Annual Report 2017-18



Compiled & Edited by : Dr. Chanchal Goyal, Scientist 'D', Informatics, System and Research Management (ISRM) Division Scientific Support: Dr. Rajnikant, Scientist 'F' & Head Research Management and Policy Planning Coordination (RMPPC) Division

Technical Assistance: Arvind Singh Kushwah (Scientist-B), Mona Gupta (Scientist-B), Madhu (Computer Programmer), Furqan (Data Entry Operator), Gaurav Pandey (Computer Programmer) ISRM Div.

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DIRECTOR-GENERAL'S MESSAGE

It gives me immense pleasure to present the Annual Report of the Indian Council of Medical Research (ICMR) for the year 2017-18. ICMR scientists worked as a team to achieve the goals in sync with government policies and programmes in the field of biomedical research. The significant findings of the year was the release of the India State-Level Disease Burden Estimates from 1990 to 2016 for every state of India that would ensure a more nuanced health policy and system development in each state. To combat tuberculosis in Mission Mode under India TB Research



Consortium, set up by ICMR, initiatives were made in the area of TB Diagnostics. TruNAT Rif, an indigenous, cost effective, rapid molecular diagnostic kit for TB/MDR-TB has been developed in collaboration with DBT and the industry. The feasibility study of TruNAT in 100 microscopy centres, at 50 districts, across 10 states has been completed. It has been recommended for roll out under RNTCP at Primary Health Centres (DMCs) in a phased manner. Mobile TB Diagnostic Vans were launched under ICMR-TIE-TB program in collaboration with RNTCP for targeted intervention to Expand and Strengthen TB Control in Tribal Populations. To speed up the process of leprosy elimination from the country, Mycobacterium Indicus Pranii (MIP), the world's 1st leprosy vaccine developed in India, is being piloted as preventive vaccine for contacts of patients in Gujarat and Bihar. Also, Nikusht, a real-time monitoring software developed by ICMR has been introduced into the National Leprosy Elimination Programme (NLEP).

During the year, ICMR launched three new diagnostic kits for the detection of Crimean-Congo haemorrhagic fever(CCHF) Sheep and Goat, Crimean Congo haemorrhagic fever (CCHF) in Cattle, Japanese Encephalitis virus (JEV) from Mosquito. ICMR signed an MoU with Federation of Indian Chambers of Commerce and Industry (FICCI) for commercialization of ICMR technologies under the program 'Health Technology Acceleration and Commercialization (HTAC).

To handle viral outbreaks, ICMR-NIV established surveillance at 25 sites in the country for Zika testing. Repeated training and capacity building was done for 25 labs + 11 IDSP labs. First case of Zika virus in the country was detected through ICMR's surveillance network. Entomological surveillance for Zika Virus has also been established. More than 50,000 human samples and 25,000 mosquito samples were screened by ICMR network. Baseline sero survey was initiated in 15 states to assess the prevalence of antibodies for dengue, chikungunya and JE in Indian population. This serosurvey would help in designing the policy for rolling out dengue vaccine. National Anti-Microbial Resistance Surveillance Network (AMRSN) continued to enable compilation of National Data of AMR at different levels of Health Care. Pfizer has partnered with ICMR as part of its Corporate Social Responsibility (CSR) activity to achieve the unified goal of reducing AMR.

ICMR's National Cancer Registry Programme continued to provide data on cancer Incidence, burden, mortality, trends, clinical care and survival. ICMR-NCDIR has developed an electronic mortality (NCDIR e-Mor) software, which aims to strengthen Medical Certification of Cause of Death (MCCD) reporting in hospitals through training, quality checks to avoid mode of dying and guide doctors in recording the underlying cause of death and report deaths.

During the year, ICMR released the Urban Nutrition Report and has taken up a project involving Nutrition Interventions in adolescent girls. For the same, 18 Navodaya Schools have been identified.

ICMR Strategic Plan - Agenda 2030 with focus on 5 major pillars – Health Research Capacity Strengthening, Research Data Platforms, Evidence to Policy, Traditional Medicine and Strengthening Program Implementation through Research, was released. The revised National Ethical Guidelines for Biomedical and Health Research involving Human Participants and National Ethical Guidelines for Biomedical Research involving Children have been developed and released. National Guidelines for Stem Cell Research were also developed and released.

ICMR established Samrat Ashok Tropical Disease Research Centre at RMRI, Patna with an aim to focus on research on various tropical diseases. ICMR also established 'School of Traditional Medicine' with an 'Integrated clinic' to validate the traditional medicine practices and generate human resource in the area at NITM, Belagavi.

Under Human Resource Development (HRD), ICMR selected 138 candidates for Junior Research Fellowship (JRF) through national level exam conducted in July 2017, 765 medical undergraduates were selected for short term studentship (STS), Post-doctoral Research Fellowship (PDF) was granted to 30 candidates and financial assistance was given to a total of 470 seminars/symposia/conferences. MD/Ph.D Programme is continuing in three universities and presently 98 students are engaged in this programme; seven students joined in three universities during 2017-18. A total of 389 non-ICMR scientists were given financial assistance to attend conferences abroad. ICMR institutes continued to provide training to various State level health officials.

