAPD, ERIC-PCR) methods have been used for epidemiological investigation. A study concluded at College of Fisheries, Mangalore, revealed that composite analysis using RAPD and ERIC-PCR allowed better discrimination than RAPD and ERIC-PCR individually and can serve as a useful epidemiological tool. The adhesion and intracellular survival of seafood associated *Salmonella* isolates was studied using Hela cells. Results suggest that seafood associated *Salmonella* have the ability to adhere and invade epithelial cells but inability to replicate intracellularly, which may account for the findings that certain serovars are involved only in gastrointestinal symptoms and very rarely cause invasive disease.
- A cross sectional epidemiological study to understand the epidemiology of viral hepatitis in primitive tribes of Orissa, Madhya Pradesh/Chhattisgarh (MP/CG) and Jharkhand was undertaken during 2006-2010 to determine the period prevalence of different hepatitis viruses markers, circulating genotypes of HBV, HCV and HBV mutants (HBsAg, anti-HBs, anti HAV-IgG, anti HEV-IgG, anti HCV-IgG, anti-delta virus-IgG, HBV-DNA, HBV genotyping, HBV core and basal core promoter mutants), HCV RNA and genotyping and identification of associated risk factors in primitive tribes of Orissa, Madhya Pradesh/Chhattisgarh and Jharkhand by RMRCT, Jabalpur, RMRC, Bhubneshwar and ICGMER, Kolkata. The study revealed that all primitive tribes belonging to Orissa State have comparatively low

prevalence of anti-HAV antibodies in age group less than 15 yr. However, the HAV exposure was noted to be over 90% in more than 15 yr age groups in all tribes. Anti-HEV prevalence was found to be on higher side in two tribes each of Orissa and MP/CG. The high prevalence of Hepatitis A and E was linked to by improper hand washing practices, open field defecation and unsafe drinking water intake in more than 95% of study participants. In view of high prevalence of the hepatitis infection in the primitive tribal population, different routes of transmission for these infections were looked into in the study population and has shown that the different risk/routes prevalent were varying in the studied tribes i.e. tattooing 7.4 to 33.6%, sharing of razor 7.4 to 30.8%, body piercing 25.6 to 46.7%, history of multiple injection 1.3 to 36.7% and shaving in barber shop 21.4 to 31.8%. The risk factors were analyzed which revealed that body piercing and history of injection were statistically significant for HBV/HCV infection. Circulating Hepatitis B Virus detected as HBV DNA was prevalent in range of 3 -4 % in all the age groups. All the HBV positive samples were of genotype D and none were with precore mutants (all were wild type). The genotype is similar to other part of the country. The prevalence of Anti HCV was high and ranged from 1-14.4% using RTPCR and the HCV RNA was of genotype 1b.

- Studies at Centre of Advanced Research on Liver Diseases were completed (November 2010) at the All India Institute of Medical Sciences, New Delhi. The results of the project suggest that admixture of genotype A and D Hepatitis B virus are more frequently present in HBV related hepatocellular carcinoma. Immunohistochemical studies of liver tissue in case of HEV infection revealed that CD8 and Granzyme positive cells are present indicating that in HEV infection the liver injury may be immune mediated rather than the cytopathic effect of the virus (as believed till date). HEV RNA +ve samples from human (n=124), monkey (n=5) and swine (n=4) in whom genotyping and phylogenetic analysis have been done, revealed that all samples belonged to genotype 1 HEV virus. Earlier studies reported that the Swine HEV is Genotype 4 and human genotype is genotype 1. This raises a possibility of HEV being a zoonotic disease. Patients with pre-existing chronic liver disease are more prone to contract HEV infection than those with normal liver and when such super infection of HEV occurs in patients with underlying chronic liver disease, they rapidly decompensate and die. HEV is hyper endemic in India and therefore patient with chronic liver disease, alcoholics and fatty liver are more prone in India to develop life threatening liver disease due to HEV super infection in such patients.
- To develop expertise in diagnosis of viral diseases, DHR/ICMR plans to establish virology laboratories in all states of the country. These laboratories will be established in a phased manner in already established existing laboratories of Institutes and medical colleges in various parts of the country, by providing infrastructure and training so that adequate facilities for the diagnosis of viral infections are established in all states of the country. Four

Grade I (highest grade) virology laboratories were established in 2009-10 (March 2009). Four more labs – three Grade I labs at Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, SMS Medical College, Jaipur, Field Station of National Institute of Virology at Allappuzha, Kerala and one Grade III lab at Pt. Jawahar Lal Nehru Memorial Medical College, Raipur (Chhattisgarh) are in final stages of approval.

- A study was carried out to understand the problem of Japanese Encephalitis (JE) infections in Regional Medical Research Centre, Dibrugarh where JE has been documented in adults in addition to children. Genotypes circulating in India have been classified as genotype III; however, using the PrM region that has been widely used for genotyping JE virus strains, the study showed genotype I sequences from csf of JE patients in North East. While studying the serological response to JE virus, West Nile (WN) reactive antibodies were also detected and demonstrated for the first time demonstrating WN virus circulation in the region. Virus specific peptides have been standardized which can be used as diagnostic tool for discrimination of JE and WN infection.
- A study on prevalence of dengue /chikungunya virus activity in Regional Medical Research Centre, Dibrugarh, Assam showed presence of IgM antibody against dengue in 34% and chikungunya in 6.6% of suspected patients. Epidemiological investigation of these cases suggests indigenous transmission as there was no history of travel to dengue/chikungunya endemic regions. Entomological investigations showed that *Ae.aegypti* and *Ae.albopictus* are well established in Assam.
- In a study on screening for drug resistant *M.leprae* using mouse foot pad in relapse cases of MB leprosy supported at (5 centers) National JALMA Institute of Leprosy & OMD, Agra, Bombay Leprosy Project, Mumbai, SIH-R & LC, Karigari, GRECALTES, Kolkata and RMLH, Delhi in the country, no resistance has been observed in any of the biopsies by mouse foot pad assay and only two biopsies exhibited single point for fol P gene of dapson. However, surveillance needs to be continued to follow the trends as the programme has now been integrating with General Health services so that remedial measures could be taken, if any.
- In a study on Natural Killer T (NKT) cells among polarized leprosy patients carried out at the All India Institute of Medical Sciences, New Delhi, the frequency of NKT cells was found to be increased in leprosy patients of tuberculoid type (both TT and BT) as compared to lepromatous leprosy (both LL and BL). Even a distinct Th1 and Th2 bias (in terms of cytokine production) has been observed among NKT cells (CD3+ CD161+), both after polyclonal stimulation with PMA as well as specific antigenic stimulation with *M. leprae* whole cell lysate. The frequency of iNKT cells (expressing the invariant chain of TCR) was comparatively higher in the case of BL/LL patients as opposed to BT/TT patients of leprosy, confirming the fact that these iNKT cells are predominantly suppressive in nature. To understand the role of homing receptors in trafficking of these cells chemokine receptor expression profile was also studied and the expression

of major chemokine receptors such as CCR4, CCR5 and CXCR3 on NKT cells of BL/LL leprosy patients was more compared to that of BT/TT. This gives us a lead to the fact that these same NKT cells in BL/LL are immunologically more robust than in BT/TT but even then fail to contain the disease in these patients. Further studies on subsets of iNKT cells as well as its synthetic ligands would need to be undertaken for promising new therapeutic modalities/ vaccine adjuvants for immunomodulation, especially for patients suffering from immunosuppressed form of the disease, i.e., BL/LL.

- A study on prevalence of multiple drug resistant (MDR) tuberculosis in HIV infected individuals supported at PGIMER, Chandigarh showed that of 64 patients who had history of taking ATT, 19 patients (29.6%) were found to have MDR -TB. Among 114 patients who had no history of ATT in past, 12 (10.5%) were found to have primary drug resistance. High prevalence of acquired drug resistance reveals that magnitude of drug resistance problem to a large extent is due to acquired resistance. This emphasizes the importance of high quality DOTS strategy and importance of providers to follow good practices. Prevalence of MDR-TB in HIV infected patents found to be higher (24.1%) than HIV-ve patients (16.1%). Increased incidence of drug resistance in HIV-TB coinfectd patients could be because of delayed diagnosis, malabsorption of anti-TB drugs or more susceptibility to transmission of drug resistance strain in HIV+ve patients.
- A comparative analysis of diffuse large B cell lymphoma in HIV/AIDS vs. in immunocompetent patients from India and in western countries carried out at Tata Memorial Hospital, Mumbai the investigators characterized the histo-pathological nature of lymphomas in the Indian populations especially in AIDS-related lymphomas (ARL). The work involving 221 cases of ARL of India found that plasmablastic, but not diffuse large B cell lymphomas, were commoner in India. This finding was in contrast to what is seen in the USA. The study did not find the incidence of Kaposi's sarcoma-associated herpesvirus (KSHV)-positive lymphomas in India, as reported previously. Likewise, germinal center origin lymphomas are also found to be rare in India.
- A study on rapid identification of mycobacteria to the species level by PCR restriction analysis in clinical samples carried out at Deptt. of Microbiology, V.P. Chest Institute, Delhi, concluded that using PCR restriction fragment length polymorphism (PRA)- DNAPRA (Hsp 65) based methodology 84.5% *M. tuberculosis* was identified in AFB positive smear. The method was very sensitive and could detect 10 organisms / ul. PRA was therefore found to be very simple and reproducible method for early detection of *M. tuberculosis*. Further, a novel restriction enzyme Nru1 was also found using bioinformatics. Using this restriction enzyme a rapid screening assay for differentiation between *M. tuberculosis* and NTM has been established in sputum samples.

Non-Communicable Diseases

Intramural Research

INSTITUTE OF CYTOLOGY AND PREVENTIVE ONCOLOGY, NOIDA

Prevention of cancer is one of the mandates of the Institute. The Institute is adopting multi-disciplinary approach to find the role of causative factors, like environmental, behavioural, genetic as well as their interaction. A main focus is on translation of aetiological factors for prevention and early detection of cancer.

Epidemiological Studies and Screening Activities for Cervical Cancer include,

- 1) Development of cost cutting measures for cytology screening for the resource limited settings;
- 2) bacterial vaginosis and its association with cervical neoplasia;
- 3) Screening for cancer cervix by combined aided visual test in a rural setting at Dadri under which 6000 women been screened during the first year of the project; and
- 4) CARE-HPV vs. other options for screening in a rural community – a demonstration ICPO-PATH Collaborative Project. (The project will test the feasibility of using fast HPV test and its expected superior sensitivity for detecting cervical precancerous and cancerous lesions in a community setting without resorting to high tech laboratories. The project is in the first year of its operation)

In the field of molecular screening for cervical cancer, ICPO has been recognized as a National Referral Centre for HPV and Cervical Cancer Screening. More efficient methods of comprehensive genotyping PGMY-reverse line blot assay have been established. Serological assays for HPV type 16 & 18 have been standardized. This activity will be continued. ICPO has successfully developed multiplex PCR to detect various HPV types. A study is being undertaken for detection of variant HPV types in Indian population for the purpose of developing HPV vaccines under an Indo-German Project. ICPO has been selected as one of the trial sites for HPV vaccine. ICPO is also involved in an Indo- German programme for development of Chimeric DNA – Based Vaccine against Human Papillomavirus type 16.

Studies on therapeutic strategies for HPV infection include, 1) Transcriptional targeting of human papillomavirus by herbal derivatives, with evaluation of antiviral and anticancer properties of crude extract of *B. pinnata* on cervical cancer cells; The different fractions of the extract were tested for its biological activities against cervical cell lines. Fraction 4 was found to have anti-cancer properties. 2) Identification and characterization of stem cells in precancer and cancer of the uterine cervix study is being performed to ascertain whether functionally equivalent stem cells may also be detected in human cervical cancers.

Molecular oncologic studies of cervical cancer include, 1) Role of transcription factor STAT3 in HPV 16 induced cervical carcinogenesis; Inhibition of STAT3 is accompanied by decrease in DNA binding activity of STAT3 transcription factor as well as reduction in phosphorylated STAT3. In addition, selective suppression

of STAT 3 increases the accumulation of P53 and Hytophosphorylation of pRb in Siha cell line. Further it was shown suppression of STAT3 induces apoptosis in cervical cancer cell line. 2) Development of cervical cancer gene data base; The project is newly initiated 3) Cycline D1 Gene Polymorphism in cervical cancer and precancer; SNP at G870A in Cyclin D1 gene showed as a risk factor whereas SNP at G1722C showed a productive role in HPV associated cervical cancer in India. 4) Single nucleotide polymorphism of cytokine genes in human papillomavirus (HPV) mediated cervical cancer; Analysis of preliminary results show that carrier genotype frequencies (CA/AA) are more common in controls (84%) then in cases (59%). Larger sample size is being investigated to reach at final conclusion.

Since there is an urgent global need for harmonization of laboratory assays for HPV DNA diagnostics and serology for HPV surveillance for implementation and monitoring of Vaccine response, ICPO has been recognized as WHO's Regional HPV Reference Laboratory to strengthen HPV-Lab Net programme in South East Asian countries since 2007. More efficient methods of comprehensive genotyping PGMV-reverse line blot assay have been established. In addition, serological assays for HPV type 16 & 18 have been standardized.

Studies on oral cancers include, 1) Field trial of a magnifying device (magnivisualizer, under patenting) for detection of precancerous and early cancerous lesions of oral cavity among chronic tobacco users in NOIDA and Ghaziabad; and 2) Role of HPV in oral carcinogenesis. Uptil now 468 driver and conductors from UP Roadways have been examined with an ordinary torch and magnivisualizer. Magnivisualizer could detect 79 lesions while torch could pick up only 37 oral lesions.

Studies are also being carried out on 1) Role of survivin in H.pylori infection and chemo-resistance in gastric carcinogenesis is being studied as survivin is a novel inhibitor of apoptosis and thus may be playing in gastric malignancy. It is a new initiative in collaboration with Medical College, Allahabad. The study is in progress. 2) Prevalence and molecular characterization of H.pylori genotypes in patients with duodenal ulcers and gastric carcinoma is being carried out in J&K (high risk zone for stomach cancer) and Delhi (low risk zone). A total of 205 endoscopic directed biopsies from J&K Region showed a frequency of 41%, 40%, 49% for gastric cancer, gastric ulcer, non-ulcer dyspepsia. Normal tissue showed a frequency of 29%. In Delhi region, results from 57 biopsies showed a frequency of 23% for cancer, 64% for ulcers and only 5% in normal tissue. The study is in progress.

NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH, AHMEDABAD

Current focus of research is on exposures to heavy metals like cadmium, lead, mercury and arsenic. Health hazards including haemolytic profile of arsenic exposed population in West Bengal have been studied. Bowen's disease and hyperpigmentation with severe Keratosis of palm and sole is illustrated.

Recent NIOH studies at informal work places are handloom and power loom weaving works, garment workers, incense stick (agarbatti) making, iron works, bidi making, fish processing, sheep breeding and



wool works. The weavers (powerloom and handloom) and garment workers were at risk to suffer from health problems such as injury, respiratory symptoms, eye problems and a range of musculo-skeletal disorders. Large numbers of young workers are engaged in stone quarries, glass works, match industries, shoe making, brick works, etc. Current study undertaken among brick making workers shows potential risk to musculo-skeletal stress and strain and exposure to brick kilns emitted toxic fumes containing suspended particulate matter. Study on 209 iron workers, nearly 65% of the iron workers reported chronic fatigue with significant relative risk in the occurrence of respiratory and eye problems. 12 lakh people are involved in sheep farming occupation in Karnataka alone. Nearly 30% of 487 test population had exceeded tolerance limits ($10 \mu\text{g/L}$) for HCH, p,p'-DDT & cyclodiene insecticides in blood samples of sheep related workers. Male and female workers engaged in bidi making at considerable prevalence of pulmonary function impairments due to their exposure to tobacco dust. Predominant complaints among the workers were cough, chronic bronchitis and breathlessness.

The consequence of climate change being rhetoric and vivid, current emphasis is on developing biophysical model to simulate heat exchange phenomena across the multiple body segments and layers, numerically define the human vulnerability to heat stress, predict heat susceptibility limits, apply geo-spatial mapping of heat related effects and disorders, and identify warning and danger zones.

Many chemicals in work environment adversely affect the reproductive and endocrine systems. Research efforts cover epidemiological as well as experimental studies on exposures of pesticides, heavy metals, solvents on male reproductive impairment. Human studies include workers of the printing press, industrial solvents and welding. Toxicity study of CS_2 shows decrease in sperm count and increased sperm shape abnormalities. Study on toxic effect of panmasala with and without tobacco reveals deleterious histological alterations in mouse testis and sperm morphology.

NIOH has been involved in long term national surveillance studies such as monitoring of pesticide residues in food commodities and cancer in north-east India—understanding the role of pesticides and tobacco. The NIOH has embarked on a multicentric



research initiatives exploring toy toxicity due to presence of heavy metals and other compounds.

NATIONAL INSTITUTE FOR RESEARCH IN ENVIRONMENTAL HEALTH, BHOPAL

Recently, after the judgment of Sessions Court, Bhopal on 7th June 2010, Government of India, in the first half of June, 2010, set up a Group of Ministers (GoM) to examine all the issues related to Bhopal Gas Leak Disaster. The Union Cabinet had passed a resolution on 24th June, 2010 directing, inter alia, ICMR to establish a new permanent research centre at Bhopal. The ICMR set up its 31st permanent Research centre “**National Institute for Research in Environmental Health**” at Bhopal, on 11th October, 2010. Even though the immediate goal of this Institute is for health research on people affected by exposure to MIC, and to study the health effects due to pollution of soil and water because of debris left by the Union Carbide Factory after the tragedy of 1984, the long term goals of the Institute shall be to focus on the entire issues of environmental health. The Institute would be focusing on research on several issues of gas-exposed victims particularly respiratory and eye related diseases, kidney diseases, cancer, genetic disorders, congenital disorders, mental and neurological health, women related medical issues and second generation children related medical issues and rehabilitation. This Institute will eventually become a Centre of Excellence to improve environmental health research and play a leading role in tackling environmental health issues. Ultimately this Institute aims at emerging as an apex research institution on environmental health in India.

REGIONAL MEDICAL RESEARCH CENTRE , DIBRUGARH

The focus of research work of RMRC, Dibrugarh continued to be cancers, cardiovascular diseases and hypertension, haemoglobinopathies among the non-communicable diseases and mosquito borne diseases, HIV and drug abuse, trematode infections, among the communicable diseases.

In the field of **cardiovascular diseases**, during 2010 the study on the *Role of ACE insertion deletion gene polymorphisms in the development of ischaemic stroke and acute myocardial infarction* was completed. Smoking was found significantly higher (49.0%) in the AMI patients. Significantly higher concentration of triglycerides (125.9 ± 60.9) was found in the AMI group than the controls (104.7 ± 54.7) or IS (112 ± 56.1) group. ACE gene polymorphism revealed overall higher prevalence of D allele of ACE gene in the young and old age groups. ENOS-4 (ab) gene polymorphism revealed significantly higher prevalence of ENOS-4 (aa) genotype in both AMI and IS.

In the field of **cancers** two studies were completed. In the study which attempted to understand the *role of tobacco in causing cancers in north-east India* the epidemiological information was collected from 2,027 cases of 4 major tobacco related cancers (TRC) viz. oral cavity (n = 735), oesophagus (n = 529), stomach (n = 333) and lung (n = 430). Tobacco chewers with habit of alcohol consumption (OR 1.04; CI 0.29-3.76); and those consuming alcohol along with smoking habit (OR 1.55; CI 0.35-6.81) were found at higher risk of developing oesophageal cancer.

Smokers with habits of tobacco chewing and consuming alcohol (OR 8.24; CI 0.90-75.22) were more prone to develop stomach cancer. Combination of smoking with alcohol consumption (OR 2.39, CI 0.25-22.70); and alcohol consumption with tobacco chewing habit (OR 2.49, CI 0.27-22.49) were important risk factors for lung cancer. The other study investigated the link between exposure to pesticides and genetic variation including polymorphism/mutations associated with ethnic variation in order to understand the *role of pesticides in causing cancers in north-east India*. In this study epidemiological information was collected from 842 cases of 2 major sites of pesticide related cancer (PRC) viz. Breast cancer (n=585) and NHL (n=257). The risk of occurrence of breast cancer among females was higher among farm workers, especially those handling fertilizers (OR 2.94; CI 1.61-5.36), pesticides (OR 2.42; CI 1.31-4.48), other chemicals while working with animals (OR 1.75; CI 1.32 -2.33), as compared to non-farm workers. Illiteracy (OR 2.63; CI 1.34-5.14), smoking in the past (OR 1.89; CI 1.01; alcohol consumption in the past (OR 2.51; CI 1.51-4.18), working in the farm (OR 2.19; CI 1.44-3.33), especially handling fertilizers (OR 2.84; CI 1.57-5.12) emerged as significant risk factors for the development of NHL cancer.

In **Trematode/Cestode infections** the study new foci of human paragonimiasis were found for the first time in Tezpur and Karbi Anglong districts of Assam. Cumulative prevalence of paragonimiasis through community and hospital based surveys in the states of Assam, Meghalaya, Arunachal Pradesh and Mizoram was found to be 1.9%. *Berytelphusa cunicularis* was incriminated as a new crab host for *Paragonimus heterotremus* infection from Sonitpur district of Assam. **Whole mitochondrial genome of *P. Westermani* genotype 1 from Arunachal Pradesh was sequenced for the first time.** In another study fishes were found to harbour at least 7 medically important species of trematode metacercariae in Assam.