Under International Cooperation in Health Research, partnerships in Health Research (under 2 MOUs) with various international organizations/agencies, were continued during the year. Total 42 exchange visits of Scientists were arranged for various international collaborative programmes/projects.

ICMR funded a total of 1213 extramural research projects (including fellowships) in various areas of health research during the year. To award excellence in biomedical research, ICMR distributed awards and prizes to 84 scientists. ICMR Scientists published over 800 research papers in national and international journals.

Balsam \$ Ray

(Balram Bhargava)

EDITOR'S DESK

The Indian Council of Medical Research (ICMR) is today the apex and premier medical research organization in the country which spearheads planning, formulation, coordination, implementation and promotion of biomedical research. It is one of the oldest medical research bodies in the world. In 1911, Government of India made a historic decision to establish Indian Research Fund Association (IRFA) with the specific objectives of sponsoring and coordinating medical research in the country. After Independence, in 1949, the IRFA was redesignated as the Indian Council of Medical Research (ICMR) with considerable expansion in its functions and activities.

In the year 2017-18, ICMR strived to achieve various goals in the field of biomedical research. A randomized controlled clinical trial comparing daily with intermittent therapy in HIV-TB coinfected individuals showed the efficacy to be better with the daily regimen which is in line with the current RNTCP policy. ICMR-NJILOMD Institute is involved in activities of Model Rural Health Research Units at Ghatampur, U.P and Una, Himachal Pradesh. The main objectives of the Institute are to develop and standardize techniques of investigation for diagnosis, treatment and assessment for better management of leprosy with ultimate goal of eradication of this disease by helping the National Leprosy Eradication Programme (NLEP). IT Based system (SMS and Robodialing) has been developed and the registrations of the TB and Leprosy patients has been initiated.

A total of 152 healthy contacts of leprosy patients were vaccinated in the Gandevi Block of district Navsari. A total nine clusters were studied to estimate the burden of TB in tribal area, out of which, four clusters have been completed covering highly remote and non-accessible mountainous areas (three clusters in Chamba district and one cluster in Jammu & Kashmir). TIE-TB project: A unique Active Case Finding Model comprising of Mobile TB diagnostic van for diagnosis of TB was initiated in 17 districts in 5 states by ICMR-NJILOMD.

TruNAT Rif, an indigenous, cost effective, rapid molecular diagnostic kit for TB/MDR-TB has been developed, validated and has been recommended for roll out under RNTCP at Primary Health Centres (DMCs) in a phased manner. Tribal Health Research Forum was set up at ICMR for addressing specific health needs of the tribal population in the country, under which studies in the area of nutrition, genetic disorders, malaria have been initiated.

ICMR through its institutes is supporting GOI and making efforts in demonstrating the best strategies which could be implemented in the field towards elimination of malaria. ICMR's National Institute for Research in Tribal Health (NIRTH), Jabalpur and Sun Pharma along with Govt of Madhya Pradesh and Directorate of National Vector Borne Disease Control Program (NVBDCP) have launched a program to demonstrate elimination of malaria from 1233 villages of Mandla district of Madhya Pradesh with the strategy of Track Malaria, Test Malaria and Treat Malaria. Training of field level workers, using mobile based app for better reporting and detection and treatment of cases is also being undertaken.Govt. of Punjab and ICMR's National Institute of Malaria Research (NIMR), Delhi are working together in low endemic districts of Punjab towards elimination of malaria.

ICMR has established Samrat Ashok Tropical Disease Research Centre at RMRI, Patna which will focus on research on various tropical diseases. The JE diagnostic kits (MAC-ELISA) manufactured by ICMR-NIV is used





by the National Vector Borne Disease Control Programme (NVBDCP) as one of the most sensitive serological test for JE. The availability of this kit was stepped up in 2017 to ensure that there is no shortfall in the testing laboratories. Herbal remedies for improving quality of life of critically /terminally ill patients were studied and the beneficial role of cocoa powder on cancer cell lines and cancer induced models was established.

ICMR-NARI developed an evidence based Intimate Partner Violence (IPV) intervention module titled "*Lets Fly High Together*" and "*Ghya Bharari Ekatra*" [in English & Marathi]. ICMR-NARI continues to aid the national programme in maintaining sustained quality of HIV-1 viral load testing during countrywide scale up. This institute has been identified as a host institute for WHO accredited laboratory for HIV drug resistance genotyping and has extended support to SAARC countries for HIVDR testing. A novel formulation with serratiopeptidase & fluconazole for use in biofilm associated *Candida* infections with properties of sustained release and prolonged activity has also been developed. An evaluation was carried out between five rapid diagnostic tests for detection of antibodies to Hepatitis C virus. Anti-HCV rapid screening diagnostic tests with performance characteristics in accordance with Drug Controller General, India have been identified through this assessment.