Malaria: *Study on Ecological succession of anophelines* revealed presence of 36 species of mosquitoes belonging to 9 genera in the state of Arunachal Pradesh whereas 19 species in 5 genera were detected from Nagaland state. Of these *An.dirus* complex is the main forest vector. *Sibling species profiling of Anopheles dirus complex vector mosquitoes* revealed *Anopheles baimaii* with evidence of presence of species X of China (occurring only in NC Hills district of Assam). *Molecular and morphotaxonomic status of Anopheles philippinensis/Anopheles nivipes* mapped the distribution of these two morphologically similar species in the 6 NE states and incriminated *An. nivipes* as the human malaria vector in Assam-Nagaland border area. *Concurrent gene flow in An. baimaii* in north-east India and Myanmar is being analyzed using a total of 4 nuclear markers viz. *ckl* (casein kinase I), *pgd* (phosphogluconate dehydrogenase), *trx* (thioredoxin reductase) and *enol* (enolase).

Mosquito borne viral diseases: Epidemic of dengue haemorrhagic fever with deaths from the state of Manipur along with detection of mixed infection of two serotypes of dengue was detected in NE. Further, cases of chingungunya and west Nile virus were detected for the first time from Assam.

Study on other viral diseases: Measles showed two circulating genotypes i.e. D4 and D8 of Indian origin from north-east India. The investigation on the prevalence of *occult Hepatitis B infection* in Lower Dibang Valley district of

Arunachal Pradesh found overall HBsAg positivity of 6.9% and 9.5% prevalence of occult infection.

Other than the regular research activities the Centre continue to extend the swine flu diagnostic facility to the north-eastern states. A Public consultation Workshop on Guide lines for Stem Cell Research and Therapy (2007) for the north-eastern region was organized by the Centre during the year. Further, during the year a total of 22 research publications came out from the Centre with average impact factor of 2.1.

DESERT MEDICINE RESEARCH CENTRE, JODHPUR

Desert Medicine Research Centre (DMRC) continued its endeavours in contributing for the improvisation of health of desert people through research, translation of research into public health measures, interventional studies and by providing referral diagnostic support to the state health department.

A fully equipped BSL-2 level laboratory has been established at DMRC, Jodhpur for providing reference diagnostic support to the state health department in molecular diagnosis of H1N1 viruses. In addition, the laboratory is also serving to diagnose dengue virus in human blood samples and in mosquito samples as referred by the state health department. The proteomic and genomic studies on human and virus samples are in progress to report the important host-pathogen relationship studies crucial in controlling prospective outbreaks of dengue and Swine flu. Having studied about 2000 human swab samples for presence of H1N1 viral genes, during outbreak in 2009-10, the laboratory has contributed significantly for control of morbidity and mortality by supporting state health department in molecular diagnosis of Swine flu during pandemic situation.

As a part of translational research, DMRC launched a collaborative programme with state Health Department for elimination of possible dengue infected mosquito foci in Jodhpur town during February, 2008. The subsequent follow up studies made during the years 2009 and 2010 showed almost negligible cases of dengue in the town. However, in other dengue endemic districts such as Udaipur and Ajmer (control towns) number of cases were reported during this period. Impact of control measures launched against dengue yielded almost complete control over dengue till the year 2010. Based on these results, a comprehensive translational research project of development of ICMR-DMRC module of dengue control for Rajasthan, has been developed.

The Centre had earlier succeeded in extracting larvicidal substance from a desert shrub, *Calotropis procera* to control larval forms of dengue vectors. The insecticidal component of latex of *Calotropis procera* is being tested at large scale for its public health utility.



Fig. Glimpses of research work at Virological laboratory, DMRC, Jodhpur

Extramural Research in Non-communicable Diseases

ONCOLOGY

The National Cancer Registry Programme (NCRP) commenced in 1982, with the objectives of generating reliable data on the magnitude and patterns of cancer; undertaking epidemiologic studies in the form of case control or cohort studies based on observations of registry data; providing research base for developing appropriate strategies to aid in National Cancer Control Programme; and developing human resource in cancer registration and epidemiology. As of October 2010 there are 24 Population Based Cancer Registries (PBCRs)- Ahmedabad rural, Ahmedabad urban, Aurangabad, Bangalore, Barshi, Bhopal, Chennai, Delhi, Dibrugarh, Guwahati, Kolkata, Kollam, Imphal, Meghalaya, Mizoram, Mumbai, Nagpur, Pune, Sikkim, Silchar, Tripura, Trivandrum and Wardha and 6 Hospital Based Cancer Registries (HBCR)- Bangalore, Chennai, Delhi, Dibrugarh, Mumbai, Trivandrum under the NCRP network. Besides, there are 16 institutions (including the 6 HBCRs) that are participating in the patterns of care and survival studies (on cancer breast, cervix and head and neck cancers) and nine other centres in the North East that are participating in development of an atlas of cancers in the North East. In all, there are 45 institutions sending 89 sets of raw data each year to the Coordinating Unit of NCRP at Bangalore that guides, directs and reports. During 2006-2008, in males, the age adjusted incidence rate (AAR) varied from 53.0 per 100,000 in the rural PBCR at Barshi to 239.2 per 100,000 in Aizawl district of Mizoram state. Among females, the AAR varied from 49.9 per 100,000 in Ahmedabad rural district to 197.4 per 100,000 in Aizawl district. The proportion of Tobacco Related Cancers (TRCs) among males varied from 33.24% in Barshi to 59.2% in Dibrugarh. Among females, the relative proportion varies from 9.8% in Thiruvananthapuram to 26.3% in Dibrugarh district. A study on trends in incidence rates over time from the year 1982 to 2005 was completed. Among males, cancers of the prostate, colon, rectum and liver showed a statistically significant increase in incidence rates. Among women, cancers of the breast, corpus uteri, ovary, thyroid, gallbladder and lung have shown a rise. Cancer cervix recorded a decline in incidence rates across all registries including the rural registry at Barshi. The study on patterns of care and survival studies is being done for three sites of cancer namely Cancer breast, cervix and head and neck in 16 centres including 5 HBCRs across the country. The number of cases on which data has been received from these centres is, cancer breast: 4235; cancer cervix: 5162; and head and neck cancers: 9196.

The North Eastern cancer atlas project aimed at obtaining an overview of patterns of cancer in the state of Arunachal Pradesh, Meghalaya, Nagaland and Tripura as well as other districts in Assam. After initiation of population based cancer registries in Meghalaya, Tripura and Nagaland, the study is now restricted to Arunachal Pradesh. The second report for the combined years 2007 and 2008 gives an idea of the prevailing patterns of cancer by district in these areas. Stomach and Oesophagus cancer in Arunachal Pradesh show relatively high incidence rates compared to the rates published in the Population Based Cancer Registries of the North East as well as in the rest of the country.

A project aimed at **screening for cancers of cervix, breast and oral cavity**, was initiated in three districts of Himachal Pradesh. The project was handed over to

the state government, after developing and providing the model to the State health services. Intervention was continued by the State health infrastructure using the trained manpower and professional for reporting.

A task force on review of cancer management guidelines has been initiated to review and understand the appropriateness of western literature on management of common cancers under Indian conditions. Guidelines for buccal mucosa cancer, stomach and cervix have been finalized.

The study on **establishment of breast cancer cell line**, studies on expression of epithelial markers, tumorigenicity in nude mice, and ultrastructure were carried out on primary cultures established from 31 breast tumour tissues. The study on genetic clinical and epidemiological factors of breast cancer in rural and urban area, was initiated at ICPO, Noida; IOP, Delhi; AIIMS, Delhi; RCC, Thiruvananthapuram and RMRC, Dibrugarh.

ICMR is collaborating with PATH, on a project funded by the Bill & Melinda Gates Foundation to assess the preparedness and feasibility of state health services for possible introduction of HPV vaccination. The formative study (first phase) carried out interviews and focused group discussions to develop strategies for this purpose. The demonstration project (second phase) immunized about 24,000 girls in Andhra Pradesh and Gujarat.

The ICMR-Merck study on clinical trials on HPV vaccine was initiated at Calcutta Medical College, Kolkata; M.S. Ramaiah Medical College, Bangalore; and Government Medical College, Nagpur. The study is to be carried out on 600 married females. The projects aims at finding out the sero-conversion rates to each component of the vaccine (type 6,11,16 & 18) at month 7, 24 and 36. Toxicity and adverse effects due to vaccine would also be monitored. 112 Subjects were enrolled in the study.

Workshops were held to identify areas of mutual interest on collaborative cancer research with University of Minnesota and European Union.

CARDIOVASCULAR DISEASES

The key areas of work undertaken by the Division in the field of Cardiovascular Diseases include community control of rheumatic fever/rheumatic heart disease, blood pressure normograms in 5 to 14 years age group school children, foetal origin of heart diseases, management of acute coronary events (MACE) registries, school based interventions to reduce cardiovascular risk factors in children, Biobank linked to MACE registries and biomarkers for CVD and diabetes.

Jai Vigyan Mission Mode Project on “Community Control of RF/RHD” has four arms including epidemiology, molecular typing of rheumatogenic strains, RF/RHD registries and research towards development of a vaccine against streptococci. A model of surveillance provided by community-based registries by four nodal registries is being replicated in other parts of the country. The epidemiological component has been completed at a centre in North India (PGIMER, Chandigarh) and another in South India (CMC, Vellore). A survey in school children (5-14 years) under registry component and a passive population based registry has been undertaken by Chandigarh, Vellore and Kochi and Indore. Satellite registry at Mumbai and another one covering a tribal population Wayanad under Kochi nodal registry; Shimla, Jammu, Jodhpur under Chandigarh nodal centre and; Dibrugarh under Vellore nodal centre have completed

data collection. The data from these registries indicate low prevalence of RF RHD in these parts of the country. The Group A Streptococcus (GAS) strains circulating in the community collected by the satellite registries from children with symptomatic and asymptomatic sore throat were subjected to molecular typing. The emm typing of GAS strains indicates the heterogeneity of the strains circulating in the community. A significant development of the project has been the up scaling of this project in four districts by Himachal Pradesh Government under NRHM.

A **study on blood pressure**, height and weight measurements was initiated in children aged 5 to 14 years as part of Jai Vigyan project on RF/RHD. The six centres Chandigarh, Vellore, Kochi, Indore, Wayanad and Shimla have collected data on anthropometric and blood pressure measurements in around 1,00,000 school-children. The satellite registries at Jammu, Dibrugarh, Mumbai and Dibrugarh are undertaking this study in 10,000 children. The data will provide countrywide norms for blood pressure and BMI in school-children.

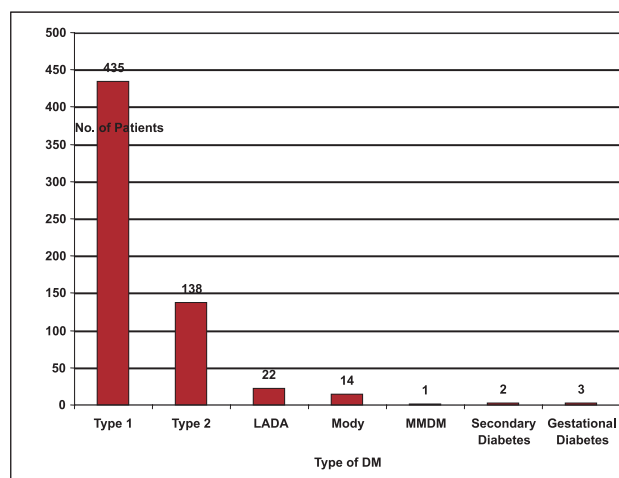
In the area of **Foetal Origin of CAD** a study titled "Relation of candidate gene variants regulating triglyceride metabolism to serial changes in childhood body mass index and coronary artery disease risk factors in young adulthood" was initiated in September 2005. The multicentric project aims to determine the frequency of polymorphisms in APOA-V gene, hepatic lipase and PPAR γ in subjects of Delhi cohort and their relation to changes in body mass index (at different stages of growth). Association between above mentioned gene variants and development of risk factors for coronary artery disease (LDL sub fractions, triglycerides, cholesterol, insulin, impaired glucose tolerance) in adults is being studied. A highly significant positive linear association between APOA-V gene (-1131T>C) and fasting serum triglyceride level has been observed in this study.

A feasibility study for **Web Based Management for Acute Coronary Events** (MACE) Registry network has been initiated in 15 centres around the country in March 2010. Phase I objectives are to establish multicentric hospital based registry of acute coronary events and to develop an efficient electronic data management system amenable to be an ultimately web based system and test its feasibility. The Clinical Coordinating Centre at St John's, Bangalore is responsible for feasibility study at 15 centres. Data collection using e CRF is ongoing.

DIABETES

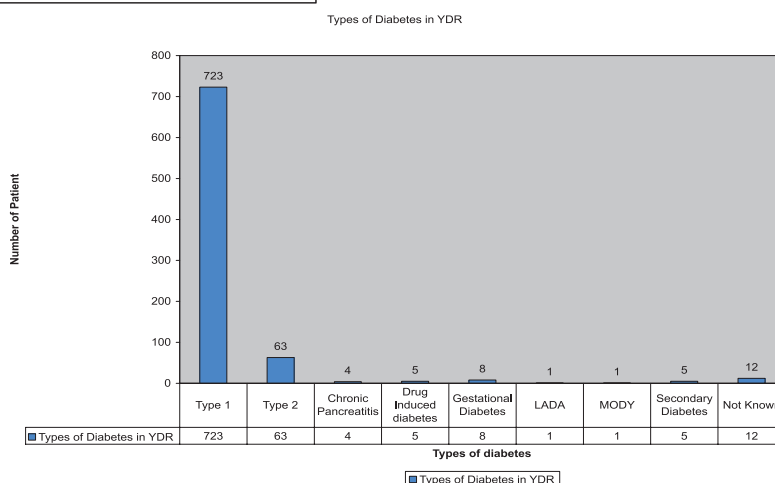
The ICMR's "Advanced Centre for Genomics in Type 2 Diabetes Mellitus" aims to undertake both research and training component. For research component, two proposals entitled, "Study of genes related to maturity onset diabetes of the young (MODY) and early onset diabetes," and "Study of genes implicated in ion channel dysfunction in diabetes," are underway so as to determine the prevalence of MODY in different regions of India and screen the known gene variants in unrelated diabetic subjects and normal glucose tolerant subjects so as to find the association with the disease. One of the novel mutations Arg263His, co-segregated in a family has been discovered and pedigree analysis is underway in 30 individuals. The training is being imparted to students, educators, health professionals and hands on training workshops are being conducted every year with participation of eminent faculty across the country. Till now, approximately 150 young researches are trained in modern techniques of genomics and genetics.

The multicentric task force project entitled “Registry of People with Diabetes in India with Young Age at Onset,” is continuing at nine centres with aim to understand magnitude of problem, disease pattern or types including the geographic variation and incidence and prevalence rate of complications. The training workshops are held at the Centres at a regular interval for issues related with reporting centres. The data

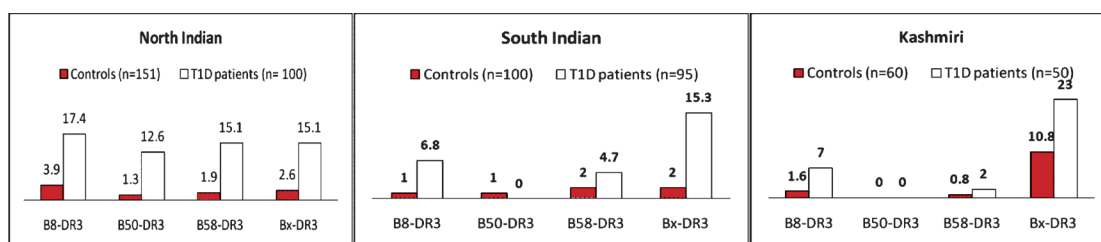


set of approximately 6000 subjects (age ≤ 25 years) is available with information on varied parameters such as duration and type of disease, treatment pattern, family history, complications, immunology profile, etc. Most common type reported so far is type 1 diabetes followed by type 2 diabetes and Maturity Onset Diabetes of the Young (MODY) and most common complications are retinopathy and neuropathy.

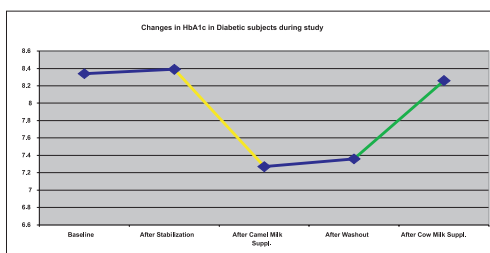
The Task Force Project on Genomics of Type 1 Diabetes is ongoing at three centres viz Delhi, Chennai and Kashmir with the aim of undertaking genomic characterization of multiple autoimmune favoring HLA-DR3+ve haplotypes in type 1 diabetes (T1D) in these ethnic groups of India. It also aims to evaluate levels of auto-antibodies present at the age of onset in these population groups. The findings of the study indicated that HLA Distribution pattern was found to be different among North and South Indian Population.



The preliminary studies on the effect of camel milk in type 1 diabetes in population of north-west Rajasthan (Raika community) indicated its important role in glycemic control, lipid profile and quality of life. Under the Task Force project on “Camel Milk and Diabetes,” two projects viz effect of camel milk on glucose metabolism in adults and the hypoglycemic/insulin like activity in camel milk using an animal model was completed in collaboration with National Institute of Nutrition, Hyderabad and SP Medical College, Bikaner. The findings of pilot study have been able to give lead regarding the effect of camel milk on biochemical parameters such as blood glucose, insulin, HbA1c, etc. The multicentric project on Genetic Basis of Resistance to Diabetes in Raika community aims to understand the genetic basis of resistance to Diabetes in Raika community.



The Task Force project on ICMR- Indian National Diabetes Study-Phase I," aims to understand prevalence of diabetes and pre-diabetes along with its association with the genetic aspects is about to complete and data analysis is in the process at three states and one Union Territory. The preliminary findings indicate the percentage prevalence ranges from 2.8-6.6% in rural and 9.1-13% in urban settings. Based on experience of phase-I, it is proposed to expand the study including more centres during phase-II.



MENTAL HEALTH

Current research in mental health has focused on the mental health problems in urban areas and study of post-disaster situations for the mental health needs and various service models available during such conditions.

A multicentric project on **urban mental health problems and service needs** has been completed at Delhi, Chennai and Lucknow. The objectives of the task force were to assess mental health problems and service needs and collate data related to existing mental health services in the selected cities. The qualitative data has been analysed to find out mental health service needs and gaps. The prevalence rates of psychiatric morbidity in total population was 59 per thousand for all mental health problems (comparable to the estimates made by the meta-analysis) and 48 per thousand for Common Mental Disorders (CMDs). The prevalence rate of psychiatric morbidity was found as 86 per thousand in lower SES, 56 per thousand in middle SES and 34 per thousand in higher SES. Depression was found to be the most common diagnosis in all the three sites.

Continuing its research activities in post-disaster situations, ICMR initiated a task force study on **Mental Health service needs and service delivery models in the disaster (earthquakes) affected population in Gujarat** at three centres viz Bhuj Ahmedabad and Rajkot following Gujarat Earthquake. The prevalence of psychiatric morbidity was found higher viz.. 61.35/1000 and 67.04/1000 in affected group (as compared to 22.29/1000 and 22.93/1000 in control group) at Ahmedabad and Rajkot centres respectively. The most prevalent psychiatric morbidity were the depressive disorders and recurrent depressive disorders, followed by anxiety disorders and dissociative (conversion) disorder and somatoform disorders in both (affected and control) groups. Mental health morbidity and psychological symptoms were higher in females as compared to males.

The study on **Mental health needs assessment and service delivery models in Tsunami affected population of coastal Tamil Nadu** has been completed at

Chennai and Nagapattinam centres. The Chennai centre has collected data from children (6-16 years). The data shows that majority of children (93.6%) showed Aggression and Dependency (81%) in their drawings. About 60% of them displayed anxiety, assaultiveness and feelings of insecurity. The commonest behavioral problems observed were bedwetting, nail biting, and temper tantrums. The Nagapattinam Centre has screened 1328 individuals using General Health Questionnaire (GHQ) and were further assessed for psychiatric diagnosis. Out of this sample, 145 were found to be positive based on the Psychiatrist's interview. Clinical diagnosis was made out in 65 of the 145 GHQ+. The trend of data shows that psychiatric morbidity in the adult population is less compared to the pilot study. Compared to psychiatric morbidity prevalence of 50% immediately after Tsunami, the prevalence rate now (five years after disaster) was observed to be only 4.9%. Post-Traumatic Stress Disorder (PTSD) continues to be rare. The clinical diagnosis made predominantly was mild depression. In addition, 75 children were studied and 7 were clinically diagnosed. Morbidity amongst Tsunami orphans and children in regular orphanage was not found to be any different (12.5% vs 16.25%).

NEUROLOGICAL SCIENCES

A prospective longitudinal study of stroke in Kolkata has been completed. The objectives of this project were to determine the natural course and outcome of the stroke patients and to measure the impact of economic and psychological burden on the family members of stroke sufferers. It is a community-based, two-stage, door-to-door study in an urban population in the city of Kolkata, selected through stratified random sampling. The prevalence of stroke-dementia increased in this cohort of stroke survivors from 12.71% to 21.54% after repeated assessments. Approximately one-third stroke survivors suffer from depression and post stroke depression is found to be associated with age, age at first stroke, educational level and gender.

An ICMR- EU workshop in the area of pediatric neurology was held from 18th to 19th Feb 2010. The experts from India and European Union identified "Creating instruments for experimental therapy for pediatric neurodegenerative disorders by clinical and molecular analysis" as the area for collaborative projects.

NON-COMMUNICABLE DISEASE SURVEILLANCE

The ICMR was identified by the Ministry of Health and Family Welfare, Govt. of India to coordinate the implementation of the Non-communicable Disease Risk Factor surveys under the Integrated Disease Surveillance Project (IDSP) in 29 States/UTs over a period of 3 years beginning in 2007. The 1st Phase of the surveys was done in 7 States (Kerala, Tamil Nadu, Mizoram, Uttaranchal, Maharashtra, Madhya Pradesh, Andhra Pradesh) and their reports have been disseminated at the national level on 15th December 2010 with key stakeholders. State level dissemination is underway.

The community based surveys were conducted in the urban and rural population aged 15-64 to provide data on NCD risk factors (alcohol, tobacco, diet, physical activity, blood pressure, body mass index) using two types of questionnaires—one at household level and another for individual level respondent. A total of 5000

households were contacted in urban and rural area of each of the seven states. The overall household response for the survey ranged from 88.6% in Kerala to 99.9% in Madhya Pradesh and Maharashtra. The percentage of current daily smokers varied between a low 9% in Maharashtra and high 42% in Mizoram. The average age of onset of smoking ranged from 17 years in Mizoram to 20 years in Maharashtra, Kerala and Tamil Nadu and in rest of the states it was 19 years. In Andhra Pradesh, Kerala, Tamil Nadu and Uttarakhand, 4-12% respondents were current daily users of smokeless tobacco. In rest of the states, it ranged from 32-48%. The mean age of initiation of alcohol consumption regularly in the age group 15-34 years was 20-22 years in all the seven states. The present survey found that the mean time spent on work related physical activity ranged from a low 128 minutes per day in Maharashtra to a high 293 minutes per day in Madhya Pradesh. By categories of hypertension, 17-21% of the respondents in all the states were found in stage I or stage II hypertension. Blood glucose estimation of the respondents was not done.

The grade I overweight was only 7% in Madhya Pradesh closely followed by 9% in Mizoram, 11% in Uttarakhand and Maharashtra where as it was 15% in Andhra Pradesh, 18% in Tamil Nadu and 22% in Kerala. The obesity of grade 2 and above was around 5% in Tamil Nadu, Andhra Pradesh and Kerala and it was around 2 to 3% in rest of the states.

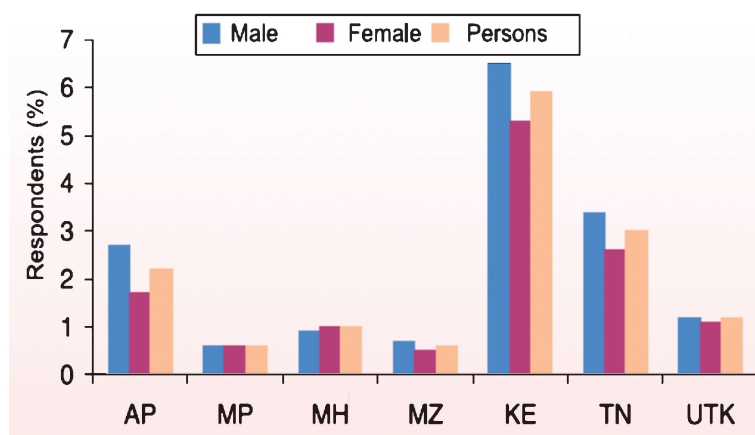


Fig: The proportion of population who reported being diagnosed with raised blood glucose by a health professional

ORTHOPAEDICS & DISABILITY PREVENTION

Musculoskeletal conditions are extremely common more so with the advancing age Council initiated a multi centric study with the aim to assess its magnitude in the Indian population in both rural and urban area, across three centres, with a focus on osteoarthritis, rheumatoid arthritis and spinal disorders. The study is being carried out at three centres viz..Delhi, Jodhpur, Dibrugarh. The screening of 10,000 study population at each centre was completed. The trend of data shows that while the Delhi Centre is reporting 8% prevalence, Dibrugarh is reporting 20% prevalence as against 16-18% prevalence of musculo-skeletal problems at Jodhpur.

GERIATRICS

ICMR has been supporting research that has focused on the health problems of the elderly. A task force project was conducted to assess the influence of social support networks and the economic factors on the functional status of the elderly. Coping

strategies with relation to health and financial problems were also studied. Thousand people aged 60 years and above from two selected localities of North and South Delhi were assessed self-rated for their personal details, education and access to social support systems, self-rated physical and mental health, functional status for activities of daily living, social health, life satisfaction, coping strategies and leisure time activities using standardized tools. Findings reveal that most of the participants were illiterate and non-working. Hypertension, dyspepsia, constipation, depression, osteoporosis were most frequent health problems. Use of hearing aid, walking aid and denture were very limited. Cognitive impairment was found in large number of subjects (69%). Majority (85%) of urban older people were found to be functional with regards to basic activities of daily living, where as 60% of them have some degree of limitation in incremental or intermediate activities of daily living. Self rated physical and mental health deteriorated with advancing age. Increasing age and poorer socioeconomic status adversely affect physical functioning. Burden of ill health, depression and cognitive impairment adversely affect physical functioning. Life satisfaction, leisure time activity, absence of depression and quality of working life positively affects behavioral functional status. The Council has initiated efforts to set up an Institute for Research in Ageing, which would be a multidisciplinary, and multispeciality centre. The broad mandate of the Institute will be to promote collaborative, applied and basic gerontological research, to develop innovative programs of interdisciplinary gerontological education and provide state-of-the-art information to policy makers, program managers, service providers, clinicians, and the general public.

ORAL HEALTH

A joint ICMR-MMU-DCI workshop on *Research Methodology for Oral Health Researchers* for oral health researchers was held on 24th to 25th August at Mullana, Haryana. The similar activity was done at Modern Dental College, Indore, Madhya Pradesh. The major objective of the workshops was to train the middle level faculty members of different dental colleges regarding developing the good research protocol. The interactive sessions provided the methodological background for training the participants. How to ask a good research question, what research design to use, what methods to use, and how to analyze the data were the components of the workshop. Dental Professionals from 12 Dental Institutions from the states of Haryana, Himachal Pradesh, Madhya Pradesh, Uttar Pradesh, Andhra Pradesh, New Delhi etc. attended the workshop

NORTH-EAST INITIATIVES

During the year 2010 eight extra-mural projects have been initiated to address the major health issues of concern to this region, nearly 90 ongoing projects at various institutions were continued. Studies on HIV, angiotensin converting enzyme (ACE) gene polymorphism and prevalence of JE, West Nile and chikungunya virus have been completed. The overall prevalence of HSV-2 in pregnant women was IgG (ELISA) positives was 8.7%, RPR reactive 1.5% and PCR positive 4.6% . ACE gene polymorphism revealed overall higher prevalence of D allele of ACE gene in the extremes of age groups (younger, up to 40 years and older, > 60 years). ENOS-4 (ab) gene polymorphism revealed significantly higher prevalence of ENOS-4 (aa)

genotype in both AMI and ischaemic stroke cases. A study on the prevalence of paragonimiasis in people living in haemoptysis endemic area in the state of Arunachal Pradesh hill tribes has also been completed. As a result paragonimiasis has now been recognized as one of the major diseases in cases of failed anti-tuberculosis treatment in Arunachal Pradesh.

The areas addressed in each of the states is as follows:

- Assam – paragonimiasis, malaria, cancer registries, esophageal cancer, HIV/AIDS, HT & CHD, filaria, mycobacteria, Thalassemia, JE, medicinal plants, nutrition and Drug Abuse
- Arunachal Pradesh– Drug resistant malaria, medicinal plants, Hepatitis, Cancer registry and paragonimiasis
- Mizoram – CHD & HT, Cancer registry, stomach cancer, HIV/AIDS and substance abuse, malaria
- Meghalaya – cancer registry, nutrition, medicinal plants, breast and oral cancer
- Manipur – cancer, HIV/AIDS and Drug abuse, Medicinal plants
- Sikkim – Cancer registries, other cancer studies
- Nagaland – Cancer registries, other cancer studies, malaria
- Tripura – Cancer registry, other cancer studies

New initiatives to boost research in the NE Region have been initiated by the Council.

For establishing new research units to provide a boost to research activities in all the 8 states Principals of all the medical colleges in the NE Region have been informed and letter of intent has been obtained from Tripura, Assam(2), Meghalaya, Manipur. Other states are in the process of providing the same. An MOU has also been drafted for this purpose and sent to respective states for comments.

For seed money grant to initiate research: Sixty four proposals have been screened and being finalized.

ENVIRONMENTAL AND OCCUPATIONAL HEALTH

Indoor air pollution is being implicated as an important factor in childhood morbidity. Therefore Council has set up a **Centre for Advanced Research on Indoor Air Pollution** at Sri Ramachandra University, Chennai. The main focus is to study the effects of Indoor Air pollution on mother-child cohort and an endovascular cohort. Training to increase manpower would also be a major activity.

Under the Indo-US Joint Program on Environment and Occupational Health 12 collaborative projects have been initiated. Many workshops were organized as part of the collaborative activities on varied topics which included climate change, Indoor Air pollution and Biomarkers in public health. The Hazardous Substance Environment system (HSES) was established at National Institute of Occupational

Health(NIOH), Ahmedabad, which helps in regular monitoring of hazardous substances in the population on the basis of technique established at Centre for Disease Control (CDC), Atlanta.

ASTHMA

The 12-centre study on prevalence and aetiology of asthma using a standardized questionnaire, surveyed a total of 169575 individuals above 15 years of age (60764 urban and 108811 rural; 85105 men and 84470 women). In all, 8990 individuals (5.3%) had a first degree relative with history suggestive of bronchial asthma, more commonly in men – the male: female ratio was 1.9 for the rural and 1.2 for urban subject. The pooled prevalence of asthma (using the questionnaire definition) across the twelve centres was 2.05% (2.28% in rural and 1.64% in urban areas). There were wide variations across the different centres. Prevalence was quite low in urban Secunderabad (0.37%) and rural Mumbai (0.74%), and relatively high at Kolkata (rural 4.52% and urban 5.52%) and rural Trivandrum (4.45%). Multiple regression models revealed that study population at individual centres, age, family history of asthma and tobacco smoking were consistently associated with higher odds of asthma.

Reproductive Health

Intramural Research

NATIONAL INSTITUTE FOR RESEARCH IN REPRODUCTIVE HEALTH, MUMBAI

The Institute has a mission to work towards better reproductive health for people in different stages of their life through research, education, outreach and service.

Institute has been pursuing research fertility regulation, male and female infertility with special emphasis on azoospermia, asthenozoospermia, testicular failure, unexplained infertility, polycystic ovarian syndrome, premature ovarian failure, endometriosis; reproductive tract infections including HIV/ AIDs, microbicides, medical termination of pregnancy (MTP), pregnancy associated disorders, osteoporosis and menopause.

Fertility regulation

The Institute conducted a study on the acceptability and continuation rate of 2 monthly injectable contraceptive-Norethisterone Enanthate (NET-EN). The results based on 17,268 women months of injection use were encouraging and useful to the policy makers/programme managers to work out the logistics for feasibility of introducing injectable contraceptives in National Family Welfare Programme (NFWP). Bone mass density (BMD) among two monthly injectable contraceptive users evaluated by DEXA revealed no significant difference in mean BMD among injection users. The results paved the way for extramural studies on pre-programme introduction of Cyclofem and Noristerat contraceptives through district hospitals and NGO clinics.

Studies were undertaken to optimize the dosage regimen of Mifepristone and Misoprostol combination for termination of first trimester pregnancies and thereby to decrease the side-effects and improve the efficacy of medical abortion. Efficacy of the medical abortion was found to decrease with increase in side-effects notably abdominal pain with increase in the gestational age. This suggested that dosage regimens for 8 and 9 weeks of gestation may be different than that for 7 weeks of gestation. This indicated that the optimizing dosage regimens in women with more than 7 weeks of gestation may increase the efficacy of medical abortion. Results also highlight the relevance of intensive IEC for effective use of family planning methods to decrease unplanned pregnancies.

Activities pertaining to increasing male involvement in reproductive health through clinic services, counseling, and community have been sustained by providing technical support and guidance to the Municipal Corporation of Greater Mumbai (MCGM) health posts.

Human Sperm Antigen (80kDa HSA) and human Seminal Plasma Inhibin (hSPI) have been shown to be promising candidates for development of anti-fertility vaccine. Active/passive immunization with immunodominant peptide of 80kDa HSA and R-17 peptide of hSPI induced immunological infertility in rats, rabbits and marmosets. hSPI and its synthetic peptides appear to be a potential candidate for the development of male contraceptive vaccine.

Infertility and reproductive disorders

Studies were undertaken to identify biomarkers of premature ovarian failure (POF) caused by autoimmunity. Several molecular and cellular targets of auto antibodies have been identified in POF and women having repeated IVF-ET failures. A 90kDa protein (HSP90) was found to be a major autoimmune target. Using *in silico* approach, ten putative immunogenic epitopes of HSP90 were identified and peptide ELISA has been established. Genetic mutations have also been identified in women with POF.

Genes related to hyperandrogenemia, insulin resistance and obesity were screened in women with polycystic ovarian syndrome (PCOS). Variants of these genes and their association with PCOS associated traits have been identified. Follicular fluid of PCOS women is also being screened with an aim to identify the key factors involved in the pathogenesis of PCOS and to utilize these proteins for therapeutic/ diagnostics purpose.

Anti endometrial antibodies (IgM and IgG) were detected in the sera of women with endometriosis. The immunodominant peptides of these targets were identified using bioinformatics approach and peptide ELISA was established. Using differential proteomics, 11 ectopic endometrium associated proteins have also been identified. Studies are underway to determine their role in pathogenesis of endometriosis.

Congenital adrenal hyperplasia (CAH) is the most common cause of ambiguous genitalia. Ninety five percent of the cases are known to be caused due to mutations in the 21 hydroxylase gene (*CYP21*). An accurate diagnostic tool based on PCR sequencing of *CYP21* has been developed to identify common mutations in CAH and thereby accurately diagnose CAH. Availability of this test would also aid in clarifying the ambiguous cases.

The entire extracellular domain of follicular stimulating hormone (FSH) receptor was systematically studied with an aim to identify regions involved in hormone binding and signal transduction. Structural and functional determinants have been identified. The knowledge of the residues involved in the hormone-receptor interaction would help in designing agonists and antagonists, which could find important applications as fertility regulating agents.

Studies on PSP94 and prostate cancer cell lines revealed that PSP94 and ITS interacting partner CRISP -3 exhibit growth inhibitory effect in a cell line dependent manner.

Infertility in men is a great cause of concern worldwide due to defects in spermatogenesis. At the institute for the first time c-kit transgenic mice of male infertility has been developed, but the mice could not survive for longer period. Attempts are under progress to modify the c-kit construct for low transgene expression and copy number.

Two in-house derived human embryonic (hES) cell lines KIND-1 and KIND-2 were studied for their differentiation propensity using molecular & cell based approaches. Based on the results, KIND-1 is being used for differentiation into pancreatic progenitors and KIND-2 into cardiomyocytes to address major disease burden of cardiovascular disease & diabetes in the country in near future.

Research on adult testicular and ovarian tissue has led to the identification of a novel pluripotent stem cells (PSCs). Studies are also being planned to evaluate the presence

of these PSCs in infertile men and women with ovarian failure due to childhood cancer.

Osteoporosis

Osteoporosis, being a silent epidemic is of great concern in India due to increasing ageing population. Studies revealed that the peak bone mineral density (BMD) norms developed from the data of healthy young men and women from high income group was less as compared to that of the Caucasian-BMD at forearm was comparatively less in men while the BMD at spine and hip were comparatively higher in men as compared to women.

Studies also showed that bio available estradiol (Bio-E2) was an independent predictor of BMD in men. Genetic studies reveal a strong association of minor alleles (polymorphic) of COLIA1 gene polymorphism with low BMD in men.

Biomarkers are early predictors of bone loss. Norms for bone turnover markers namely osteocalcin, bone specific alkaline phosphatase, C-terminal crosslinking telopeptide of type 1 collagen and deoxypyridinol were established for Indian women in relation to BMD measurements. Indigenous ELISA for osteocalcin has also been developed.

Sexually transmitted infections/HIV

A high priority is being given to pursue research programmes such as development of simple, cost-effective and sensitive diagnostics for RTIs. In-house tests have been developed for diagnosis of a *Chlamydia trachomatis* and *Human papillomavirus* (HPV). Genotyping of high risk HPV 16, 18 and low risk HPV 6 and 11 has also been standardized. These tests are being evaluated for screening of clinic based as well as community based population under various research programmes.

Factors which determine resistance /susceptibility to disease caused by RTI/HIV are being investigated . Studies conducted to determine HLA and their associations with serodiscordant couples as well as mother to child HIV transmission revealed the association of specific alleles with sero positivity and negativity.

Several key molecules having anti-bacterial and anti-HIV activities have been identified and isolated from natural sources such as *Scylla serrata* antilipopolysaccharide factor-24 (SsALF-24) from crab, hemoglobin alpha peptide (RVFHb α P) from rabbit vaginal fluid and rabbit epididymis, hemoglobin beta peptide (REHb β P) from rabbit epididymis. Anti-HIV potential of human surfactant protein (SP-D) is also being explored.

A database on antimicrobial peptides, CAMP (Collection of AntiMicrobial Peptides) with 4020 entries has been developed. Studies have been initiated to establish the relationship between the structure and the antimicrobial activity of peptides.

CD4 independent 160kDa HIV binding protein on human spermatozoa has been identified as Mannose Receptor (hMR). HIV binds specifically to hMR present on vaginal epithelial and cervical cells. The potential of the inhibitors of hMR and CD4 receptors in prevention of sexual transmission of HIV is being explored.

The training modules such as trainer's guide, trainee's modules and training program were developed after field-testing at six sites in the country. These are being used for training in the NACP-3 and RCH-2 programmes under National Rural Health Mission (NRHM). In addition, the Institute also contributed in the development of Operational Guidelines for programme managers on prevention and control of RTIs/STIs.

Anti-retroviral therapy (ART) adherence is a major problem encountered by current HIV management program. A multicentre study at 30 ART centres was undertaken to assess factors associated with ART drug adherence. Findings reveal that overall 75.5% of the interviewed 2924 participants in the study had optimal adherence (>95%).

A clinic based study involving HIV infected couples revealed that counseling and reproductive health services help HIV infected people to use condom consistently which could prevent transmission of HIV and pregnancy. An intervention model (community based program) to promote communication between husband and wife on issues related to sex and condom use and to reduce sexually transmitted infections/HIV among couples has been developed.

The model developed for adolescent friendly service delivery in urban Mumbai has been replicated at 8 public health care facilities of Karjat block in Raigad district of Maharashtra. The Government of Maharashtra is sustaining the project with technical support from the Institute and has adopted the process of training, information education and communication strategies and Management Information System for institutionalizing Adolescent Reproductive and Sexual Health (ARSH) services in other districts is ongoing.

Apart from the above scientific achievements, the Institute has also established a state of art National Centre for Pre-clinical Reproductive and Genetic Toxicology to support the on going and future research activities. The Centre is engaged in preclinical toxicological evaluation of molecules developed at the Institute as well as from industries. *In vitro/in-vivo* genetic toxicity tests viz micronucleus assay, chromosome aberration, COMET, AMES mutagenicity have been employed to determine the safety of various compounds.

The National Centre for Primate Breeding and Research (NCPBR) is being established to provide high quality non-human primates for biomedical research. The quarantine building and out door breeding facility will be functional by mid 2011.

GENETIC RESEARCH CENTRE, MUMBAI

Genetic Clinic Services

Prevention of birth defects: Services provided

Genetic Screening

Genetic Screening is "the testing of apparently healthy people in the population to identify those at increased risk of genetic disease themselves or whose children (including future children) may be at increased risk of disease".

Genetic screening includes carrier, prenatal and newborn screening. Carrier screening is often considered by couples who want to have children, but who are concerned that they may “carry” gene for a certain disorder that has the potential to affect their children. Newborn screening identifies biochemical or other inherited conditions in newborns that may result in mental retardation or other complications. Newborn screening is a effective measure in preventing mental retardation.

Postnatal screening

Mental health in children is an integral part of an individual’s well being. Fragile X syndrome is a common inherited cause of mental handicap and it is second most common cause of mental retardation in males. Therefore, it is important to identify this condition. Using a commercially available fragile X antibody protein FMRP a simple, rapid, cost effective test was developed and validated to identify this syndrome. During 2010-11, we have diagnosed 35 cases of mental retardation, 22 cases of primary amenorrhoea and short stature, 28 cases of disorder of sex developments and 30 couples with bad obstetric history. Appropriate genetic test and counseling was provided to all patients.

Genetic Research

Screening for Mental Retardation

Chromosomal disorders

Chromosomal disorders include aneuploidies like Down syndrome, Trisomy 18, Trisomy 13 and microdeletion syndromes like 22q11.2 deletion, Angelman syndrome, Prader Willi syndrome. Down syndrome is the commonest chromosomal disorder leading to mental retardation. It is caused by an extra copy of chromosome number 21 due to meiotic nondisjunction during gamete formation. At present tests such as karyotyping and Fluorescent *in-situ* Hybridisation (FISH) are utilized for diagnosis of Down syndrome. In 2010-11, 90 cases of Down syndrome have been diagnosed.