As follow up to the thrust area by the government to expand the research activities on alarming health issues attributed to increasing pollution of rivers, NCDIR has set up a Population Based Cancer Registry in Kamla Nehru Memorial Hospital, Allahabad (Uttar Pradesh), to determine the magnitude of various types of cancers along the course of Ganga. "Cancer Samiksha" a web based tool on assessment and analysis of cancer by ICMR - NCDIR has been developed for the public, academia, researchers, media and policy makers to visualize and analyse the cancer registry data published by NCRP for the period 2012-2014.

The electronic mortality (NCDIR e-Mor) software has been developed to strengthen the medical certificate of cause of death (MCCD) with features to generate MCCD and Death report (Form 4 and 2 respectively) to aid in death registration.National Ethical Guidelines for Biomedical & Health Research Involving Human participants, and National Ethical Guidelines for Research Involving Children were released which have to be followed for all biomedical and health research in the country. "Definition of terms used in limitation of treatment and providing palliative care at end of life" guidelines were released. ICMR Guidelines on Diagnosis and Management of Celiac Disease were also published.

ICMR-NICED established the association of Consumption of raw areca nuts by pregnant mothers with high infant mortality in Saiha district of Mizoram. A novel methodology was established for developing a research database for zoonotic and emerging infectious diseases in India.

The cancer screening of three common cancers viz oral, breast and cervix is being rolled out in 158 districts of the country and NICPR has been designated as one of the training hubs for training the master trainers of ASHAs, ANMs, staff nurses and Medical Officers. There was Establishment of National Tobacco Testing Laboratory at NICPR. This is a state-of the art laboratory intended to provide scientific inputs for implementation of directives of WHO Framework Convention on Tobacco Control (FCTC) in the South-East Asia Region, contribute to technology validation and assist Government of India in development and monitoring of strategies for harm reduction of tobacco products.

ICMR-NIN has developed guidelines for optimal duration and time of sun exposure for adequate cutaneous synthesis of vitamin D. This information can help education interventions for reducing the prevalence of vitamin D deficiency in the country. NIN also developed the indigenous technology for fortification of rice with iron, folic acid and vitamin B12 that has the potential to address anaemia that is widespread in India.

The CTRI, maintained by NIMS, brings all clinical trials to public domain which empowers patients to participate in relevant clinical trials pertaining to their conditions, particularly life threatening diseases. It is a free and online searchable database.

In 2017, 138 JRF were selected; 765 MBBS students had qualified for carrying out the STS research fellowship; 86 candidates were awarded MD/MS/DM/MCh/MDS thesis support; 20 Emeritus Medical Scientists have

been working for ICMR in different areas of biomedical research; 470 Seminars/Conferences/Workshops were provided support; 389 International Travel Grants to non-ICMR scientists were granted. ICMR offers an array of awards in biomedical sciences; 84 awardees were awarded in different award categories.

Two supplementary issues of IJMR entitled, "Microbes & Health" and "Research in Non-Communicable Diseases" were brought out. During the year, volumes 17 (with botanical names Na-Ny) and 18 (with botanical names Oc-Ox) of 'Review Monographs on Indian Medicinal Plants' covering monographs on about 234 medicinal plants species carrying multidisciplinary information with 5222 citations were published. Vol. 15 as part of series on "Quality Standards on Indian Medicinal Plants" and Vol I of Safety Review monographs on Indian medicinal plants were also published.

ICMR participated in the 105th Indian Science Congress held at Manipur University ; 26th World Book Fair held in New Delhi during 6th-13th January, 2018 and several other prominent exhibitions across the country and had put up the display and sale of ICMR publications.ICMR Awards for Popular Medical Books in Hindi were given; the First & the Second Prizes carried a sum of Rs 100,000/- and Rs 50,000/- respectively along with the Certificates and the Mementos. ICMR organized a Hindi Day lecture at ICMR Hqrs on the topic "उच्च रक्त चाप: निवारण और उपचार"".

ICMR-ISRM Division received 170 detailed adhoc proposals online; 1255 SRF/RA fellowship proposals online and Seven 'Call for proposals' programmes were also launched during the year which resulted in receipt of 1157 proposals online. These proposals were completely reviewed online by an average of 3 experts. Total 7 issues of ICMR e-English Bulletin were designed; each issue was dedicated to a special cause, depending on the cause taken up world-wide during that particular period.

The MoUs signed with effort of IHD Division were between ICMR; Department of Health and Family Welfare; MOH&FW and International Vaccine Institute, South Korea for enhancing the vaccine research and capacity building in vaccine area at New Delhi on 21st August, 2017; and other MoU between ICMR and Inserm, France was signed on 10th March, 2018 at New Delhi during the visit of Hon'ble President of France to India.

The ISRM Division worked tirelessly to increase the virality and outreach of ICMR social media, and introduced 5 social media handles. The outreach of Facebook and twitter increased 10 times during the year. A tremendous effort was made by ISRM division to implement PFMS module across all its institutes and successfully achieved the target with the support of Health Ministry. ISRM Division helped in reduction of environmental pollution and economic burden through digitization of proposal submission, online review process, reducing hard copies of Annual report, and introducing e-bulletin of English. ICMR, through digitization, thus helped to curb economic burden of researchers in the form of Cost (Printing cost + Page cost + Speed post cost + Man power cost for each proposal) and environmental burden in the form of saving pages, saving trees, hence reducing environmental pollution.

One of the major recommendations suggested by PEC was the merger of smaller institutes and centres of similar nature of work which would provide ample benefits like overhead savings, flexible financial allocation, improved efficiency, proper resource utilization, shared clinical support and infrastructure rationalization, as a result 7 ICMR institutes were merged. Regional Medical Research Centre (RMRC), Gorakhpur was announced with the up-gradation of NIV, Unit at Gorakhpur, to a full fledged centre.

(DR CHANCHAL GOYAL)

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COMMUNICABLE DISEASES

ommunicable and infectious diseases pose serious public health problems. ICMR's research efforts in the area of communicable diseases were made by 16 institutes/centres including Regional Medical Research Centres (RMRCs) and their field stations located in different parts of the country as well as by granting ad hoc projects in extramural mode in universitties/medical colleges and other organizations. The research activities carried out by different ICMR Institutes and their outcome are detailed in this chapter.

INTRAMURAL RESEARCH

NATIONAL INSTITUTE FOR RESEARCH IN TUBERCULOSIS, CHENNAI

CLINICAL RESEARCH

- STREAM Study Multi-country trial to evaluate shortened drug regimens in Multi Drug Resistant Tuberculosis.
- SHINE Study Multi-country trial to evaluate shortened treatment regimen in minimal Tuberculosis in children.
- TBM Kids Trial Multi-country trial to determine optimal regimen for tuberculous meningitis in children.
- Evaluation of prevalence of Tuberculosis in inmates of the Institute of Mental Health.
- Study on the effectiveness of food supplementation on treatment outcomes and nutritional status in TB adults on retreatment regimen.

 Cambridge Chennai Centre Partnership on Antimicrobial Resistance in TB: Focus on novel diagnostics and therapeutics.

SOCIO-BEHAVIORAL RESEARCH

- Estimating the burden of TB among the tribal population and developing an innovative health system model of strengthen TB control in the tribal areas.
- Monitoring adherence to TB treatment using novel strategies (99DOTS, MERM).
- Strengthening implementation and operational research under RNTCP.
- Utilization of school students as ambassadors in TB sensitization.

HEALTH ECONOMICS STUDIES

- Understanding the economic burden of TB patients at the household level.
- Identifying costs contributing to catastrophic expenditure in TB patients.

EPIDEMIOLOGY

- Monitoring and evaluation of the TB free Chennai initiative.
- Retrospective observational time series study for fifteen years of relational impact of climatic factors on TB: Multi-centric study.
- Study of TB prevalence in homeless population in Chennai.

BACTERIOLOGY

• Molecular drug resistance characterization of XDR strains of M.tb has led to identification

of more promising markers for improving both sensitivity and specificity of detection of resistance and cross-resistance to 1st line and 2nd line anti-mycobacterial drugs for the XDR/MDR strains specific for the region and India.

- Validation of indigenous diagnostic kits (Tru Nat) for Tuberculosis.
- WGS of drug resistant strains of *M tuberculosis*
- Testing of newer molecules and compounds for anti-tubercular activity.
- Protecting and improving public health globally: Building laboratory, surveillance and workforce capacity to detect respond to and prevent drug resistant TB in India.
- Determination of Early Bactericidal Activity of anti-tubercular drugs.

BIOCHEMISTRY & CLINICAL PHARMACOLOGY

- Pharmacokinetic study of second-line anti-TB drugs in children with MDR-TB was the only study from India which showed the existing drug dosages to be adequate.
- Pharmacokinetic study of second-line anti-TB drugs in MDR-TB adult patients.
- Pharmacokinetic drug-drug interactions between first line anti-TB and anti-diabetic drugs.

IMMUNOLOGY

- Study of association of M paratuberculosis with Crohn's disease in humans and of Johnne's disease in cattle.
- Biophysical and biochemical characterization of DNA binding proteins of M tuberculosis.
- Prevalence of TB in cattle and animal handlers in Chennai (Fig. 1).
- Characterization of mycobacterial intermediary metabolic enzymes as drug targets by comparative omics.
- Whole genome sequencing and transcriptome analysis of M tuberculosis clinical isolates from bovine and human origin.

• Molecular analysis of monocyte subsets in TB.



Fig. 1: Post-mortem identification of tubercular lesions in the organs of the culled animals.

HIV STUDIES

- Analysis of patterns of HIV drug resistance in South Indian population showed a lower prevalence of thymidine analogue mutation in those receiving a tenofovir based regimen, suggesting better scope for recycling of NRTIs class of drugs.
- Study on HIV -1 drug resistance pattern in ART experienced children with virological failure revealed a low rate of baseline NRTI and NNRTI mutations.
- Molecular characterization of the envelope of vertically transmitted HIV-1 strain from infants with HIV infection showed unique characteristics that identify early transmitted viruses.
- Screening of sera of HIV-2 infected cohort identified a unique sample that exhibited potent intra and inter type cross neutralization potential.