Single gene disorders: Molecular tests would confirm mental retardation caused by mutations in single genes like MECP2 (methyl CPG binding protein 2), FMR1 (Fragile X mental retardation 1) which are responsible for Rett syndrome and Fragile X mental retardation syndrome (FraX) respectively. Rett syndrome is commonest cause of mental retardation in females, whereas Fragile X is the second commonest cause of mental retardation in males. During 2010-11, we have identified 40 cases of Rett syndrome and screened for presence of mutation in MECP2 gene. Known and novel mutations have been identified in MECP2 gene.

Inborn errors of metabolism: Inborn errors of metabolism comprise a large class of genetic diseases due to defects of single genes that code for enzymes that facilitate conversion of various substances (substrates) into others (products). In most of the disorders, problems arise due to accumulation of substances which are toxic or interfere with normal function, or to the effects of reduced ability to synthesize essential compounds. Inborn errors of metabolism (IEMs) individually are rare but collectively are common. The common presenting symptoms of IEMs are failure to thrive, developmental delay/ neuroregression, skin rashes, abnormal urinary odour,

coarse facies, hepatosplenomegaly. These can be diagnosed by specific tests that assay the biochemical enzyme or look for abnormally accumulated substrates in the body/ urine. Molecular diagnosis of biochemically confirmed cases of IEMs such as Tay Sach Disease (2 cases, HEXA gene) and Gaucher disease (1 case, GBA gene) by whole gene sequencing have been performed during 2010-11.

Disorders of sex development: Disorders of sex development include intersex, gonadal dysgenesis, sex reversal syndromes, congenital adrenal hyperplasia. These disorders are common and molecular diagnosis is necessary for genetic counseling. Mutation analysis for many genes involved in sex development viz. SRY, SF1, DHH, CYP21, and SOX9 are being carried out. 15 cases of disorder of sex development have been diagnosed. Mutations in many such genes have been identified and this has helped in genetic counseling of the families.

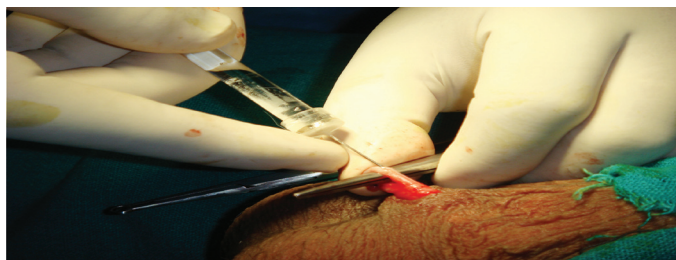
Genodermatoses: Genodermatoses include genetic disorders of skin. Skin is the largest organ of the human body and protects the human body from harmful external agents. Genetic diseases such as epidermolysis bullosa, congenital ichthyosis are serious diseases with high morbidity and mortality. Molecular diagnoses for two cases of ectodermal dysplasia (EDA, EDAR, EDARADD gene) have been performed and mutations were identified in EDA and EDARADD gene. Molecular diagnosis of Griscelli syndrome has also been performed which is a hair and skin pigmentary disorder with fatal complications of haemophagocytosis syndrome. A common mutation in Rab27 gene has been observed in these cases.

Extramural Research

REPRODUCTIVE HEALTH

Comparative long-term retrospective follow up study of RISUG injected and vasectomized (NSV) subjects is being carried out on 50 NSV subjects and 69 subjects identified out of 139 subjects who received RISUG injection during limited Phase-III Clinical Trial conducted during 2000-02. No serious adverse clinical symptoms were noticed in both the above mentioned Groups after 9 to 10 years post RISUG injection and all the RISUG injected subjects are maintaining azoospermia indicating very high and long term contraceptive efficacy of the RISUG. 69 subjects have been and followed for various clinical and laboratory investigations. of approximately similar characteristics have also been identified and followed for the similar investigations.

Phase-III Clinical Trial with an Intravasal Injectable Male Contraceptive – RISUG® is currently ongoing on at 4 centers in the Country and 64 subjects who received the RISUG injection under this trial have been followed. All subjects are maintaining the clinical efficacy of the drug. No side effects have been noticed in any of the subjects post RISUG injection upto 2 years of follow up. The first batch of RISUG was developed by M/s Icubed G Idea, IIT, Kharagpur and tested at LNJP Hospital, Delhi for its efficacy and safety.



Phase-IV Multi-centric study with Centchroman: Centchroman is a non-steroidal weekly oral pills indigenously developed by CDRI, Lucknow. This pill is to be taken twice a week on fixed days for first three months, followed by one pill in a week thereafter. A study has been initiated at 22 centers to evaluate efficacy & side effects especially ovarian cysts, return of fertility after discontinuation and to record any long term / rare/ unknown side effects with the use of Centchroman. A total of 1512 cases have been enrolled at 16 HRRCs of the Council 776 cases enrolled for the Centchroman and 736 for the Cu-T, enrollment could not be initiated at other centres for want of Ethical committee approvals and some other issues like non availability of subjects. Results of the study will be useful to consider this method to be included in the programme..

A Randomized Controlled Trial of three Vasectomy techniques : Fascial interposition improves the effectiveness of ligation and excision, many vasectomy providers find fascial interposition difficult to practice and time consuming. A clinical trial of three surgical vasectomy occlusion techniques has been initiated to determine if the technique of cautery and excision without fascial interposition is more effective than ligation and excision with fascial interposition. This study could thus provide evidence for the use of a more effective and simpler technique for providers. Fifteen hundred healthy sexually active men, who have chosen vasectomy as a means of contraception, will be recruited at 5 sites in India. All the centres have obtained the ethical clearance and have completed the codal formalities the budget has been released.

Total four centers has been started the study and total 267 cases has been enrolled in the study and one center delaying to start the study due to some local administrative problems, 107 cases have completed the 2nd follow up visit and 25 cases have completed the final visit.

The study will help to identify the best technique of vasectomy which may form the part of the National Family Welfare programme. All the cases enrolled in the study for failures and any side effects.

Phase III clinical trial with subdermal single-rod contraceptive implant 'Implanon' effective for three years is being evaluated through 22 centres for its contraceptive efficacy, side effects, continuation rate, menstrual bleeding pattern and return of fertility. A total of 3161 women have been enrolled in the study and followed for 89,687 woman months of use and no method failure has been reported September, 2010. A total of 1639 women have completed the stipulated 3 years of use with a continuation rate is 65.1 per cent at 3 years. Return of Fertility is being observed in ex-Implanon users exposed to the risk of pregnancy. Of the 2202 women who discontinued Implanon use and registered for return of fertility (ROF), majority (1732 women) of the ex-Implanon users accepted some contraceptive (OCP-546, IUCD-228, Injectable-25, Male condom-709, Female sterilization-177 and other conventional methods-47 women) during the one year follow-up for ROF. Of the remaining 407 ex-Implanon users exposed to the risk of pregnancy, until September 2010 a total of 304 women, have conceived within one year of discontinuation of Implanon. The remaining 103 women who have not conceived are in different periods of the one year follow-up for ROF. The rate of return of fertility in the study has been observed

to be 74.7% at one year, which is as expected in the normal population wherein the fecundity at one year ranges from 70-80% indicating that fertility is not impaired in Ex-Implanon users.

Sexual Behavior and Contraceptive Use among HIV Positive People is being studied at three centres to explore the changes in the sexual behavior and contraceptive use among HIV positive people (knowing their HIV status) and the factors that influence them and also to explore the perspectives of the health care providers and program managers on this issue. The study is being carried both in married and unmarried women and men. A total of 112 participants have been enrolled in the study until September, 2010 including 32 participants of I/V drug users of which 14 participants are on anti-retroviral treatment.

Prevalence of Infertility in India is being evaluated through a community based survey in 13 States of the Country to study the prevalence of primary infertility, childlessness and secondary infertility in urban and rural parts of India and to identify the possible risk factors for infertility the Council is conducting a. The survey is ongoing and a total of 5174 urban and 10418 rural households have been interviewed till date.

The Assisted Reproductive Technologies (ART) Bill & Regulations – 2010 has been drafted after incorporating comments following public debate and also issues related to foreign couples and citizenship of the child/children born through surrogacy. The revised draft Assisted Reproductive Technology (Regulation) Bill & Rules-2010 has been submitted to the MOHFW, GOI which has been forward to the Ministry of Law & Justice for evaluation.

WOMEN'S HEALTH

Maternal morbidity and mortality

Maternal morbidity and mortality is unacceptably high in our country. The Council is carrying out studies addressing this area through task force multicentric projects and ad-hoc studies.

Pre-eclampsia and eclampsia contribute to 5% maternal mortality in India. A study on low dose versus standard dose magnesium sulphate regimen for management of eclampsia-a randomized controlled trial is ongoing at 10 sites. A total of 2149 eclampsia cases were screened and 1336 were enrolled. Antepartum/intrapartum eclampsia was seen in 83% cases, while 17% women had postpartum eclampsia. Interim analysis indicated that the rate of recurrent convulsions was significantly higher in the low dose group than in the standard dose group but the number of maternal deaths in cases with recurrent convulsions was three times less in the low dose group than the standard dose group. The secondary maternal and neonatal outcomes were similar in both study groups except for signs of drug toxicity which were significantly lower in the low dose group. A detailed risk analysis of appearance of recurrent convulsions is being done with respect to socio-demographic data, medical conditions of the participants at baseline, timing of drug administration, time taken to achieve control of convulsions, and whether any dose was skipped and the reason thereof. Results of this study would inform providers on the use of low dose magnesium sulphate and promote its use in eclampsia patients.

Anaemia in pregnancy

Anaemia in pregnancy results in 20% maternal mortality directly and indirectly. In spite of the national programme consumption of iron by pregnant mothers remains low. A study compared the oxidative stress (OS) during oral iron supplementation in daily vs. weekly schedule among pregnant mothers. Preliminary interim analysis of 250 women indicated that the intake of dietary iron is 30% less of recommended allowance. There were no significant difference in birth weight of newborns in the two groups. A retrospective study of 54,326 pregnancies during 1986 and 2008 indicated that the mean birth weights and gestational age at delivery have not changed much over the twenty two years despite a small increase in mean hemoglobin. It was found that anemia (Hb < 10 g/dl) was significantly associated with preterm labor and low birth weight (< 2.5 Kg) but there is no association with perinatal mortality. The population attributable risk of anemia causing preterm labor is 10.15%. If anemia were to be removed from the cohort the prevalence of preterm labor would come down by 10.15%. The findings from the study can be used as the baseline to design larger prospective multicentre studies to assess the effect of anemia on pregnancy.

Preterm labour

Preterm labour and delivery contribute to more than 35% of neonatal deaths in India. The pathogenesis of preterm labour is not well understood. A study was carried out to evaluate clinical, ultrasonographic and laboratory predictors of preterm labour. The results showed significantly poor orodental hygiene of women who delivered preterm indicating infective etiology. In biochemical analysis only Serum Ferritin and Alkaline phosphatase were significantly different between the preterm and term delivery groups but there was no statistically significant difference in the insulin growth factor binding protein results. The study concluded that it is unlikely to be able to predict chances of preterm delivery in low risk women in the antepartum period using the biochemical markers and may be more useful when undertaken in high risk women.

Recurrent spontaneous abortion

Recurrent spontaneous abortion (RSA) is a significant health problem affecting 2-5% of couples in the reproductive age group. Genetic, anatomical, hormonal and environmental factors have been implicated in the etiology of RSA but a sizable proportion remains unexplained. It has been suspected that approximately 80% of unexplained RSAs are due to immunological causes. There is an interesting relationship between HLA-G (non-classical Class-I antigen) and classical class-I MHC gene expression. Samples were collected from 50 full term, 25 first trimester and 25 samples of recurrent spontaneous abortion to see the expression pattern of HLA-G and also see the effect of two glucocorticoids i.e. dexamethasone and hydrocortisone using a semi-quantitative RT-PCR. The HLA-G transcripts are seen in significant amount in first trimester placenta but in RSA none or very low expression was seen. When trophoblast cells were incubated for 72hrs in a serum free medium containing increasing doses of dexamethasone and hydrocortisone, dose dependent increase in HLA-G transcript was seen at drug concentrations ~500ng/ml and higher. Marginally higher expression of HLA-G transcript with dexamethasone as compared to hydrocortisone was observed.

Prevention options for HIV/AIDS

An ICMR Task-Force study is being carried out at 4 sites to understand **Community and the health care providers' perspective on male controlled biological option for HIV prevention**. A total of 134 in-depth interviews with health care providers and community stake holders have been conducted. Data is being analyzed to study regional variations around male circumcision and its significance in context of HIV prevention. Themes around knowledge, tradition, social norms, fear and communication strategy are emerging from the data analyzed. It seems that efforts to promote circumcision may have to focus on developing communication strategies around translating evidence into community friendly messages on efficacy of male circumcision to prevent HIV among men giving due cognizance to cultural issues and acknowledging the intense traditional beliefs and sensitivities around circumcision.

Comprehensive molecular analysis of HIV incidence, genetic diversity and anti-retroviral drug-resistance mutations in diverse risk groups across western India is being studied. MHAbce V.2 results showed dual-probe reactivity with subtype B and C probes suggestive of infection with two subtypes. Sequence analysis of 14 gp160 Env clones exhibited B/C recombination with distinct breakpoints. In the phylogenetic tree, sequences of 3 clones clustering with subtype B sequences from USA and sequences of 9 B/ C recombinants clustered away from both B and C sequences. Further analyses revealed 2 Env clones with pure subtype C and 3 pure B. **This is the first report of dual infection of subtype B and C in a case of heterosexual transmission from Western India and adds to the growing literature of dual infection cases.** Both dual infection and recombination have the potential to complicate efforts of vaccine design as it may pose problems for eliciting the broad immune responses necessary for an effective vaccine.

A study was carried out for design and characterization of an *E.coli* expressed outer domain (OD) based immunogen (OD_{EC}), based on the sequence of the HxBc2 strain. The OD_{EC} designed immunogen lacks the variable loops V1V2 and V3 and incorporates 11 designed mutations at the interface of the inner and the outer domains of gp120. OD_{EC} bound CD4 and the broadly neutralizing antibody b12. Upon immunization in rabbits, it was highly immunogenic and the sera showed measurable neutralization for four subtype B and one subtype C virus including two b12 resistant viruses OD_{EC} is the first example of a gp120 fragment based immunogen that yields significant neutralizing antibodies for future development.

Limited information is available on HIV-1 Indian clade C sensitivities to autologous antibodies during the course of natural infection. Finding out specific epitopes that conferred enhanced neutralization of viruses at molecular level would aid in designing strategies for Env-based vaccine design. A total of 37 complete envelope clones (Env) were amplified at different time points predominantly from the plasma of five Indian patients with recent HIV-1 infection and envelope-pseudotyped viruses were examined for their magnitude of sensitivity to autologous plasma antibodies during natural course of infection. The study identified novel residues in clade C HIV-1 Env that were found to confer enhanced virus neutralization by acting on different sites on Env and modulated Env structure and conformations.

Microbicides

Identification and characterization of anti-viral compounds with potential for development of microbicides to prevent HIV infection and transmission: To facilitate development of microbicides, a total of 150 extracts from various parts of 30 medicinal plants were prepared using different solvents. Eight plants are being further investigated for isolating anti-HIV compounds. Out of these 8 plants, extracts prepared from 4 plants showed TI values more than 10 using these two different assay systems. The extracts from 6 out of 8 plants also failed to elicit any significant increase in pro-inflammatory cytokines (IL8, IL1 β , IL6, IL10, TNF, IL-20p70) when incubated with vaginal keratinocytes (V_k2/E6E7), which is an important parameter for any extract to be further proceed as a microbicide candidate. The extracts/fractions from different parts of 3 plants also inhibited reverse transcriptase activity. The extracts prepared from plant code NBRH-10 has also shown anti HIV activity using R5 strain of HIV-1 (NLAD8) and PM1 as host cell line.

Phase I clinical trial with 'BASANT' polyherbal gel (a vaginal microbicide) was carried out to study its safety, acceptability and vaginal sensitivity. The cream was observed to be safe and well tolerated. Nearly 30% women experienced self limiting mild burning / itching sensation in the vagina for initial 5 minutes after cream application. All adverse events were mild and resolved within the study period. The cream was accepted positively by the women and their partners. However, its alteration of the cytokine levels, especially post-cream use elevated IL6 and IFN - γ levels needs to be followed carefully in the future to assess its impact on vaginal mucosal inflammation and, consequently, susceptibility to HIV infection.

Under the Indo US collaboration on Maternal & Child Health and Human Development research a total of 35 proposals were received in 2008 and out of these 5 have been funded. A meeting of the Joint Working group was held in Oct 2010 and the progress was reviewed and both groups expressed satisfaction at the progress of this collaboration and endorsed idea of having a MCH centre for promoting basic. Clinical and operational studies in the area of Maternal and Child health. A workshop on Neonatal infections was held in Delhi at the same time in which about 120 researchers from all over the country participated. Priority areas have been identified in this area. Proposals under the collaboration are being invited from both the Indian and the US scientists to jointly apply for collaborative research projects.

CHILD HEALTH

Pharmacokinetics of anti tubercular drugs in children: impact of age, nutritional status, and HIV infection in south: Younger children and those with malnutrition have lower blood levels of key first-line anti-TB drugs. These interim findings have important clinical implications and suggest that the existing dosages of anti-TB drugs, especially in young children may have to be increased in order to achieve optimal blood levels. The impact of acetylator status and sex on blood levels as well as the correlation with TB treatment outcomes are being studied.

Estimating the burden of Pediatric HIV in India in a high prevalence district of Belgaum: This study aims to estimate the burden of pediatric HIV using a three pronged strategy in a high prevalence district. Prospective follow-up of infected mother-

infant dyad, family screening of positive males and females from ICTC centers and screening of sick children identified by IMNCI-HIV algorithm derived by ICMR Sub-Committee of experts is being used for detection of HIV infected children in Belgaum district. The project is also testing the feasibility of using Information Communication technology software adaptation of 'CommCare' under one strategy.

National retinoblastoma registry is enumerating all the cases of Retinoblastoma in the Country and studying the risk factors for survival: The Indian Retinoblastoma(RB) Registry is in operation from April 1st 2009. As on August, 31st 2010. The preliminary RB registry data shows that there are 781 cases of Retinoblastoma seen in the country. The total evaluable cases are 612.

Solar powered Radiant warmer under fabrication: Low birth weight infants and premature babies are associated with a very high neonatal mortality mainly due to adverse environmental influences, proness to hypothermia , not able to maintain temperature and develop pneumonias etc. To bridge the gap between the Sick Newborn Care Units (SNCUs)in District hospital set up. Solar powered radiant baby warmer is being fabricated to prevent Hypothermia and therefore increase the survival of the high risk new born. This will provide supervised care for the high risk newborns at the district hospital level . The Solar powered Baby warmer is environment friendly. In rural areas where power supply is erratic and where there is plenty of sunshine this product will help in the care of high risk new borns and infants. The solar powered portable culture incubator will help.

Solar powered portable culture incubator will help in culturing bacterial cultures of human Fluid using solar power..The samples could be collected from the door step. Cultures could be carried out in the district hospital level. There will be no need to bring the samples to be culture to the Medical colleges.

Centre for Advanced Research in Newborn Health at the Department of Pediatrics has been started at AIIMS, New Delhi : The broad objectives of the CAR are to generate quality evidence of clinical/program relevance on key neonatal health issues viz. neonatal sepsis, feeding and nutrition of low birth weight infants; and neurodevelopment outcome of high risk neonates to contribute toward capacity development in neonatal health research.

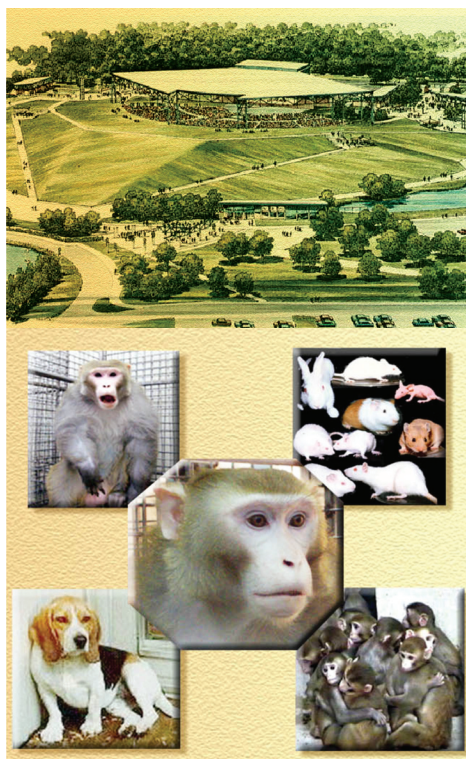
The Task Force projects on neonatal health include testing effectiveness of a package of home based newborn care interventions delivered through a trained village level worker at five rural sites; evaluating efficacy of probiotics VSL#3 in prevention of neonatal infections; determining the causative organisms of neonatal sepsis in the community and their antimicrobial susceptibility pattern; testing feasibility and acceptability of Kangaroo mother care method (skin to skin contact) for low birth weight babies in the community; assessing different modes of iron supplementation and the markers of iron toxicity; pediatric HIV, creating a database through network of HRRCs for childhood morbidity and mortality; interaction between anti TB drugs and anti retroviral drugs in children; causes of anemia in pediatric HIV; use of zinc supplementation in the recovery of CD4 levels in a double blind control study to enumerate the common causes of childhood mortality and morbidity from preliminary and secondary level hospitals.