BIOMEDICAL INFORMATICS

- Established a database for drug resistant TB and TB drugs.
- Exploring the drug resistance mechanisms in HIV-1 proteases showed that the protease inhibitor currently in use do not undergo

conformational changes to enable binding to the protease enzyme.

• In silico analysis of variable loops of HIV-1 gp120 protein aids in differentiation of single tropic and dual tropic viruses.

INTERNATIONAL CENTRE FOR EXCELLENCE IN RESEARCH

- Study of host immune responses in filarial infection and strongyloidosis showed alteration in cytokines and cellular populations which was reversed with therapy.
- Study of immunology of TB with malnutrition showed diminished chemokine responses in latent TB.
- Study of TB comorbidity with diabetes mellitus showed alteration in circulating level of antimicrobial peptides and reversal with treatment and also revealed activation of pathways associated with complications.

PUBLIC HEALTH IMPORTANCE

• A randomized controlled clinical trial comparing daily with intermittent therapy in HIV-TB coinfected individuals showed the efficacy to be better with the daily regimen which is in line with the current RNTCP policy. This study has provided the only global evidence for such a comparison (Fig. 2).



Fig. 2: KM survival analysis of regimens during the 6 months of treatment.

• A multicentric cohort study of sputum positive pulmonary patients treated across the country with intermittent RNTCP regimen determined the success rates, failures and recurrence rates under programme conditions which can be used as reference for assessing the current daily regimen.

- A pharmacokinetic study of rifabutin which compared 300 mg thrice weekly with 150 mg daily dose showed that both doses produced similar effective therapeutic levels. This finding can be used by the programme to choose the dose of logistic convenience.
- A study on psycho social issues facing MDR TB patients identified the need for counsellors to ensure treatment adherence and improve quality of life of patients.
- A randomized clinical trial using a fluoroquinolone as a part of treatment regimen of 4 months duration achieved faster sputum conversion at 2 months indicating scope for shortening TB treatment duration.

NATIONAL JALMA INSTITUTE FOR LEPROSY AND OTHER MYCOBACTERIAL DISEASES, AGRA

Institute has a major thrust on leprosy, tuberculosis, HIV, Filariasis etc and has established its leadership in all important aspects of leprosy and mycobacterial research. The Institute is participating in and cocoordinating several multi-centric studies on leprosy and tuberculosis. The Institute is also involved in research activities of Model Rural Health Research Units at Ghatampur, U.P and Una, Himachal Pradesh. The main objectives of the Institute are to develop and standardize techniques of investigation for diagnosis, treatment and assessment for better management of leprosy with ultimate goal of eradication of this disease by helping the National Leprosy Eradication Programme (NLEP). Main thrust areas of tuberculosis research are early and rapid diagnosis, drug sensitivity testing, experimental chemotherapy and immunotherapy and operational research. The Institute has well trained multidisciplinary team of scientists and clinicians.

MAJOR PROJECTS UNDERTAKEN

Targeted Intervention to expand and strengthen TB Control in tribal populations under the Revised National Tuberculosis Control Programme, India

Baseline survey has been completed at all sites. A sample size of 4900 was drawn for each site. For intervention phase of the project, thirty five Mobile TB Diagnostic Vans (MTDVs) were deployed to all the seventeen districts of 5 states (Fig. 3). In Rajasthan, a total 12,762 presumptive TB patients have been examined, out of which 662 TB patients were found sputum positive and 906 TB patients were X-Ray positive. Till date, 854 TB patients have been initiated on treatment.



Fig. 3: Mobile TB Diagnostic Vans in tribal areas.

Estimate the burden of TB among the tribal population and develop and Innovate Health System Model to strength TB control in tribal area

A total nine clusters had to be studied to estimate the burden of TB in tribal area, out of which, four clusters have been completed covering highly remote and non-accessible mountainous areas (three clusters in Chamba district and one cluster in Jammu & Kashmir). Till date, a total 150 chest symptomatic samples have been collected and sent to the NJIL&OMD for further examinations (sputum microscopy and culture).

To develop an IT based leprosy and TB patients monitoring system in order to ensure complete treatment of the patients

IT Based system (SMS and Robodialing) has been developed and the registrations of the TB and Leprosy patients has been initiated. Till date, 97 patients have been registered.

Programmatic implementation and comparison of MIP vaccine immunoprophylaxis and rifampicin chemoprophylaxis under the National Leprosy Eradication Programme (NLEP) in high endemic settings

A total of 152 healthy contacts of leprosy patients were vaccinated in the Gandevi Block of district Navsari (Fig. 4). Out of the 152 contacts, 5 contacts had also been given the first booster dose. As per knowledge available, the MIP vaccine side effects occur till 6-8 weeks. Since the day of last vaccination 8 weeks have elapsed and no side effects have been reported.



Fig. 4: MIP vaccination at Navsari.