Nevirapine levels in HIV-infected children receiving antiretroviral therapy with fixed dose combinations: The PI has been able to enroll 79 children (58 male and 21 female)

receiving fixed dose combination ART in the study. The mean age of these children is 7.3 \pm 3.6 years. Majority of the children enrolled in the study when classified by their WHO HIV disease Clinical stage belonged to T1 (56.9%), T3 (34.2%), T4 (6.3%) and T2 (2.5%) . Excepting 11 children who had advanced / severe immunodeficiency, rest had none to mild immunodeficiency at baseline. The mean absolute CD4 count at baseline was 1169 \pm 695 / mm³ and mean percent CD4 was 26.3 \pm 9.9%. Of the children enrolled in the study, only 31 (39.3%) had a detectable plasma viral load. It is reported that the mean absolute CD4 count at 6 months during follow up was 1132 \pm 654 cells per cumm. The mean percent CD4 has increased to 29.3 \pm 8.8%. The plasma viral load was detectable in 43% (n=31) children. The enrollment in the study is completed. The nevirapine levels are being analysed in LCMS-MS.

NATIONAL ANIMAL RESOURCE FACILITY FOR BIOMEDICAL RESEARCH (NARF-BR)

At Genome Valley, Hyderabad is being established through private-public partnership for provision of large animal facility to Industry as well as government organisations for research. Both state and central ministries are involved including cooperation from several ministries in the country viz Health & Family Welfare, Department of Biotechnology (DBT), Department of Environmental Forest, Scientific & Industrial Research (CSIR), Science & Technology (DST), CPCSEA, Industry & Commerce, Legal experts, ICMR etc. At the behest and guidance of the high level committees and representatives from the above organizations, ICMR has devised a concept proposal and an EFC has been submitted through the Department of Health Research, MOHFW for Planning Commission's approval. In order to dissuade encroachment of the land till such times the actual construction work is initiated for the animal facility, a boundary wall around the land has almost been completed at the site of NARF-BR in the Genome Valley at Hyderabad.



Nutrition

Intramural Research

NATIONAL INSTITUTE OF NUTRITION, HYDERABAD

National Institute of Nutrition (NIN) employs multi-pronged and multi-disciplinary approach to Nutrition research. The Institute firmly believes that integrating laboratory, hospital and community based research can help in evolving pragmatic approaches to combat nutritional problems confronted by the country today.

COMMUNITY STUDIES

Epidemiological studies on obesity, consumption pattern of carbonated beverages among young adults were carried out.

A study assessed the infant and young child feeding practices and undernutrition among pre-school children at district level in the state of Madhya Pradesh. The study results will help suggest intervention strategies at district level to combat malnutrition among children.

Multi-component health and nutrition intervention trial among adolescents resulted in a significant increase in the health and nutrition knowledge of the adolescents. In addition, favourable changes were also observed in the perceptions, behavioural practices among adolescents. More focus should be given on promotion of healthy foods and lifestyles practices and regulated TV viewing.

Future focus will be on developing appropriate intervention strategies for prevention and control of obesity and associated non-communicable diseases like diabetes, hypertension and cardio-vascular diseases.

Sports nutrition

The Institute's Work Physiology & Sports Nutrition Division has been supporting Sports Authority of India and Sports Authority of Andhra Pradesh by providing nutritional recommendations to Indian Athletes time-to-time. Based on the studies carried out on Indian Athletes to assess the energy requirements based on their expenditure pattern, "The Nutrition and Hydration Guidelines for Excellence in Sports Performance" was published in collaboration with ILSI-India. The report was submitted to Director General, Sports Authority of India, New Delhi.

Event and phase specific energy allowances were made and menu planning was done for the Indian Athletes in Common Wealth Games-2010. For the weight category sports like boxing, weight lifting, judo and wrestling; necessary adjustments in both diet and training components were done in consultation with the coaches and trainers, so as to achieve desirable body weight and optimal performance.

Extension & training

The institute has produced a wide range of nutrition education material like brochures, leaflets, posters and CD Rom as part of different research studies. Four educational films on 'Adolescent Nutrition', 'Dietary Guidelines', 'Food Labels' and 'Unhealthy

Foods' were developed in association with the Educational Multi-media Research Centre (EMMRC), Hyderabad. Many nutrition awareness programmes, popular and radio talks aimed at different groups of the community were also delivered

The second batch of M.Sc. (Applied Nutrition) programme affiliated to NTR University of Health Sciences, Andhra Pradesh was commenced and 16 students have been admitted. In addition, 10 participants (including 4 in-service candidates) were trained in the short-term PG Certificate Course in Nutrition.

Efforts are on to evaluate the use of space technology enabled village resource centres (VRCs) developed by Indian Space Research Organization (ISRO) for dissemination of nutrition knowledge in rural areas.

CLINICAL STUDIES

A study has evaluated efficacy of a lactobacilli preparation on bacterial vaginosis (BV) and vaginal immunity in healthy subjects and in patients with BV. It was found that overall 2.9% of the women in the study had serum Vit A deficiency ($<20\mu\text{g/dl}$). Only women with BV (05) had vit. A deficiency when compared to other groups. The serum Vitamin A levels were significantly ($P<0.005$) lower in the BV (47.9 ± 2.55) compared to the BV negative and intermediate flora. Similarly serum Vit A was significantly low in women with cervical inflammation. Serum Vit D deficiency was seen in 54% of the women studied and was significantly lower in women with internal flora and a higher proportion of women with cervical inflammation had Vit D deficiency though this was not significant. Overall 90.6% of the study population had serum zinc deficiency ($<70\mu\text{g/dl}$). Among women with BV and without BV, women with BV had significantly low levels of serum Zinc compared to women with normal flora or intermediate flora and significantly ($p<0.01$) higher proportion of women with BV (97.4%) had serum zinc deficiency.

BASIC STUDIES

Micronutrient research

The revision of nutrient requirements and recommended dietary allowances (RDAs) for Indians has been suggested as an instrument in formulating several national activities related to food, nutrition and health which was completed. This document will form the basis in formulating the guidelines for food fortification by the national regulatory bodies like FSSAI, which is being taken up with other stakeholders.

A state-of-the-art in vitro human intestinal cell line model for screening for micronutrient bioavailability has been established. This facility is being utilized by food industry to screen their products for micronutrient bioavailability. As a screening tool this facility can provide scientific basis for combining micronutrients for optimum utilization with minimum interaction for food fortification.

Studies on micronutrient interactions in experimental model systems suggest that iron and zinc negatively interact with each other during absorption when supplemented together. However, the extent of these interactions appears to be minimal when both of these nutrients are supplemented at a iron:zinc molar ratio of $1:<1$.

Further, evidences of these interactions support that improving zinc status helps iron absorption and reduces the negative interaction leading to iron induced oxidative stress.

A factor having ferric reductase activity in human milk which can enhance bioavailability of iron has been identified. Further studies are in progress to understand the chemical identity of this factor.

Future studies are looking into a wide array of areas like dietary diversification for ensuring higher bioavailability of iron when included in a regular meal; A network program "India-Crop Bio-fortification" has been initiated with the support from Department of Biotechnology.

Ocular biochemistry

On evaluation of B-vitamin status of diabetic retinopathy patients, for the first time an association of hyper homocysteinaemia and vitamin-B12 deficiency with diabetic retinopathy was found.

In connection with the work on impact of agents with potential use in functional foods for age related diseases, it was shown that rutin, a flavonoid present in many dietary agents particularly fruits and vegetables, inhibits advanced glycation end product formation on eye lens protein and also aldose reductase of eye lens. These findings may have prospects for alleviating diabetic complications, particularly diabetic retinopathy and diabetic cataract.

Studies on rats suggest that feeding LCn-3PUFA both at prenatal and postnatal is beneficial for the normal function or retina.

It was found that prolonged insulin resistance in rats causes biochemical alterations in the eye lens which may have implications for insulin resistance mediated cataract.

It has been hypothesized that deficiency of nutrient(s) (primary or as a consequence of hyperglycemia/insulin resistance) may predispose some of the diabetic individuals to develop secondary complications. Thus, it has been proposed to carryout extensive/ comprehensive nutritional profile of diabetic subjects with complications. It is also proposed to conduct experimental studies, if an association is found with nutrients and/ or dietary factors in human studies, to substantiate the role of those nutritional/ dietary factors in the development of diabetic complications. Then, randomized clinical trials could be initiated with human diabetic subjects.

Endocrinology and metabolism

The effects of maternal micronutrient on the body composition, insulin resistance and macronutrient metabolism in albino rat models were studied. It was observed that a variety of micronutrient deficiencies mimicking human situations during pregnancy, lactation and thereafter, modulated the body composition in the offspring. Further, they were associated with altered myogenesis, insulin expression and secretion in / from pancreatic β -islets. Altered oxidative / corticosteroid stress appeared to be underlying / associated with these changes in the offspring. While the changes in the associated biochemical/molecular changes appeared to be reversible, albeit, partly by rehabilitation, the phenotypic changes however appeared irreversible.

A rat model for obesity: WNIN/Ob (sumo rat) has been developed at NIN, but the biochemical and molecular basis for this condition are not yet known. Working on a hypothesis that impaired insulin signaling in the brain is responsible for the hyperphagia leading to obesity in the WNIN/Ob rats. The results suggest that impaired hypothalamic insulin signaling but not low insulin levels in the brain and the consequent failure to attain satiety may underlie hyperphagia in WNIN/Ob rats.

As part of the efforts to generate a database on the phenolic content of plant foods commonly consumed in India and their contribution, their health beneficial effects including anti-oxidant activity (AOA), total phenolic content and AOA was determined (by two different methods: FRAP and DPPH – radical scavenging activity) in a variety of commonly consumed plant foods in India. In general, phenolic content and antioxidant activities showed a wide range of distribution. The results also indicate that phenolics contribute to the anti-oxidant activity of plant foods commonly consumed in India but are significant contributors only in some food groups.

Lipid chemistry

Studies have been carried out in weaning 50 days old lean and obese rats of WNIN/Ob to understand the mechanism of vitamin A-mediated control of obesity. Results suggest that chronic feeding of vitamin-A enriched diet ameliorates visceral adipose tissue growth, obesity and improves insulin sensitivity, possibly by decreasing PTP1B (protein tyrosine phosphatase 1B) levels in soleus muscle of obese rats. In another study, wherein the health effects of coconut and virgin coconut oils were studied, no adverse effects were observed with regard to various lipid parameters, inflammatory and cardio-vascular markers in healthy normal weight and over weight subjects.

Stem cell research

Studies carried out in the Institute have demonstrated the prophylactic effects of pyridoxal 5 phosphate (PLP) towards the beta cell protection in diabetogenic mice induced with STZ underlying its antioxidant function. The beneficial response was more with PLP pre-treatment than post treatment. PLP could be a promising nutraceutical molecule for treatment of diabetes, as it is easily absorbed, non-toxic and a relatively low cost dietary supplement.

Enriching the microenvironment of pancreatic progenitors; ductal epithelial cells (DEC) and nestin positive cells (NPC) with PLP and RA along with growth factors has recreated physiological environment for beta cell expansion and increased *in vitro* generation of functional neo-islets. *In vivo*, transplanted neo-islets rescued hyperglycaemia and process of regeneration / tissue repair was evident in the pancreatic tissue of the diabetic mice (STZ). Dietary supplementation to the microenvironment for beta cell mass expansion appears significant as nutritional environment recapitulates the prenatal and early post-natal period of the developmental process.

Cow pea derived Isoflavones had beneficial effects in protecting the bone mineralization in the osteoporotic rat model system. Studies established that in critical situations like osteoporosis, supplementation with Diazine and isoflavone derived from the common foods like Cow peas could provide high content of PE. This could be explored for management of Osteoporosis.

Food chemistry

The data in the nutritive value of Indian foods (NVIF) which is the only food composition data available in the country is very old. A proposal was therefore put forward to the government to generate a totally new Indian food composition database which was sanctioned recently. Work on the project has been initiated by procuring required instruments and recruiting project staff. Training of project staff and installation of instruments is in progress. In all 82 nutrients will be analyzed in all the Indian food items that will be gathered through a nationwide sampling plan.

Molecular biology

Recent studies showed that, not only the macrophages, but also another primary immune cell such as T cells also migrate into the adipose tissue during obesity. However, the aftermath of T cell migration is not well understood. The scientists of the institute are trying to understand role played by the infiltrated T cells in the development of obesity and diabetes.

Interestingly, endoplasmic reticulum (ER) stress is implicated to be the link between obesity and associated inflammation and insulin resistance. However, the source and nature of trigger is not well understood. Preliminary investigations hint that the stromal vascular fraction of the adipose tissue contributes significantly more to the inflammatory milieu compared to that of adipocytes in the adipose tissue. Therefore, it has been hypothesized that the stromal vascular fraction plays a major role in development of insulin resistance as fatty acids induced ER stress in the stromal vascular components and studies are underway to check this.

MicroRNAs (miRNA) belong to a novel class of small non-coding RNA molecules and are implicated in regulating variety of biological processes that include embryonic development. It is proposed to study the miRNA profiles and understand their contribution in development of obesity and diabetes using the WNIN obese rat models.

Pathology

The Electron microscopy unit was commissioned and 4 projects of urgent public health relevance were successfully completed. The research findings indicated that in diet and cancer studies, n6 diets had deleterious effects on tumorigenesis. It was observed that variation in dietary proteins does not affect the toxic changes at low toxin concentrations. Studies on role of dietary aldose reductase inhibitors in human cancer, maternal Vitamin B₁₂ restriction induced changes in adiposity, hyperglycemia and insulin resistance are in progress.

FOOD AND DRUG TOXICOLOGY RESEARCH CENTRE (FDTRC), HYDERABAD

The centre, in collaboration with Bioserve Biotechnologies Pvt Ltd, Hyderabad, has developed PCR based diagnostic kits for detection of food and water borne pathogens. Primers to *E.coli*, *V.cholerae*, *V.parahaemolyticus*, *salmonella staphylococcus aureus*, *Bacillus cereus* were used and PCR based uniplex detection method was developed.

Commonly consumed foods in Andhra Pradesh were analyzed for presence of pesticides, heavy metals, fluoride and mycotoxins. Risk assessment considering the average food intakes revealed that except cadmium, which was present at high levels in sorghum, the intake of contaminants through foods was lower than accepted daily intake (ADI).

A study conducted in a Village of Nellore district, Andhra Pradesh indicated that many people were suffering from kidney malfunction and were found to be having high serum levels of fluoride silica and strontium. Drinking water in that area had high levels of fluoride, silica and strontium. An epidemiological study is in progress to understand the role of these micronutrients in the etiology of fluoride toxicity.

Pesticide residues in foods and carbonated beverage are a public health issue. LCMS based detection of organo pesticides has been standardized.

A rapid investigation and analysis was carried out at the request of Ministry of Health and Family Welfare (MoHFW) to assess the extent of fungal and aflatoxin contamination in the rice variety PAU201 developed by PAU Punjab that was held up in rice mills due to non-acceptance by Food Corporation of India (FCI), which indicated levels well below the GOI limit of 30 ppb. On the basis of the results of this investigation and risk assessment of aflatoxin contamination, the GOI accepted the rice variety for release in the open market.

Exposure to environmentally present lead is known to be toxic. The exposure could be more toxic to those who suffer from iron deficiency anaemia. Using rats as experimental models it was shown that exposure to lead (Pb) in iron deficient rats suppressed the immune system and had adverse effect on intestinal probiotic organisms. These effects could be mitigated by thiamine, a nutrient.

Under preclinical toxicology testing safety testing of stem cells have been initiated. Acute and chronic toxicity, allergenicity of Bt cotton and Bt Okra will be completed. Human Papilloma Vaccine, Genoep I (for use as anti-cancer agent against prostate cancer) VNJN-21 a synthetic peptide for treatment against AIDS have been tested.

NATIONAL CENTRE FOR LABORATORY ANIMAL SCIENCES (NCLAS), HYDERABAD

The major focus of research at NCLAS is on the two obese mutant rats (WNIN/Ob & GR-Ob) developed at the centre. By detailed genotyping over 500 DNA belonging to F0, F1 and F2 progenies with F344 rats carried out at Rockefeller University, US, the mutation is identified on chromosome no.5 and further in that chromosome, an area of 1.5 bp showing maximum polymorphism need to be explored. Recently two more aspects of these models came to light i.e. hypertension, as well as reduction in bone mineral density, bone mineral content, and bone specific alkaline phosphate. These make them ideal models for studying obesity associated with hypertension, as well as for osteoporosis. Effect of long term exercise on these animals showed benefits such as improved glucose tolerance, reduced insulin resistance and body weight and lipid profile.

Body composition studies on rodents were attempted using non-invasive methods like TOBEC and DEXA, the results which were compared with conventional invasive chemical analysis. The study showed that for hamsters and guinea pigs, DEXA is more reliable than TOBEC.

Studies linking asthma with obesity, nesfatin, (a new satiety protein) and obesity are underway. Studies on behavioral research, genetics and epigenetics using these rats will be initiated along with another project on the impact of micro flora on obesity. Further these mutants will be tested for their use in screening anti-diabetic and anti-obesity drugs (both synthetic and natural).

Extramural Research

A multi-centre study entitled “Health profile of population of Dhar (M.P.) district” with the objectives of assessment of micronutrient deficiency based on biochemical markers like ferritin, B₁₂, folic acid, zinc, selenium etc is completing its tenure in February, 2011. The study is being carried out in Badwani block of Dhar district where 90% population is tribal. Information is also being collected on utilization and accessibility of health facilities. The preliminary analysis of the data indicates the prevalence of deficiency of various micronutrients ranges between 30% to 70%.

Centre for Promotion of Nutrition Research and Training with special focus on North- East, Tribal and Inaccessible Population

It has analyzed more than 5,000 human blood/blood serum/urine/salt samples for various parameters such as lipid profile, vitamin A, vitamin E, vitamin C, zinc, selenium, copper, urinary iodine, salt iodine etc. Two Ph.D students, five M.Sc. students and one D.M. student are using the facilities of the Centre for their research work. They are working on diverse research issues like randomized clinical trial with Iron, Folic acid and Vitamin B12 to combat anaemia, micronutrient load during different trimesters of pregnancy, study on haematological parameters in young adult women (19-25 years) and on prevalence of peripheral neuropathy in patients with cystic fibrosis on Vitamin E supplementation. The centre has also initiated various collaborative activities with other ICMR Institutes as well as AIIMS, New Delhi besides carrying out external quality control with International agencies/ organizations. The laboratory has been granted accreditation under Medical Testing Laboratories by the National Accreditation Board for Testing and Calibration Laboratories (NABL), Department of Science and Technology, Government of India.

One of the important activities is to support individual scientists from different parts of the country. Currently 26 projects are ongoing and 35 projects are under consideration.

In the area of Diabetes research the Council under an MOU with University of Minnesota have identified 8 areas of research in which the Indian scientists and the scientists of the University of Minnesota would work together, 8 proposals have been received and evaluated of which 3 have been recommended for funding. The Council has taken initiatives to develop low cost technologies for diagnosis and monitoring of Diabetes and will be supporting 3 researchers for the same .

Food Safety: ICMR-ICAR panel has been constituted to address various issues related to food safety such as fruit ripening agents, role of oxytocin in growth of vegetables and production of milk and health effects thereof, use of antibiotics in honey and safety aspects as well as benefits and adverse effects on health, if any of consumption of vegetable juice such as Lauki.

Basic Medical Sciences

Intramural Research

NATIONAL INSTITUTE OF IMMUNO-HAEMATOLOGY, MUMBAI

Haemoglobinopathies and Enzymopathies

A monoclonal antibody against haemoglobin A₂ has been developed and its applicability to study thalassemia carrier status is being tested. Several rare red cell enzyme deficiencies were detected i.e. Phosphoglycerate kinase, Triose Phosphate isomerase etc. In a patient with hereditary stomatocytosis a novel A 858 D mutation involving AE1/SLC4A1 gene was also detected.

Transfusion Medicine

A Single Stranded Conformational Polymorphism (SSCP) based molecular technique to detect different variation of ABO blood group antigen has been established. It will have future application in studying chimerism, forensic medicine etc.

Cytogenetics

Fanconis' anaemia is an important childhood problem where aplastic anaemia alongwith Myelodysplastic Syndrome (MDS) is produced. Some of these cases progress to acute leukaemia. There are many subtypes of Fanconi's anaemia. Now in the Institute some of the major subtypes of Fanconi's anaemia can be diagnosed. This facility is not available elsewhere in the country.

Leucocyte Biology and Pediatric Immunology

Major congenital immunodeficiency detection platform is now available in the Institute. This has facilitated detection of more than 100 such patients over the year. Prenatal diagnosis for these diseases has now also been offered.

Clinical and Experimental Immunology

Alloimmune neutropenia is due to antibodies developed against neutrophil alloantigens in various circumstances. The distribution of important neutrophil antigens (NA1, NA2) has not been worked out in India. In a randomly selected population 21.8% were found to be NA1/NA1, 40% were NA1/NA2 and 38.8% were NA2/NA2. This will help in developing methods for detection of alloimmune neutropenia.

Thrombosis and Hemostasis

In 2010 it was shown that in hereditary protein C deficiency cases, only 8-10% patients show the mutations and in other cases no defect could be found in Vitamin K dependent pathways to explain the deficiency. This year it was possible to demonstrate that 6% of such patient have subclinical vitamin K deficiency (normal prothrombin time) but 40-50% of such patients have one, two or three polymorphisms at the transcriptional regulation site which could explain such deficiency.

Pharmacogenomics of Haematological Disorders

Two polymorphisms of cytochrome P450-2C9 gene i.e. CYP2C9*2 and CYP2C9*. 3 were found to be mostly associated with warfarin associated hemorrhagic problem. It is being expanded into a large number of patients.

Human Resource Development

NIIH has become a part of International Scientific Standardization Committee Laboratory for microparticle assay.. Institute conducted Training for Prenatal Diagnosis of thalassemia for five centres each in Eastern and Western Regions of the country. Conducted Training for National Reference Laboratory for HIV infection every quarterly for 20-30 candidates to teach them the proper execution of ELISA and other screening for HIV infection, which involves four states i.e. Maharashtra, Goa, Daman & Diu and Madhya Pradesh. A CD was prepared for training in Chorionic Villus Sampling for Gynecologists. In addition to above 25 candidates were trained in Autoimmune disease workshop, 25 candidates attended workshop on Flowcytometry, 10 were trained for blood coagulation analysis, blood bank training was given to 3 technicians and 5 doctors and 3 WHO sponsored fellows were trained for red cell serology. Four candidates joined Doctorate of Medicine in Clinical Haematology at NIIH.

REGIONAL MEDICAL RESEARCH CENTRE, BELGAUM

The Centre is established to conduct research on herbal medicines as a major thrust area due to its close proximity to Western Ghats, one of the 25 biodiversity hot-spots in the world.

Revitalization of local health traditions

The Centre focused on systematic participatory documentation of local health traditions (LHT) related to primary healthcare and their rapid assessment, pre-clinical (pharmacological/ toxicological) and clinical evaluation on high priority local health practices and encouraging local health traditions by strengthening local self help groups to meet the primary healthcare needs of community.

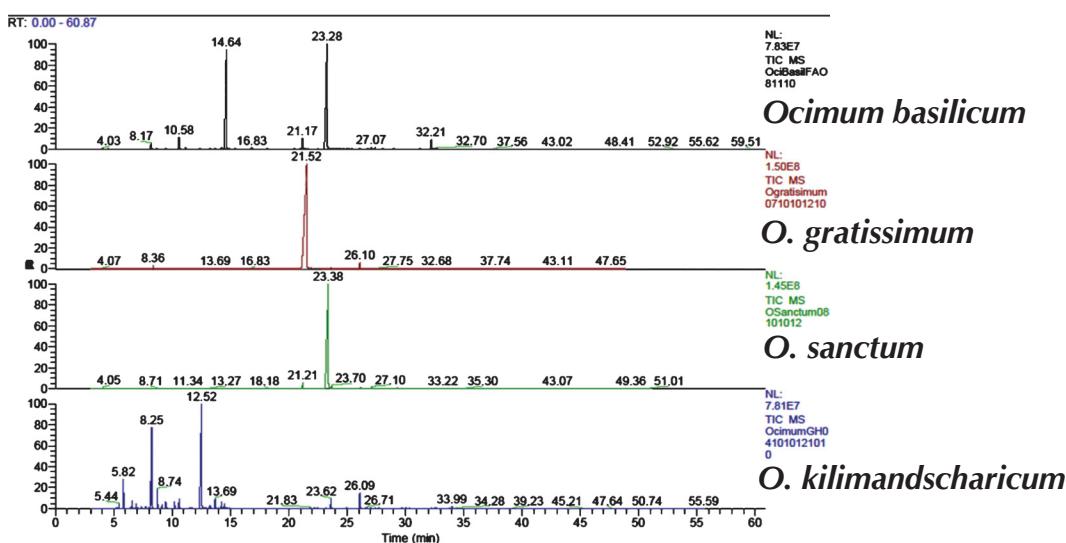
Two blocks (*talukas*) in Northern Karnataka, Gokak and Hukkeri of Belgaum district were selected. Traditional practices for arthritis, constipation, pain abdomen, fever and ulcer were documented, and taken up for toxicological and pharmacological evaluation. All the toxicological studies were carried out as per OECD guidelines. All the formulations were found to be safe. The anti-arthritic activity of the selected lead practice is under limited clinical evaluation at BMK College of Ayurveda, Belgaum and results are encouraging. The recruitment of more patients is in progress.

Demography of patients attending to traditional healers in Belgaum region

RMRC has prepared directory of traditional healers in Belgaum region. Traditional healers claim treatment for various diseases. However no systematic information regarding demography of patients visiting these healers and their level of satisfaction is available. A study has been launched with the hope that leads will be obtained for further research in the area of drug development.

Chemoprofiling, antimicrobial and antioxidant activities of the essential oils of the medicinal and aromatic plants of Western Ghats

Important medicinal and aromatic plants from the Western Ghats were selected based on their traditional use viz., *Coleus aromaticus*, *Ocimum basilicum* L., *Ocimum gratissimum*, *Ocimum sanctum*, *Ocimum kilimandscharicum*, *Feronia elephantum*, *Vitex negundo* and *Cytoscline purpurea*. Volatile secondary metabolites have been identified from *Coleus aromaticus*, *Ocimum basilicum* L, *Ocimum gratissimum*, *Ocimum sanctum*, *Ocimum kilimandscharicum*, *Feronia elephantum*, *Vitex negundo* and *Cytoscline purpurea* plants. The chemoprofiling of *Ocimum* species showed variations in their phytoconstituents. Essential oils of *F. elephantum* and *C. purpurea* exhibited good antimicrobial activity. Diterpens and diterpenoids are reported for the first time in the essential oils of *V. negundo* and *C. purpurea*. Further characterization will be carried out by isolation, purification followed by spectroscopic characterization for elucidation of structure.



GC analysis of the essential oils of *Ocimum* species

The presence of high amount of carvacrol along with three new chemotypes i.e. methyl chavicol, α -calacorene and α -corocalene (low amount) from *C. aromaticus* have been reported for the first time indicating that these plants can be used for antimicrobial/antioxidant activities. *Ocimum* species found as a rich source of eugenol, methyl eugenol, methyl chavicol and camphor which are the potential candidate plants for screening of biological activities.

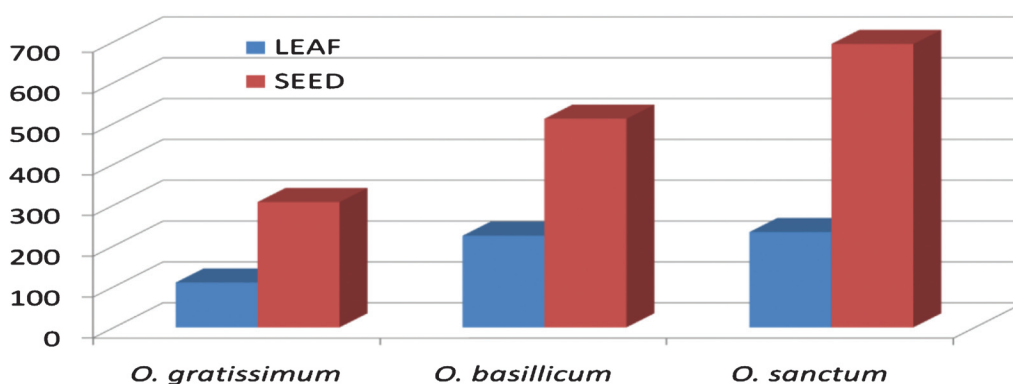
Screening of anti-diabetic activity of *Feronia elephantum* Corr

Two plants *F. elephantum* and *B. arundinacea* have been selected on the basis of traditional use for treatment of diabetes. Both plants extracts showed anti-diabetic activity on the streptozotocin induced male wistar rats. Further studies are in progress.

Quantitative and qualitative comparison of DNA isolated from seeds & leaves of *Ocimum* species

The tissue of choice for isolation of DNA for PCR and other downstream applications has generally and conventionally been fresh leaves. Transportation of leaves and pre-processing requirements often include maintenance of cold chain preservation in freezer. Suitability of seeds as alternative samples for genomic DNA isolation was investigated on three species of *Ocimum*: *O. sanctum*, *O. basilicum* and *O. gratissimum* in comparison with their leaves. DNA was isolated from equal masses of fresh leaves and seeds of the 3 species by employing CTAB/NaCl method and quantified at 270 nm in Nanodrop spectrophotometer.

The yields of DNA from seeds for each of the three species was almost double than from the leaves. The quality of the DNA was also good for subsequent downstream applications like RAPD and ISSR fingerprinting assays. Seeds, that do not require fresh collection or cryopreservation, can therefore be better alternatives for extraction of total genomic DNA from plants.



Yield of DNA in leaves and seeds of *Ocimum* species

INSTITUTE OF PATHOLOGY, NEW DELHI

Tumor Biology

Studies have been undertaken on identification of diagnostic, predictive/prognostic biomarkers and drug targets for breast, prostate, brain, urinary bladder cancers and hematological malignancies.

Breast Cancer

Two breast cancer cell lines have been established from young breast cancer patients which have been characterized for Epithelial Markers, Anchorage Independent growth, Ultrastructural analysis and cytogenetic studies. Most of the chromosomes of both the cell lines exhibited several translocations and several marker chromosomes. Gene expression and hypermethylation study of early onset breast cancers showed hypermethylation and up-regulation of genes in Ion channels and their functional role in vascular endothelium, MAPK signaling pathway, TNFR signaling pathway

and Hemoglobin's chaperone pathways. Study on characterization of Host Immune Profile Associated with Progression of Superficial TCC of Bladder by Microarray Analysis showed that out of 84 genes studied, 14 genes are up-regulated and 35 genes are down-regulated in the TH1-Th2-Th3 array. The chemokine CCL11 and cytokine IL12, genes of the JAK-STAT pathway and MAP kinases are up-regulated in tumour tissue when compared to adjacent normal appearing mucosa. NFκB signaling pathway showed dysregulation of 20 genes in tumour compared to normal adjacent mucosa and these included MyD88, REL and the Jun-Fos pathway genes.

Tobacco associated Cancers

Studies on tobacco associated cancers showed that the genetic predisposition or host susceptibility to various carcinogens in tobacco may be regulated by polymorphisms in genes encoding detoxifying enzymes. Polymorphisms in three genes [CYP1A1 (*Msp1* and *Nco1*), NAT2 and NQO1] analyzed in oral cancers showed marginal risk for homozygous variant AA genotypes of NAT2 and significantly higher risk for variant NQO1 genotypes. Study on immunogenetic profile of Nasopharyngeal cancer in a high prevalence region of North-East India has been initiated with aim to investigate association of EBV with NPC and to analyze if polymorphisms in the HLA region could explain ethnic variation leading to the high incidence of NPC in North-East India. Amplification conditions for three markers of HLA region (D6S2704, D6S265 and D6S510) were standardized using gradient PCR with 6-FAM-labelled forward primer and GeneScan -500 LIZ Size Standard (Applied Biosystems). Capillary electrophoresis and genotyping was performed with Data Collection Software Version 2.0 on ABI PRISM 3100 xl Genetic Analyzer.

Chlamydia

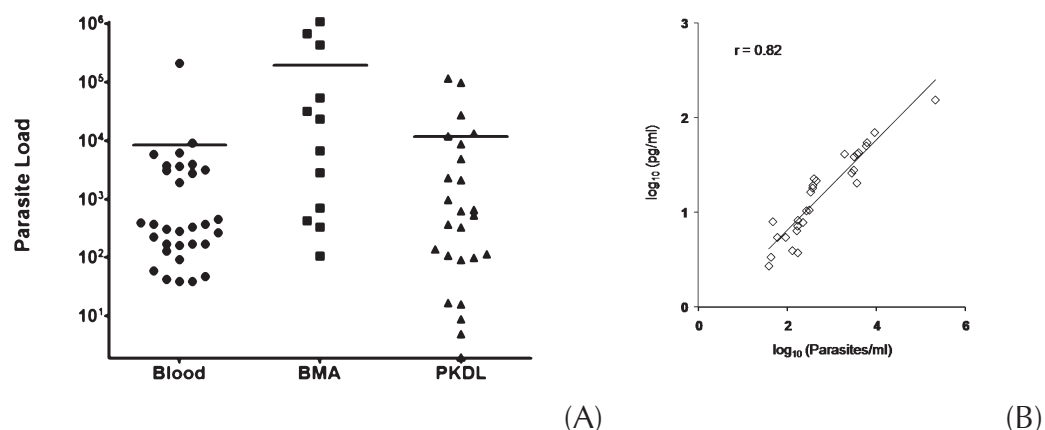
Research is focused chiefly on female genital chlamydial infection for improving the reproductive health of women. To investigate whether IL-17A (IL-17) and IL-22 are produced in response to *Chlamydia trachomatis* infection, the levels of cytokines were determined in the cervical wash and in the supernatant of cervical and systemic cell cultures upon *C. trachomatis* antigen stimulation. *C. trachomatis* infection appeared to activate local IL-17 and IL-22 production more efficiently than IFN-γ production.

Study on modulatory role of antichlamydial agents in *Chlamydia trachomatis* infection with response to azithromycin in infertile women showed that azithromycin with its properties apart from antibacterial activity may contribute to its therapeutic potential in treatment of chronic recurrent infection in infertile women.

Leishmaniasis

To develop a rapid and accurate method to detect and quantify *Leishmania* parasite to facilitate early diagnosis of Leishmaniasis and monitoring of antileishmania therapy, real-time assay was applied to estimate parasite load in clinical samples of visceral leishmaniasis (VL) and post kala-azar dermal leishmaniasis (PKDL) patients. Circulating levels of IL-10 correlated significantly with parasite load suggesting that the high parasite load in VL is strongly correlated with a high level of IL-10, implicating IL-10 as a marker of disease severity. The assay is applicable for diagnosis as well as

prognosis of both kala-azar and PKDL, providing a simple molecular tool to monitor the efficacy of anti-leishmanial drugs or vaccines.



(A) Scatter plot showing parasite load in Blood, BMA and PKDL samples. (B) Correlation of IL-10 level and parasitic load in blood samples of VL patients.

Studies on histone2A (H2A) in antimony resistance of *Leishmania donovani* demonstrated over expression of H2A gene in a drug-sensitive laboratory strain as well as in a field isolate of *L. donovani* which resulted in conversion of SAG-sensitive parasites into a resistant phenotype. Moreover, H2A over expression resulted in a significant decrease in susceptibility towards other anti-leishmanial drugs currently in use, i.e. amphotericin B and miltefosine, pointing to its role in drug resistance. Evaluation of quantitative expression of selected genes directly in lesion tissues of VL, PKDL and CL patients highlighted substantial differences in gene expression patterns, providing an indication of the genes involved in pathogenesis in the three different forms of Leishmaniasis.

Adult Stem Cell Biology

A novel arithmetic approach for fool-proof production of growth arrest in 3T3 cells suitable for human epidermal culture has been established for growing human Cultured Epidermal and submitted for patent.

Environmental Toxicology

Studies on health hazards of phthalate vis-à-vis idiopathic male infertility showed presence of two or more phthalate compounds in blood samples of 74% of infertile patients by Gas Chromatography; however 47.6% of control subjects also showed presence of phthalates indicating ubiquitous presence of these compounds in the environment. Still significant differences were observed between fertile and infertile subjects in terms of phthalate exposure. While Di-isohexyl phthalate (DIHP) and Dimethyl Phthalate (DMP) were present in the infertile group, they were not observed in fertile controls. Further, di-isodecyl phthalate (DiDP), Di-isooctyl phthalate (DIOP), IBCHP, DINP and BEHIP were observed in only 4.8% of control samples. On the other hand DBP, DEHP and BEHIP were present in 47.3%, 30.4% and 27.7% of infertile patients respectively.

Assessment of pesticide exposure in tea garden workers of north-eastern state of India (HEBM) has shown presence of acephate, heptachlor, parathion, malathion, DDT, chlordane, ethion and phosalone not only in maternal and cord blood but more reliably in placental tissue. Further apart from the exposed population, the pesticides have also been observed in directly un-exposed housewives who might have got exposure through use of chemical for house hold cleaning and through dietary routes. The study has further revealed that presence of pesticides can be linked to various clinical manifestations in the exposed / un-exposed population as well as changes observed in various foetus, placenta and new born baby.

Human Resource Development

A “Hands on Training on Tissue Microarray (TMA)” in June 2010. Twelve participants attended the workshop.

A workshop on “Foundation workshop on Clinical and laboratory medicine research” in association with Moving Academy of Medicine and Biomedicine, Pune in July 2010 in which almost 60 students participated.

Extramural Research

During 2010-2011 under extramural research the division of Basic Medical Sciences has funded total 514 ongoing projects out of which 54 were Task Force projects, 247 were Ad-hoc projects and 267 were Fellowship applications. In addition to this 194 new projects and 246 new fellowship applications were received.

Total 296 projects funded during the year 2010 – 2011, of these 247 were on-going and 49 were new. Besides projects 246 new applications for SRF and RA were received out of which 72 were recommended for the support.

Genomics and Molecular Medicine

ICMR Centre for Advanced Research in Cancer Genetics & Genomics at ACTREC, Tata Memorial Centre, Navi Mumbai

With 2-5% of all cancers being hereditary, we have an estimated burden of 20-50,000 new hereditary cancers annually in India. These families require specialized genetic counseling and testing and tailored preventive and therapeutic approaches for which there are only 2 Cancer Genetic Clinics in the country (this ICMR centre & Adyar). Genes underlying Hereditary Cancers (RB, TP53, BRCA1, XP, MMR etc) control fundamental biological processes like cell cycle, proliferation, DNA repair etc. Hence findings of novel mutation in these genes and Genotype-Phenotype studies in large families could catalyze basic and translational research in diverse fields of biology. Pediatric malignancies is a neglected area due to its relative rarity (less than 5% of all cancers) and translational research based on somatic genetic alteration could help understand “clinically relevant” molecular changes in Childhood Cancers common in India.

Within 3 years of inception the ICMR Centre for Advanced Research in Cancer Genetics & Genomics has become the Apex Referral Centre in India for comprehensive clinical and laboratory genetic services and genetics research for all major cancer

predisposition syndromes with cases and families being referred to it from all over the country and Indians residing in Europe and USA.

Model of Comprehensive Cancer Genetics Unit (dedicated Cancer Genetics Clinic with trained genetic counselors running daily plus Cancer Genetics Lab) established for the first time in India and best international practices in pre-test counseling, genetic testing, post test counseling, screening and medical management have been tailored for Psycho-Social-Cultural dynamics unique to Indian families. This has culminated in the registration of this Genetics Counseling Centre and Genetics Lab under the PNDDT ACT for Pre-natal genetic counseling and testing for hereditary conditions.

This ICMR CAR is the only lab in the country which conducts and issues clinically relevant reports with advice for clinical management for carriers of germ line mutation in a wide range of cancer associated genes (BRCA1, BRCA2, RET, TP53, RB, MMR, CHK2 etc) and is presently free of cost to patients due to ICMR support.

With 830 pedigrees, DNA Bank of 725 cases & EBV cell lines from 250 cases, this is the largest collection of clinical & research resources in diverse hereditary cancers outside USA & Europe. of the 830 families registered in the Genetics Clinic, 386 families were registered in the last 2 years.

The centre has **identified several novel germline mutations / Variants** in BRCA1, BRCA2 and TP53 gene in the Indian families. **Informative STR loci for Indian population have been established** and clinically relevant report for **serial qualitative / quantitative assessment of post transplant chimerism status** has been issued so far for 31 donor-recipient pairs who have undergone allogeneic BMT at **3 centres (ACTREC, Chennai, Jaslok)** free of cost.

Medulloblastoma Projects (Commonest Paediatric Solid Tumour)

Genome wide miRNA profiling of medulloblastoma, a common malignant brain tumour in children: miRNA profiling of medulloblastoma tumour tissues (n=19) & normal cerebellum (n=4) performed using Taqman microRNA array containing 365 miRNAs and genome-wide expression profiling identified Four molecular subtypes (A to D) of medulloblastomas: A) activation of WNT signalling pathway; B) activation of SHH signaling pathway; C and D): Common gene expression signature that includes transcription factors involved in CNS development (subtype D expresses neural differentiation genes; Subtype C: proliferation controlling genes at higher level). 206 miRNAs expressed in medulloblastoma tumour tissues and normal cerebellar tissues and miRNA profiling identified identical molecular subtypes as the expression profiling of protein coding genes. Differential expression of some protein coding genes & miRNAs specifically expressed in each molecular subtype confirmed by Real time PCR. Molecular subtyping could be done for an independent set of medulloblastomas. A number of miRNAs were found to be up-regulated specifically in WNT signaling associated medulloblastomas. Two of the three miRNAs transiently transfected in medulloblastoma cell line inhibited proliferation, increased radiation sensitivity and reduced anchorage-independent growth.

Creation of Genetic disease registry, DNA banking and EBV transformed cell lines from informative families of rare genetic disorders, SGPGI, Lucknow

Till date blood samples from 1828 individuals have been collected and DNA has been / is being extracted and stored at -80°C . This includes samples from 890 probands with various genetic disorders and clinical presentations with possibly genetic etiology. The number of samples from family members of the patients with genetic disorders is 719

DNA extracts from blood or liver of fetuses with various malformations and was stored. has been stored. Cells from amniotic cell cultures done for prenatal diagnosis are also stored for microarray based cytogenetic analysis in future.

Association with VEGF polymorphisms: In women with unexplained recurrent miscarriages, recent reports had evaluated the association with vascular endothelial growth factor (VEGF) polymorphisms. VEGF is a growth factor beloved to be of significance in placentation and genetic polymorphisms leading to low VEGF levels may predispose to recurrent miscarriages. Four polymorphisms of VEGF gene namely; -1154 G/A, -2578 C/A, -2549 I/D, & +936 C/I in patients with recurrent miscarriages were investigated. The -1154A allele and +936T allele significantly increased the risk of RM. The -1154AA genotype and +936CT genotype also predisposed to Recurrent Miscarriages. Prenatal diagnosis was provided to families with Congenital adrenal hyperplasia, Pompe disease and Apert syndrome. In all cases where mutation has been identified; it helped in confirmation of the diagnosis. Use of MLPA for detection of deletions and duplications in cases of mental retardation without obvious cause is being evaluated. In cases where MLPA helped in identification of etiology, genetic counseling was provided. These families can be helped by prenatal diagnosis to prevent the recurrence of similar problem in the next pregnancy. The microarray analysis identified microdeletion in 2 cases with idiopathic mental retardation. The genes involved in the deleted region in a case of polydactyly showed correlation with the phenotype. The results can be of great use for providing genetic counseling to the family.