Astudy on endemicity of leprosy and utilization of health services in selected areas of Chhattisgarh and Uttar Pradesh: Role of RLEP-PCR in reducing endemicity

A total of 101 patients and 175 contacts were recruited from Mahasamund district of Chhattisgarh and 106 patients and 191 contacts were recruited from Ghatampur of UP. In Chhattisgarh, 56 (55.44%) MB patients and 45 (44.55%) PB cases were recruited where as in Ghatampur, 50 (47.16%) patients were MB and 56 (52.83%) were PB cases. In Chhattisgarh, 24 (23.76%) were found to be AFB positive while in Ghatampur, the number was 27 (25.47%). 53 (52.47%) leprosy cases were found to be RLEP-PCR positive out of 101 patients in Chhattisgarh and in Ghatampur the RLEP-PCR positivity was 64 (60.37%).

Molecular epidemiology and anti-tuberculosis drug resistance in HIV positive and negative children with tuberculosis

Sputum samples from 17 pediatric patients with suspected TB were screened for *M. tuberculosis*. 8 (47.0%) and 7 (41.1%) patients were found positive for acid fast bacilli and growth on LJ medium, respectively. Of 7 isolates, 2 isolates were identified as MDR isolates of *M.tuberculosis*.

Study of profile of deformity in new leprosy cases and to analyze predictive risk factors in the development and progression of the disability

Concordance between clinical nerve involvement, monofilament testing, thermal testing and SNCV/ MNCV was observed. Changes in NCVs parameters were seen in peripheral nerves other than those clinically involved. Association of serum cytokine and anticeramide levels in relation to clinical profile and status of NFI are being studied.

Multicentric trial to study the effect of early active mobilization as compared to three weeks immobilization following tendon transfer procedures for claw hand

27 patients have been surgically corrected for claw hands of which 13 were randomised in Early Mobilization and 14 were randomised in Conventional/Delayed Mobilization.

Prevalence of tuberculosis infection and disease among pediatric household contacts of Multi-Drug Resistant tuberculosis patients-A multi centric prospective cohort study (PAMPER-STUDY)

Total 975 participants were screened, 105 Index cases (MDR-TB) were recruited and recruitment target of 300 paediatric contacts have been achieved. Follow up of the pediatrics contacts of MDR-TB cases is ongoing in this trial from NJIL&OMD and SN Medical College, Agra.

Whole proteome analysis of aminoglycosides resistant isolates of *Mycobacterium tuberculosis*

Secretory protein profiles of aminoglycosides resistant with total susceptible isolates were compared and analyzed. Fifteen over expressed proteins were identified in resistant isolate which belonged to various categories. Molecular docking of proteins with undefined role with streptomycin showed that it binds to their conserved domains and suggests that these might neutralize/compensate the effect of drug. Interactome also suggests that over expressed proteins along with their interactive partner might be involved in *M. tuberculosis* virulence and resistance. Cumulative effect of these over expressed proteins could involve in resistance and these might be used as diagnostic markers or potential drug targets.

Evaluation of *in-vitro* and *ex-vivo* antimycobacterial activity of selected plants traditionally used in tribal medicine against MDR *Mycobacterium tuberculosis* isolates and their active fractions investigation

Bioactivity guided fractionation of two plants *Ochrocarpos longifolius* Calophyllaceae) and *Mesuaferea* (Calophyllaceae) traditionally used in traditional medicines extract was carried out using organic solvents. HPLC of active solvent fractions of *O. longifolius and M. ferea* revealed that common

compound with RT 25.8 min might be responsible for potential anti-TB activity in both species. Active fractions also exhibited intracellular activity inside THP-1 macrophages cell lines. IC_{50} of plant extracts on THP-1 was found to be higher than MIC values against *M. tuberculosis*, indicating that the cells were not adversely affected at concentrations that are effective against *M. tuberculosis*.

Rapid diagnosis of genital tuberculosis in infertile women by Loop-mediated isothermal amplification (LAMP) assay: A comparative study of the diagnostic modalities

The objective of this study is to compare the FGTB diagnostic modalities of histopathological finding, microscopy (Z-N staining–AFB), Mycobacterium culture (LJ medium) and LAMP amplification assay (IS6110 and mpb64 genome sequence from *M. tuberculosis*). A total of 34 endometrial biopsy samples were collected from infertile women aged between 25 to 40 years and studied. The LAMP assay using IS6110 primers showed positive results in twenty seven (79.4%) specimens, whereas LAMP using mpb64 primers was positive in twenty nine (85.2%) specimens.

Immunoreactivity of differentially expressed proteins of clinical isolates of *Mycobacterium tuberculosis*

Antibody response to various commercially synthesised peptides Rv2588c, Rv0951, Rv2973, Rv1911c, Rv2901c, Rv0148, Rv1656, Rv3358, Rv2809 and PPD was analysed by ELISA. Significantly higher antibody reactivity was noted to peptide Rv2588c in TB patients in comparison to healthy individuals (p<0.0001). Sensitivity of 78% and specificity of 73.3% and Area under curve (AUC) was observed to be 0.761 with this antigen. This protein shows promise as candidate antigen for sero-diagnosis.

Characterization of drug resistant HIV-1 mutants of Agra region, India by genomic and proteomic approaches

Study focused on those patients who have taken first line ART at least for a period of more than one year up to maximum six years. Record of 4432 patients were screened those who were registered for first line antiretroviral therapy from 2011 to 2016 at ART centre, SN Medical College, Agra. The nucleoside reverse transcriptase inhibitors (NRTIs) drug resistance mutation M184V and NNRTIs drug resistance mutation K103N were noted to be highly pre-dominant among three categories of first line antiretroviral therapy failure patient. This would help in management of first line ART failure patients of this region.

Investigation on cellular markers and their implications in detecting treatment efficacy of tuberculosis

investigated T regulatory cell The study associated markers and subsets, Th17 cells for their use in TB treatment monitoring in category I pulmonary TB patients. The cellular marker CD25+ and the cellular subsets CD4+CD25+, CD4+CD25+CD39+ were efficient in predicting TB treatment response in intensive as well as continuation phase of anti-tuberculous therapy on par with sputum microscopy. Cellular subset CD4+CD25+FoxP3 predicted clinical resolution of the disease (with chest X-ray resolution) and was also able to predict treatment failure. The findings from the follow-up study were confirmed in a validation group that comprised of treatment completed category I patients (n=10) which also showed a marked decline in the above said marker levels like the follow-up group.

Study of TCR mediated proximal and distal T cell signaling events in peripheral blood and pleural fluid of TB pleurisy patients

Significantly higher intracellular level of calcium was noted in cells from pleural fluid of TB pleurisy patients as compared to the intracellular calcium levels in their blood after addition of anti CD3. *M. tuberculosis* antigens significantly reduced intracellular levels of calcium. Interestingly, the reduction was more in blood as compared to pleural fluid of TB pleurisy patients.

Proteomic profiling of exosomes for the identification of potential biomarkers for tuberculosis in HIV patients

A total of 60 individuals (18 sputum smear positive tuberculosis patients, 40 sputum smear negative suspected TB patients and 2 apparently healthy humans) were included in this study. Exosomes were isolates from the blood samples of study participants using ultracentrifugation. Exosomes recovered from blood samples of study participants were characterized using scanning electron microscopy. The diameter of the exosomes was around 40-110 nm.

Identification of genetic mutations and risk factors associated with the conferring of resistance to second line anti-tuberculosis drugs in Indian isolates of *Mycobacterium tuberculosis*

A total of 278 suspected TB patients were included in this study. Out of 278 sputum samples, 27 *M. tuberculosis* isolates were recovered on LJ medium. Of the *M. tuberculosis* isolates, 19.0% and 38.0% were pan-susceptible and resistant to all four first line drugs. The presence of XDR-TB was found higher in male as compared to female and previously treated cases as compared to new cases. A total of 17 XDR *M. tuberculosis* isolates were spoligotyped and SIT26/CAS1_Del was found to be the most common spoligotype.

DNA Fingerprinting of *Mycobacterium tuberculosis* isolates from defined population by using IS-6110 probe

DNA fingerprinting of isolates from KMC, Manipal to trace the transmission by using IS 6110 probe was done and IS 6110 ranging from 0-18 copy number were observed from these group. No correlation was observed with drug sensitivity profile and distribution of IS6110 element in this population.

Spoligotyping–A secondary molecular marker for typing of *Mycobacterium tuberculosis* isolates with low copy numbers of IS-6110

Genetic diversity was studied using spoligotyping in Udupi district, Karnataka. Out of 111 clinical strains of M. tuberculosis isolated from sputum samples of pulmonary tuberculosis patients, in a SITVIT WEB analysis 57 (51.35%) strains were clustered into 11 shared types (SIT) with SIT 48/ EAI1 SOM having the major cluster of 14 (12.6 %) strains followed by SIT1942/CAS1 Del with 11 (9.9%) strains. 23 strains (20.72%) had unique spoligotypes and 31 (28%) were orphans. Indooceanic lineage was the most prominent lineage found with more than 50 % of the isolates belonging to this lineage followed by East African Indian, Euro-American and East Asian. Spoligotyping of thirty isolates from repository of NJIL&OMD revealed clusters into five shared types. SIT1942/ CAS1 Del formed the biggest cluster with 9 isolates, SIT 236/EAI5 formed the second cluster with four isolates, SIT100/Manu 1included three isolates and SIT 288/CAS2 included 2 isolates.

ZOONOTIC DISEASES

One hundred tenclinical samples (82 raw milk samples from domestic livestock species and 28 fecal samples) were screened for the presence of *Mycobacterium bovis* to understand the transmission dynamics and prevalence of zoonotic tuberculosis in Agra region. None of the milk samples were found positive for acid fast bacilli and *M. bovis*. Three milk samples collected from dairy animals and commercial dairy units were found positive for the presence *M. bovis* using PCR targeting *oxyR* gene.

Strengthening of Mycobacterial Repository for translational studies (Phase-I)

Aim of this project is to serve as a collection centre for mycobacteria of common interest and supply of reference and well characterized strains/DNAs/ RNAs/culture filtrates/lysates.