Upgrading the skills in Diagnostic Molecular Biology in Medical colleges in and around Bangalore under coordination of Sir Dorabji Tata Centre for Research in Tropical Diseases, IISc Campus, Bangalore

Council had established a network of five hospitals including Kempegowda Institute of Medical Sciences, Bangalore Medical College, St. John Medical College, M. S. Ramaiah Medical College and Sir Dorabji Tata Centre for Research in Tropical Diseases, Bangalore on 1st October 2008 by providing minimum infrastructure facility for capacity strengthening in the field of PCR based Molecular Diagnosis for specific infectious diseases with the aim to understand the prevalence and management of common infectious diseases in the region. The centres have completed two years of their tenure. They have standardized PCR based techniques for diagnosis of different infectious diseases for e.g. MRSA, Tuberculosis, RSV and HIV-1. The technical personnel have been trained. The facility will enable the techniques to be available to the patients attending the OPDs of these institutions and the establishment of additional techniques enables to carry out epidemiological studies. The construction and commissioning of PCR suitable state of art facilities has been completed. Soon the PCR machines will be installed in the centres.

Stem Cell Research

Stem Cell Research has emerged as cutting age sciences with recent scientific breakthroughs, celebrity patient advocates, and conflicting religious beliefs have come together to bring the state of stem cell research specifically embryonic stem cell research into the political crosshairs. Understanding the promises the area of Stem cell Research and Regenerative Medicine, meeting the needs of several patients suffering from incurable diseases Council has been proactive in promoting basic as well as translational research in the area of stem cell research and therapy. Since the inception of the activities in the field Division of BMS has been involved in several activities including formulation of Guidelines for Stem Cell Research and Therapy, promoting basic research, pilot studies to evaluate safety and efficacy of the autologous stem cells in different conditions and evaluation of clinical trial applications submitted by biotech companies through Drug Controller General of India. Different Expert Groups were constituted to review the proposals received and quarterly meeting was held to expedite the review process. Outcome/progress of the studies was assessed annually. Total 7 meetings were held during the period of 2008-2010. Council has received twelve such applications through DCGI for allogeneic stem cell transplantation for marketable products developed by biotech companies. Out of which six clinical trials have been approved and others are still under consideration.

During the year 2010-2011 total 26 projects were received out of which 8 were approved for funding, 8 were rejected and 10 have been asked to revise. Besides basic research projects ICMR has developed two protocols in consultation with the experts to initiate multi-centric clinical trials for Critical Limb Ischemia and Spinal Cord Injury. The project Coordinators have been identified and been given responsibility to initiate these trials after identifying centres and conducting workshop for common protocols.

As suggested in the Guidelines for Stem Cell Research and Therapy (2007), Department of Health Research has constituted a *National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT)* with the secretariat at ICMR. The NAC-SCRT will oversee/monitor activities at National level.

Public Consultations on Guidelines for Stem Cell Research & Therapy

Guidelines for Stem Cell Research and Therapy were formulated jointly by ICMR and DBT in 2007. ICMR organized Public Consultations in different regions of the country to have consensus/public opinion over the policy document. Four Public meetings were held in Mumbai for Western Region (20th February 2010), at Bangalore for Southern Region (10th April 2010), at Kolkata for Eastern Region (17th April 2010) and at Dibrugarh for North-Eastern Region (14th May 2010). Council received overwhelming response in all the regions except eastern region. Participation representing all the stakeholders was observed. Students, clinicians, researchers, health administrators, Pharma-Biotech companies, lawyers, religious groups, NGOs attended the public discussions and have also participated by putting up the queries and suggestions. The final round of Public



Consultation for Northern Region is scheduled to be held at New Delhi. Stem cell research is developing at a very fast pace. Understanding the implications of translation of this technology, after analyzing the outcome of the issues and suggestions received during the Public Consultations the policy document will be revised.

ICMR Centre for Advanced Research in Pharmacogenomics at JIPMER, Puducherry

The objective of the centre was to obtain basic information on the allele and genotype frequency of genes encoding for important Phase I and Phase II drug metabolizing enzymes and transporter in South Indian population. For the first time, normal distribution of important variant alleles of phase 1 and phase 2 enzymes was established. It showed that the prevalence of *CYP3A5*, *CYP2A6*, *CYP2E1*, *TPMT*, *UGT1A1* and *MDR1* polymorphisms in the South Indian population were markedly distinct from other world populations. This basic genetic data will help for the development of appropriate strategies to ensure safer therapeutics, better efficacy and will improve the quality of public healthcare in this population. The established frequencies in the genes will be used for studying the phenotype variation in the South Indian population. The outcome of the study may form the basis for further studies on the clinical application of Pharmacogenomics information in Indians. Second objective is to promote advance research on the clinical application of Pharmacogenomics information in common clinical conditions. The outcome may lead to more safer and efficient drug therapies in disease conditions. Study on effect of genotyping of *CYP2C9*, *CYP2C19* and *MDR1* in individualizing phenytoin dose requirement in epileptic patients showed *CYP2C9* genetic polymorphism has significantly influenced the dose requirement as well as steady state level of phenytoin in epileptic patients. *CYP2C9**3*3, *CYP2C19**2*2, *MDR1* CT/TT genotype patients required lower dose of phenytoin to avoid phenytoin toxicity and based on the study it is suggested that routine genotyping for *CYP2C9* in epileptic patients prior to the initiation of phenytoin therapy may benefit them not only in preventing phenytoin adverse reactions but also helps in deciding the loading dose requirement. Study on effect of *CYP2C9* and *MDR1* genotypes on the plasma levels of glibenclamide showed that the genetic polymorphisms of *CYP2C9* and *MDR1* did not influence the plasma levels of glibenclamide in diabetic patients of South India. However, the genetic polymorphisms have an influence on the control of diabetic status of type 2 diabetes mellitus patients on therapy with glibenclamide and suggested to promote advanced research on the gene-drug interaction in patients receiving chronic drug therapy for diseases conditions like tuberculosis. The outcome may lead to safer drug therapies in these conditions. Study on genotype frequency and phenotype expression of *CYP2C9* in patients receiving anti-tubercular drug therapy the observations are that one month of antituberculosis treatment causes a significant decrease in the metabolic ratio of phenytoin implying increased induction of *CYP2C9*. The induction of *CYP2C9* was not found to be significant in individuals with deficient enzyme activity as in *CYP2C9**1*2 and *CYP2C9**1*3.3. Thus the presence of a polymorphic *CYP2C9*



gene could affect the degree of induction by antituberculosis treatment. Study on association of MDR1 gene polymorphism with morphine requirement for patient controlled analgesia after total abdominal hysterectomy in south Indian population showed that CT genotype patients require a higher per Kg dose of morphine than TT genotype to maintain the same level of analgesia. Patients with TT genotype are at increased risk of developing morphine side effects nausea and vomiting when compared with CC and CT genotypes. Besides research work the center was also involved in capacity building activities. The department of pharmacology had conducted six annual national workshops in pharmacogenomics techniques training of large number of young researchers in the field of pharmacogenomics. The centre has done remarkable progress during last three years.

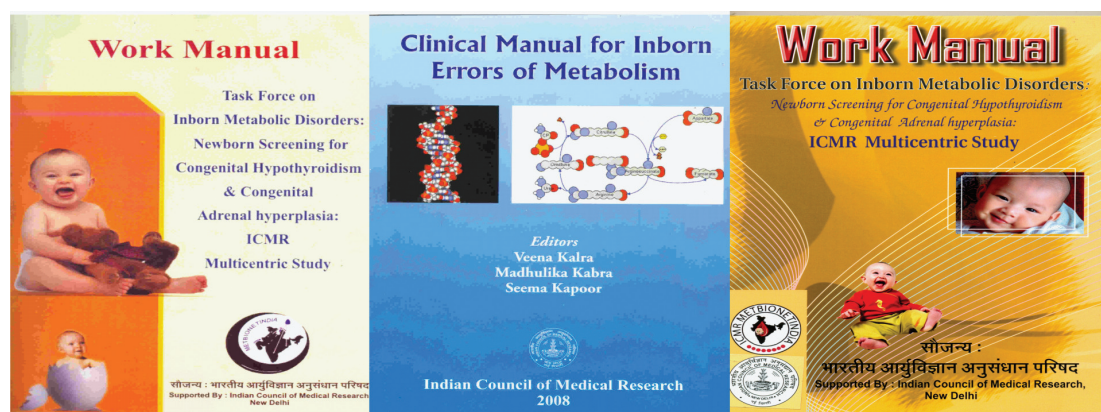
Community control of thalassemia: Establishment of molecular characterization of haemoglobinopathies and prenatal diagnosis of Thalassemia and Sickle cell disease

The objectives of this multicentric study are to establish molecular technology for characterization of mutations in hemoglobinopathies as well as facilities for first and second trimester prenatal diagnosis at 5 regional centres in Maharashtra, Gujarat, Karnataka, W. Bengal and Punjab. The 5 centres have been given the necessary equipment which were installed and local training given for their operation. At site training has also been given to 3 centres at Nagpur, Kolkata and Valsad for molecular diagnosis using the reverse dot blot hybridization (RDB) and ARMS techniques.

Each centre is screening antenatal women and their husbands (when needed) to identify couples at risk for b-thalassemia major, Hb E b-thalassemia and sickle cell anemia. A total of around 7000 women have been screened so far, the largest number being at Nagpur. All the centres are now able to carry out DNA isolation and PCR and are standardizing the other molecular techniques. They are in process of procuring licenses from their respective State Governments for getting their centres approved for prenatal diagnosis.

National Task Force on Inborn Metabolic Disorders -Newborn Screening for Congenital Hypothyroidism & Congenital Adrenal Hyperplasia- a multi-centric study (NTF-IMD)

The NTF-IMD entered the Phase II of the study and under this initiative newborn screening has been completed in more than 50,000 newborns. It is expected that



by end of year 2012 about 1 lakh newborns will complete screening in different parts of the country. The study has 5 newborn screening centres at Delhi, Mumbai, Kolkata, Chennai and Hyderabad along with 3 high risk screening centres at Delhi, Hyderabad and Bangalore.

Short Term Studentship (STS-2010)

Short Term Studentship program provides a unique opportunity to undergraduate medical students to familiarize themselves with research methodology by undertaking short duration research projects. It is very popular among undergraduate MBBS or BDS students and is the first program under ICMR which has become paperless. Application and proposal submission and its review and evaluation by experts are online. During 2010 about 2278 students applied and 790 students were selected. Proposals were received from 232 medical colleges from all parts of country. This year the stipend of selected students was raised from Rs 5000/- to Rs 10,000/- for two months.

National Task Force on ICMR Research Oriented Medical Education (NTF-ROME)

The Council has set up and funded a new National Task Force study in order to encourage recipients of Short term studentship to further enhance their skills and learning in research methodology by attending intensive short term trainings. This is to promote research culture at the undergraduate level. Regional hands on workshops in different aspects of clinical research (both hospital and field based), laboratory medicine, clinical trials, medical ethics, data analysis & communication etc were held. In addition national/ regional medical students' research conferences were organized with the aim to improve quality of research & research milieu in medical colleges. During 2010, 5 regional workshops were organized and were attended by over 300 students.

Biomedical Ethics

ICMR-FERCAP Research Ethics Training Courses in Lucknow: Under a major initiative to strengthen the status and functioning of the ethics committees in India the Council has conducted two training workshops namely Human Subject Protection Course and Standard Operating Procedures Training at Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow. Both of these training were attended by members of institutional ethics committees from 12 medical colleges and research institutions from Lucknow and neighboring areas. The courses were organized by the Council in association with Forum for Ethical Review Committees in Asia and Western Pacific Region (FERCAP).

Centre for Advanced Research on Evidence Based Medicine established with the goal to improve the quality of health care and health policy in India and to partner the Cochrane collaboration in its mission of preparing, disseminating and maintaining systematic reviews of the effects of interventions and activities identified under each of these, which is an agreement between the ICMR and the publishing partner of The Cochrane Collaboration, John Wiley and Sons Limited to ensure provision of The Cochrane Library to all residents of India with internet access the point of use. The work done includes six introductory workshops of one day in evidence- informed health Care,

five systematic review protocol development workshops of four day each, five review completion workshops of one day each, two half day systematic reviews for diagnostic test accuracy and 39 presentations were made over the period in various workshops and conferences involving more than 800 participants. Seven concurrent workshops were organized for editors, clinicians, students, media, consumers and policy makers. The 3rd Winter Symposium of the Christian Medical College, Vellore and the 3rd South Asian Regional Symposium on evidence-informed healthcare was held.

The Centre for Advanced Clinical Pharmacodynamics for evaluation of pharmacodynamic effects of drugs has standardized the methods a) mechanical pain model; b) using temperature –radiant heat pain model , hot air pain model, cold presser test and ischemic pain model chemical pain model. A study on standardization of recording of saccadic eye movements and determination of saccadiac peak velocity was done.

Under a Task Force on Indian Normatives for Cinical Laboratory Parameters (INCLAP) which aims to set up our own standards of Clinical Laboratory Parameters and Normative Values in view of the varied ethnicity of people of India totally different from the western population on the basis of which current range of values for different tests are available, a proposal for pilot study was finalized.

International Health

The International Health Division (IHD) co-ordinates international collaboration in biomedical research between India and other countries as well as with national & international agencies such as Ministry of Science & Technology, Indian and foreign missions and WHO etc. There are few specific agreements signed by the Ministry of Health and Family Welfare with other countries and rest are those signed directly by ICMR with international organizations/ institutions such as INSERM (France), German Federal Ministry of Education and Research (BMBF), Helmholtz Association (HGF, Germany), National Institutes of Health(NIH)/Centers for Disease Control (CDC, USA), Canadian Institutes of Health Research (CIHR, Canada), University of Sydney and George Institute for International Health, (Australia) etc.

The purpose of these Agreements and Memoranda of Understanding (MoU) has been for exchange of scientific information; exchange of scientists/technicians; joint execution of scientific projects and organization of joint scientific meetings, seminars, workshops and symposia in identified areas of cooperation.

The meetings of Joint Working Group (JWG) or Joint Steering Committee (JSC) with various countries/international institutes/organizations are organized to review, develop and finalize joint collaborative programmes, decide future plans of action and identify priorities for bilateral cooperation. Progress under MoUs/Letter of Intent (LOI) ICMR with CIHR (Canada), University of Sydney and George Institute (Australia), INSERM (France), BMBF and HGF (Germany), Boston University and University of Minnesota (USA) to work together on health issues of mutual importance has been made during the year.

Joint Steering Committee (JSC) meeting of IG-SCID under ICMR –HGF MoU held on 7th April, 2010, at ICMR, Hqrs., New Delhi

Eighth INSERM-ICMR Joint Working Group (JWG) meeting held on 21st June, 2010 at the INSERM head office, Paris, France

The bilateral meetings of ICMR-HGF JSC in India, ICMR-INSERM JWG in France; ICMR-CIHR JSC in Canada; Indo-US Occupational & Environmental Health JWG in USA; Indo-US HIV/AIDS & Maternal & Child Health JWG in India were held during the year wherein number of collaborative research projects were approved and new modes of collaboration were identified.

Meeting of Indo-US Joint Working Group under Indo-US Joint Statement on HIV/AIDS & STD on 1st & 2nd November, 2010 at ICMR Hqrs., New Delhi

The International Health Division facilitated the organization of international workshops: Canada India Network Initiative (CINI) workshop at Vancouver, Canada; Indo-US workshop on Environmental and Occupational Health at Atlanta, USA; Indo-Australia workshop on Road Traffic Injuries in Sydney, Australia; ICMR-CIHR expert group meeting at ICMR, New Delhi; Indo-US workshops on MCH and HIV/ AIDS were held at New Delhi during 2010.

MoUs such as ICMR-HGF, ICMR-CIHR were drafted and exchanged for renewal of collaboration. New MoUs with Global Alliance for Chronic Diseases (GACD) and Foundation for Innovative New Diagnostics (FIND) have been prepared and processed for necessary approval of Government of India. A Letter of Intent (LOI)

between ICMR and INSERM for collaboration and setting up of an International Associated Laboratory (IAL) in the field of Immunology/Haematology was signed in December 2010 during the visit by delegation led by His Excellency, the President of France to India.

Letter of Intent was signed between ICMR & INSERM at ICMR Hqrs., New Delhi on 6th December 2010

The IHD supports and coordinates the international travel of Indian scientists engaged in approved bilateral research projects under various MoUs and joint statements with other countries. A total of 48 exchange visits of scientists/officials to and from India were arranged under various international collaborative programmes.

Applications for research projects involving foreign assistance and/or collaboration in biomedical/health research are submitted by the Indian investigators to ICMR for approval of Govt. of India through Health Ministry's Screening Committee (HMSC). The International Health Division of ICMR acts as the Secretariat for HMSC. The projects are peer reviewed by the concerned Technical Divisions at ICMR and then placed before the HMSC for consideration and decision. During the year 2010, three meetings (upto Dec. 2010) of Health Ministry's Screening Committee were organized wherein 78 projects for international collaboration/assistance with agencies from USA, Germany, France, Canada, Australia, WHO and several other foundations were approved by the Committee.

The Division also organized visits by various visitors to ICMR from foreign countries/agencies such as New York University, University of Athens, PATH, Erasmus University, Academy of Finland, University of Amsterdam, John's Hopkins Institute etc.

Prof. Christian Streffer from Germany visited ICMR Hqrs. and IG-SCID on 8th Dec. 2010

Visit by a delegation from University of Amsterdam to ICMR on 18th Jan., 2011

The ICMR International Fellowship Programme for Indian biomedical scientists aims to augment capacity strengthening of institutions involved in basic, applied, epidemiological and clinical sciences through exposure of Indian researchers to the latest international advancements in knowledge, to understand the disease and find strategies for their prevention and cure. The ICMR International Fellowships have been awarded to six Senior and twelve Young Indian scientists during the year 2010-11.

The mission of the virtual Indo-German Science Centre for Infectious Diseases (IG-SCID), established at ICMR is to co- ordinate joint research in identified areas of infectious diseases and to initiate proactive scientific cooperation with equal participation of Indian and German scientists. The Council has taken up a project entitled, "Managing the Indo-German (ICMR-HGF) Science Centre for Infectious Diseases" which is in operation with IHD. Under this programme four collaborative projects have been approved and funded. A fellowship programme is being prepared to Indian and German scientists for training in newer technologies under IG-SCID initiative.

The joint calls for collaborative research proposals between ICMR and MRC, (UK) and ICMR-BMBF (Germany) were announced through respective websites in 2010-11.

Publication, Information and Communication

During the year 2010-11, activities undertaken in the field of publication, information and communication are detailed below.

PUBLICATIONS

Indian Journal of Medical Research

The Indian Journal of Medical Research (IJMR), a peer reviewed monthly biomedical Journal published in two volumes, 12 issues every year, continued to publish quality original research articles in the area of biomedical research as well as review articles (both solicited and unsolicited) on topics of contemporary biomedical interest in addition to Editorials, Commentaries and Letters to the Editor (Correspondence). New sections viz. View Points, Perspectives, Systematic reviews with meta analysis, and Students' IJMR have been added from 2010. The IJMR is covered by all global abstracting and indexing services.

The IJMR is available full text free on the net with a searchable menu. IJMR archive is also made available at <http://ijmr.in> and all articles published in the IJMR since inception (July 1913) are now available full text free. Indian Medical Research Memoirs (38 in number, full text) are also available on this website.

The IJMR has switched over to Online Manuscript Management System and editorial processing of the articles is now being done online. This has shown a positive impact on number of submissions and led to a decrease in processing time.

The visibility and readership of the IJMR has increased globally as evident from increasing number of submissions across the globe and also number of hits and downloads at the site. The peer review process has been improved and made more rapid and unbiased with increase in number of international reviewers. Efforts were continued to expand the reviewers panel further. Increasing use of e-mail was continued to communicate with authors and reviewers to save time. The current impact factor of IJMR is 1.516.

A special section on "Cardiovascular Disease Research" was brought out in November 2010 with Drs D Prabhakaran (Public Health Foundation of India, New Delhi) & Salim Yusuf (Population Health Research Institute, Canada) as guest editors.

Annual Report

Annual Reports of the ICMR and Department of Health Research (DHR) (2009-10) were brought out during the year. They are available at the ICMR website.

Hindi Publications

ICMR Patrika

The Council continued to bring out ICMR Patrika, the in – house periodical in Hindi. The Patrika can be accessed at the ICMR website. During the year 2010-11, articles were published on *Malaria Niyantran : Pragati evam Chunautiyan, Mahilaon mein Tambakoo Sevan tatha Vaishvik Tambakoo Niyantran Nitiyon mein Unki Sapeksh*

Bhagidari, Influenza A H1N1 ke liye Vaccine, Bharat mein Aushadh Pratirodhi kshayarog ka Chikitsa Prabandh, Bhartiya Ayurvedigyan Anuasandhan Parishad : Gauravpurna 100 Varsh, etc.

Other publications include **Varshik Prativedan**, the Hindi version of the Council's Annual Report 2009-10, **Varshik Prativedan (Swasthya Anusndhan Vibhag)**, Annual Report of the Department of Health Research (DHR), Ministry of Health and Family Welfare for the year 2009-10, and **ICMR Network (2010)**.

Video Films on Various Disease Conditions

Small films on six diseases viz. Leprosy, Blood Disorders, Genetic Disorders, Cancer, Occupational Health Hazards and Polio were prepared during the year.

INFORMATION AND COMMUNICATION

Library and Information Services

As part of modernization of ICMR Library & Information Network the subscription for the ICMR e-consortia of core journals Lancet, Science, Nature, and NEJM for all ICMR Library & Information Centres has been renewed for one more year as the usage is satisfactory among ICMR institutes. Subscription for full text electronic data base ProQuest Health & Medical Complete including ProQuest Medical Library (covers about 1530 journals) has been renewed for one more year located at four ICMR institutes as the usage of this database among ICMR institutes is found satisfactory.. The subscription has been renewed for JCCC@ICMR (J-Gate Custom Content for Consortia) (provides access to content of about 1941 journals) and J-Gate as the usage of these databases are found satisfactory. ICMR has continued as a member of ERMED Consortia, an initiative taken by DGHS and MOHFW to develop nationwide electronic information resources in the field of medicine for delivering effective health care. The consortium will be coordinated through it's headquarter set up at the NML. It provides easy access to 2754 medical journals from 9 leading publishers across the world but also make online journals available to medical scholars working in the country through the electronic media.

The progress in terms of modernization of all ICMR institutes has been reviewed by expert Committee members and found satisfactory . Orientation/training programmes were organized for scientists on ERMED & ICMR e-consortia, ProQuest Health & Medical Complete, JCCC@ICMR, J-Gate etc.. at ICMR Hqrs., New Delhi as well as all ICMR institutes.

Scientometric Studies

The annual document '2009 Research Output of ICMR Institutes' with analysis of publications from all ICMR institutes including Regional Medical Research Centres was brought out. A total of 564 papers were published by ICMR institutes during the calendar year 2009. The Tuberculosis Research Centre (TRC), Chennai topped the tally with 67 papers followed by NIMR, New Delhi (58), NICED, Kolkata (49), NIIH, Mumbai (47) and NIRRH, Mumbai (43). Of the 564 papers, 449 (79.61%) were covered by SCI/JCR 2009, while 480 (73.28%) were covered during 2008. In this category of SCI/JCR 2009 covered papers, top five institutes were as follows :

TRC, Chennai (53); NIMR, New Delhi (48); NICED, Kolkata (43); NIRRH, Mumbai (39) and NIIH, Mumbai (38). A total of 289 journals were used for publishing 564 papers with the *Indian Journal of Medical Research* publishing the maximum papers (52). Of the 289 journals, 211 were covered in SCI/JCR 2009. A total of 178 journals had an impact factor (IF) ≥ 1.000 . *New England Journal of Medicine* had the highest Impact Factor (IF, 47.050) among the SCI/JCR covered journals. Nine journals (*N Engl J Med*, *Lancet*, *Science*, *Nat Biotechnol*, *Genome Res*, *Proc Natl Acad Sci USA*, *Thorax*, *Emerg Infect Dis* and *J Clin Endocrinol Metab*) had IF of ≥ 6.000 . The top five Institutes in terms of total IF were NICED, Kolkata (221.432); TRC, Chennai (181.282); NIRRH, Mumbai (144.390); NIMR, New Delhi (110.159) and National Institute of Virology (NIV), Pune (81.073). However, there is a slight increase in the average IF/paper of the Council from 2.750 (2008) to 2.778 (2009).

Bioinformatics Centre(BIC)

The BIC conceived an ambitious project for creating a repository of all raw data generated from extramural and intramural research of ICMR. The main objective of the project is to store data at one Central and secure place, annotate these data and perform analysis of these data using high end Business Intelligence tools. A proposal was prepared during the year for the project. A Request for Proposal (RFP) was prepared in consultations with experts in the field and was published in the leading newspapers and on the ICMR website and pre bid meeting with the vendors was held. Further decision on the project is pending.

The extramural project information system has been converted to web based. The projects are linked to the Programme Officers. Programme Officers can access projects under them through internal ICMR website and also can update some of the information. The DG and other senior officers can view details of all the projects. User training of the software package is in progress.

A website (<http://www.dhr.gov.in>) of the Department of Health Research (DHR) has been created and is maintained by BIC. The main features of the site are Mandate of DHR, Schemes to achieve the Objectives, Results- Framework Document (Rfd), Guidelines for processing Translational Research projects etc.

Biomedical Informatics Centres of ICMR have successfully achieved their initial objectives of providing services and training, database development and research during the first phase of the project. It is proposed to create a Central Genomics Unit of ICMR.

The BIC develops software packages for other ICMR programmes. It developed online software for uploading proposals for Short Term Studentship (STS) programme of ICMR. The programme also has online review system. With help of this package, STS 2010 was fully paperless.

The BIC also prepared package for 'Management of Acute Coronary Events' A project of the Division of NCD. This interactive package takes data from patients visiting various hospitals in the country for cardiovascular problems. The software is applied in several hospitals in the country. For the security purposes, different levels of people have been given different access to the software.

Other Areas

Tribal Health Research Forum

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Technology Transfer Initiatives

Initiatives were taken to transfer Council's technologies for commercialization. Memorandum of Agreements have been signed/are underway between BCIL and various ICMR institutions. The agreement received from various divisions, labs and extramural projects were examined.

The ICMR entered into an agreement as non-exclusive basis with NRDC, New Delhi to commercialize ICMR's technologies. Few more technologies like Resazurin Reduction Test PCR based diagnostics kits for detection of food & water borne pathogen A technology related to novel primers based diagnosis of pathogenic Mycobacterium assigned to NRDC for industrial partnering. Two Companies HLL, Mumbai and a Hyderabad based Company M/s Virchow's Biotech had shown interest to take up this technology.

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Showcasing ICMR's Technologies

For showcasing ICMR's technologies the IPR Unit displayed their patented and non patented technologies at various exhibitions which considered more close for industrial partnering. The exhibitions provide unique platform where national or international companies connect with leaders in India's scientific community, policy makers & regulators, life sciences industry and State Governments. The IPR Unit participated in the Bangalore Bio-2010 and National Science Congress, 2010.

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These events not only provide the opportunity for exhibition, but provide platform for partnering along with a Multi Track Conference.

Health Systems Research

To meet the health needs of the people in the complex geographical, socio-economic, cultural, political, demographic and epidemiological environment in India, the Division of Health Systems Research (HSR) is engaged in fostering health systems research in the country through providing grant in-aid for ad-hoc research projects on the various issues of HSR, developing and implementing multi-centre research project on issues of national importance and improving the research skills of faculty and other staff working in medical colleges and universities through conducting regional workshops on research methodology and proposal writing.

The HSR Division has provided grant in-aid for 28 ad-hoc projects to medical colleges, universities and other, non-government agencies across the country. Some of the areas on which projects have been funded include Public, public-private and NGO partnership for improving RCH services (3 projects); health insurance for population living in rural areas and urban slums (6 projects); strengthening research capacity and effective knowledge utilization (9 projects); reduction of gap in the health system manpower & service delivery (5 projects); reducing gender discrimination and improving adolescent health (5 projects).

The HSR Division has also operationalized three multi-centric Taskforce projects during this year in order to study the access and delivery of healthcare services among rural-urban migrants in the context of livelihood insecurity and vulnerability due to migrant status.

Capacity building activities: A three day workshop on research methodology and proposal writing has been conducted at Bhubaneswar covering, Orissa, West Bengal, Bihar and Jharkhand. Twenty research proposals were prepared and presented by the participants on conclusion of the workshop. These were reviewed and suggestions for improvement were given. Four more workshops in other regions of the country are planned.

Social and Behavioural Research

During the year, the SBR Unit has taken a new research initiative in the following four areas of high programmatic relevance:

Delivery and Utilization of Health Services and Newer Technologies: Utilization of services by the communities is affected not only by their own perceptions and beliefs about the diseases, the treatment, and service providers but also the manner in which services are organized and delivered to the people. Distance to service facility, timing, range of services & provision for supplies, sex and behaviour of the providers etc become important factors for people of different sections of society and gender accessing the services.

Gender Issues: Due to policy shift, the issues such as women reproductive rights, informed choice, right to information, right to decide, right to effective and accessible services and right against harmful practices have come to occupy the centre stage. Discrimination against women in health provisions, violence against

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Adolescent's Behaviour & Health: Adolescents, who constitute about 22 percent of our population have been recognized both nationally & internationally an important and critical group of population. The reproductive health matters including sexuality of adolescent is a very major area of concern. Other issues concerning this group are adjustment, stress, substance use, early marriage and pregnancy, social and sexual abuse, STDs, reproductive health and population control. There is a need to understand the awareness and other social and psychological dynamics so as to plan effective service programmes including sex education for this group of population.

Diseases with Stigma: Diseases such as HIV/AIDS, tuberculosis and leprosy which have stigma associated with them pose peculiar and serious difficulties to both the patients as well as the health services and providers of services. Denial of the disease and not seeking the services and desertions of patients by the families for fear of stigma and infection further complicate the problem. Lack of privacy of services and confidentiality of diagnosis are deterrents for seeking the services. Social and behavioural research on these issues should provide leads for planning effective intervention strategies to combat stigma and ensure effective treatment for the diseases.

Through a 'call for proposals' 42 concept proposals were received of which 13 full proposals have been received for further review.

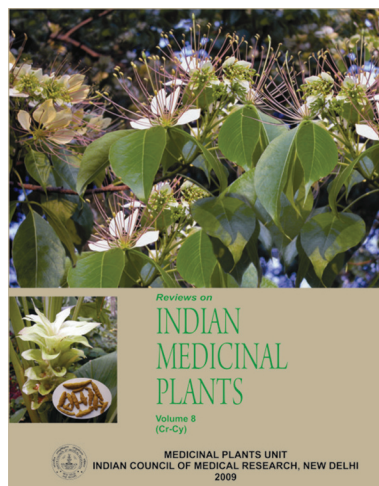
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Medicinal Plants

Review Monographs on Indian Medicinal Plants:

The programme aims at consolidation of Indian research contributions (published information) at the various National laboratories/institutions across the country in the area of medicinal plants and present the compiled information in series on Reviews on Indian Medicinal Plants.

During the year Eighth volume (with botanical names Cr-Cy) has been published covering monographs on about 218 medicinal plants species carrying multidisciplinary information as part of series on Reviews on Indian Medicinal Plants. The 10 volume



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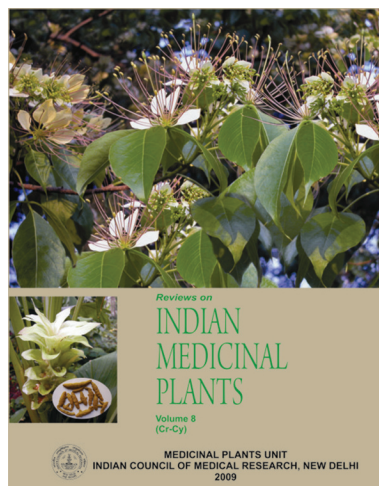
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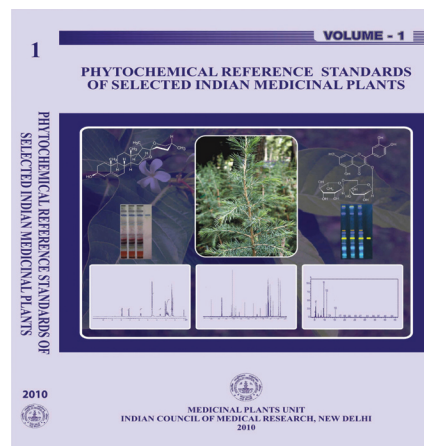
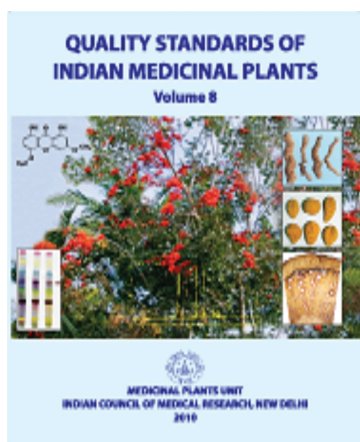
(with botanical names Ec-Ex) covering monographs on about 423 plant species is under print.

Earlier, 8 volumes of Reviews on Indian Medicinal Plants (with botanical names starting with A, B and Ca-Co, Da-Dy) covering multidisciplinary research data on about 1,936 plants covering about 36,500 citations have been published.

Each Monograph includes regional names of the medicinal plant, its sanskrit synonyms as well as the Ayurvedic description (wherever available), ethnobotanical studies, apart from the habitat and the parts used, properties and uses on one hand, and the details of botanical, pharmacognostical, chemical, pharmacological and clinical data on the other, backed by complete references and bibliography on each aspect of the information cited, besides the colour photographs of important medicinal plants.

Quality Standards of Indian Medicinal Plants: The programme aims at development of Quality Standards of important Indian medicinal plants and preparation of monographs thereof. The programme is in progress at various national laboratories/ Institutions in the country. The monographs are on the pattern of WHO guidelines and focus on the diagnostic features and phytochemical studies, including markers besides having information on pharmacological, clinical, toxicological aspects along with dosage, adulterants/substitutes etc.

The Quality standards on 35 medicinal plants were developed, monographs prepared, finalized, technically reviewed and published as Vol. 8 as part of series on Quality Standards on Indian Medicinal Plants. Earlier 7 volumes have been brought out containing quality standards of a total of 239 plants. Monographs on another 35 plants are being finalized for 9th volume.



Generation of Phytochemical reference standards and Development of Repository of Reference Phytoconstituents of Important Indian Medicinal Plants: Phytochemical reference standards (PRS) are ideally those compounds in the plant which are therapeutically active. However, in many cases the therapeutic activity of the plant is attributed to a number of phytoconstituents present in the plants. Under such circumstances any compound that is unique to the plant or the major compound or the major chemical constituent can be regarded as the PRS.

During the year the first volume containing monographs of 30 important PRS entitled "Phytochemical Reference Standards of selected Indian Medicinal Plants"

was published and released by the Hon'ble Union Minister for Health and Family Welfare Shri Ghulam Nabi Azad on the occasion of the inaugural ceremony of Councils centenary celebrations in November 2010.

The samples of marker compounds isolated are stored in the repository (quantity of each varying from 100mg to 1 g as per recommendations of the review committee). The work on 30 other monographs is under progress.



Manpower Development

Junior Research Fellowship

The Council conducted tenth National Level Examination for selecting JRFs to augment biomedical research in the country. Every year 150 JRFs (i.e. 120 for life sciences and 30 for social sciences) are selected for doing Ph. D. in biomedical sciences in different institutions. The number of candidates appeared in the year 2001 was approx. 2000 which increased to more than 14,000 in 2010-11. The examination was conducted at 7 centres (Chandigarh, Chennai, Delhi, Guwahati, Kolkata, Mumbai and Hyderabad). So far 715 JRFs have availed these fellowships in various national level institutions.

The top areas selected by JRF's were molecular biology (8.4%), immunological studies (6.6%), gene expression (3.7%), genomics (2.7%), and metabolic disorders (2.5%).

Financial Assistance for MD/MS/DM/MCh thesis in priority areas of Biomedical Research (50/Yr.)

Financial assistance of Rs.25,000/- is provided to MD/MS/DM/MCh students who are in the 2nd year. The Steering Committee has recommended financial assistance to a total of 226 students out of 563 proposals received from 2003 till date.

MD / Ph. D. Programme- 25 per year

The programme was revived to identify young medical graduates with brilliant academic record for pursuing post graduation and later to absorb them in its research cadre. The candidate who passes all MBBS examinations in the first attempt with 60% or more aggregate marks is eligible for the examination. Under this programme selected medical graduates are provided financial assistance for 4 to 5 years. The eligible candidates were selected through national level examination.

Programme is ongoing at three centres i.e. King George University, Lucknow, NIMHANS, Bangalore and Sri Ramachandra Medical College, Chennai. So far 35 candidates have joined.

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Short Term Visiting Fellowship- 50 per year

The objective of the award of the Short Term Visiting Fellowship programme is to provide opportunity to a scientist employed in a medical college, research institute, university etc. and actually engaged in research in the field of biomedical sciences to learn advanced research techniques/ methods in use in other institutes in India. The tenure is three months.

Other Training/ Skill Development Programmes: Training course were attended by 15 scientists.

Financial Support for Participation in International Conferences/Training Programmes/ Workshops for Non-ICMR Scientists

One of the major mandates of the Council is capacity building of biomedical scientists of the country by providing them financial assistance for participating in International Conferences/Training programmes/ Workshops etc. Out of about 400 applications 97 scientists were awarded during 2010-2011.

ICMR Post Doctoral Fellowship (50 per year)

The Council has initiated a new programme to strengthen the scientific environment at its Institutes. Also, this will enable the younger generation to do advanced research in ICMR's State of Art Institutes for 3 years. So far 27 candidates have joined during the year.

**The Organizational Structure
of
Department of Health Research**

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graph TD; A["The Organizational Structure of Department of Health Research"] --> B["Secretary (DHR) and DG, ICMR"]; B --> C["Joint Secretary"]; C --> D["Director"]; D --> E["Under Secretary"]; E --> F["Section Officer"];
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Secretary (DHR) and DG, ICMR

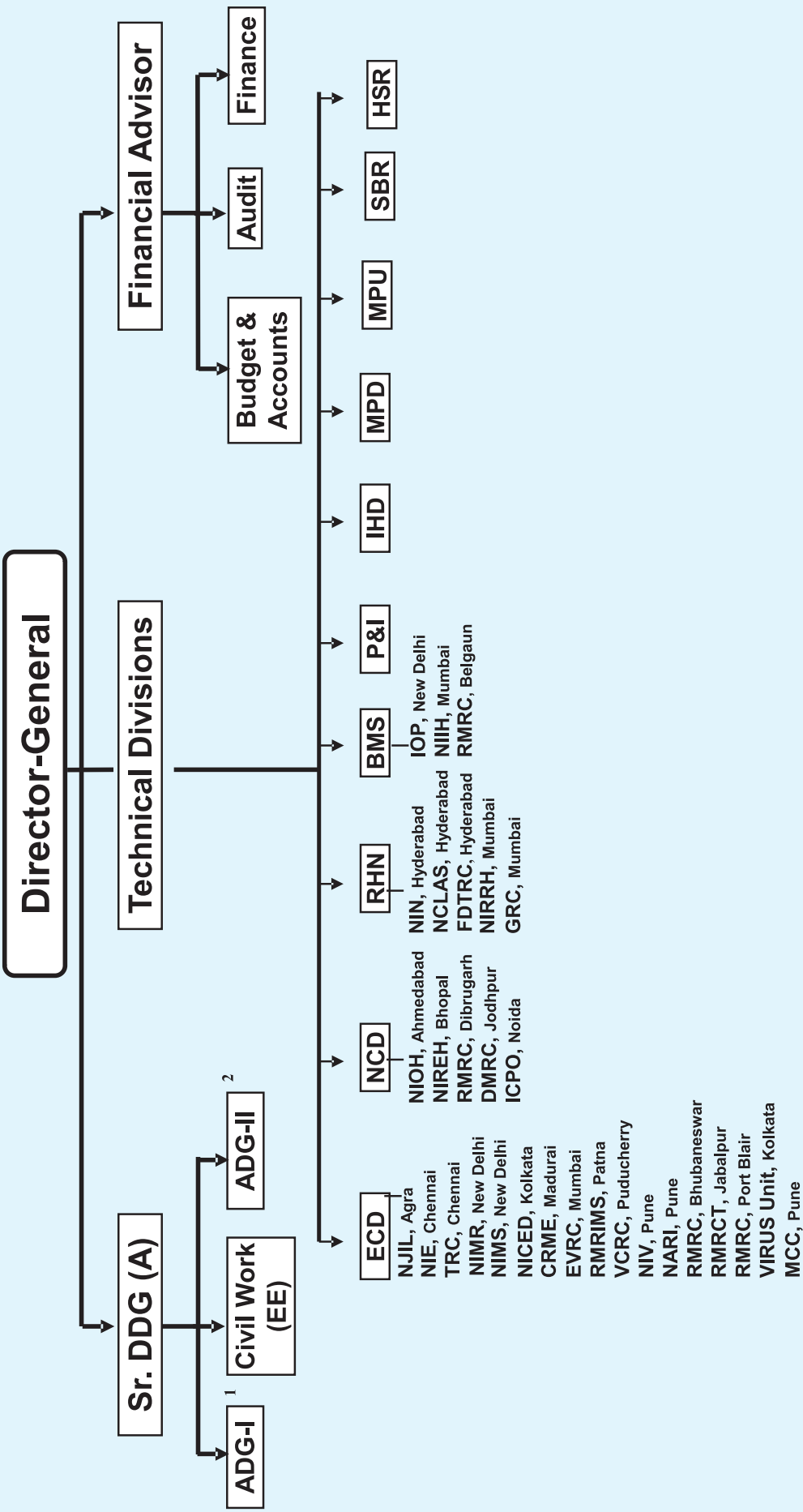
Joint Secretary

Director

Under Secretary

Section Officer

Organizational Structure of Indian Council of Medical Research



ECD – Epidemiological & Communicable Diseases **BMS** – Basic Medical Sciences **MPD** – Manpower Power Development
NCD – Non-Communicable Diseases **P&I** – Publication, Information & Communication **MPU** – Medicinal Plants Unit
RHN – Reproductive Health and Nutrition **IHD** – International Health Division **SBR** – Social & Behavioural Research
HSR – Health Systems Research