Induction of autophagy as a strategy for treatment of tuberculosis

Standardized processes were developed and prototype inhalable particles containing rapamycin or nitazoxanide alone or in combination with isoniazid+rifabutin were established. Rapamycin as well as nitazoxanide induce autophagy in human-

origin macrophages infected with *M. tuberculosis in vitro* and significantly reduced survival of the bacteria in the macrophage in a dose-dependent manner. Dose-dependent killing of M.tb and restoration of lung and spleen architecture were observed in experimentally infected mice treated with inhalations containing nitazoxanide (NTZ). Adjunct NTZ with INH and RFB cleared culturable bacteria from the lung and spleen and markedly healed tissue architecture.

Efficacy of α-PD-1 in immune reconstitution and adjunct immunotherapy against *M.tuberculosis*

Study revealed crucial role of anti-PD-1 in recruiting polyfunctional T cell responses and improving bacterial containment in both lung and spleen. Therefore, α -PD-1 might act as an adjunct to anti-tubercular treatment in restoring suppressed immune response of active tuberculosis patients.

To study the efficacy of IL10/STAT3 directed immunotherapy in augmenting the potential of rBCG30 Tice(R) against pulmonary tuberculosis in BALB/c mice

The present study attempted to improve rBCG-30 invoked anti-TB immunity through modulating the anti-inflammatory signaling induced by IL-10. In term of protection, immunotherapy resulted into better protective ability against infected animals, though differences were not significant. Further studies are warranted to identify cocktail of immunomodulators that can enhance the immunogenic potential of recombinant BCG30.

NATIONAL INSTITUTE OF CHOLERA AND ENTERIC DISEASES (NICED), KOLKATA

STUDIES ON CHOLERA AND OTHER ENTERIC BACTERIAL DISEASES

A policy brief was prepared on the appropriateness of the introduction of Oral Cholera Vaccine in targeted populations of India. It was approved by the competent authority for uploading on the ICMR website. Wider dissemination of this policy brief at the national level has been recommended. Inputs were sought from experts in this area for further revision of the policy brief if necessary.

Person-to-person transmission of cholera in endemic settings was shown to have huge impact on disease occurrence, which may differ substantially in different settings. Longitudinal enquiry revealed that inappropriate water handling at the community was a significant risk factor for persistence of endemic gastrointestinal infections, indicating urgent need of public health interventions by adopting suitable point-of-care water disinfection to control the water-borne enteric infection (Fig. 5).



Fig. 5: Field investigations & on-site analysis of environmental water samples off the coasts of India.

A study has confirmed that *Vibrio cholerae* strains frequently modify their genetic as well as phenotypic attributes probably to achieve better survival adaptability to the environment along with acquiring highly virulent traits. An integrated surveillance is required to track the distribution of currently circulating polymyxin B sensitive *V. cholerae* O1 strains, an attribute of Classical *V. cholerae* in various geographical regions of India affecting diverse populations to elucidate their actual clinical and epidemiological significance. (Fig. 6).



Fig. 6: Emergence and dissemination of Polymyxin B sensitive V. choleraeO1 strains in different states in India.

Relapse and recrudescence of typhoid fever has been reported among hospital admitted patients after treatment with parenteral third generation cephalosporinfor7daysormore.*Salm*.Typhiisolates showing resistance against fluoroquinolones, azithromycin, antimicrobials recommended for typhoid treatment, further complicated the situation challenging the management of typhoid fever.

Retinoic acid was found to improve mucosal immunity in *Vibrio cholerae* infection. Use of ellagic acid against H. pylori infection has been found to be a promising antibacterial agent against *H. pylori*-associated gastroduodenal diseases in humans.

Studies on therapeutic peptides against human *Salmonella* infections as drugs and vaccine adjuvants revealed that gold nanoparticle tagged synthetic antimicrobial peptide (Au-VG16KRKP) had potent anti-*Salmonella* effects in cell culture experiments as well as animal model of infection. In another study, extensive immunogenicity and toxicity have been investigated out in mice following introduction of a candidate peptide vaccines and polysaccharide-peptide conjugate vaccines against *Salmonella enteric* serovars Typhi and Paratyphi infections. The novel candidate vaccine showed significant humoral and cell mediated immunity as well as memory response against *Salmonella* Typhi infection in a mouse model.

A multisite typhoid disease burden estimation study has been initiated among children aged 9 months to 14 years residing at the urban slums in and around Kolkata, West Bengal (Fig. 7). One epidemiology based study is in progress addressing the climate and non-climate factors for determination of risks and prediction of outbreaks of waterborne diseases. It was observed that improving the understanding of the effects of different extreme water-related weather events on waterborne diseases is an important step towards finding ways to mitigate the risks.

To study the mechanism of probiotic action in persistent diarrhea in children caused by enteroaggregative *E.coli* using an animal model, a mouse model of persistent EAEC infection was established. It was revealed that indigenous probiotic bacteria Lbs2 (MTCC) could decrease the duration and severity of infection.

VIRAL DISEASES

ICMR-NICED has initiated an Influenza burden study among elderly urban population.

Nationwide dengue burden estimation was undertaken by sero-surveillance, where NICED was one of the multi-sites, which conducted the study at different districts of West Bengal.

On request from State Govt. the circulating Dengue serotypes was determined during the Dengue season (July-Sept) in West Bengal in 2017. Screening of >1000 dengue NS1 seropositive samples from all over West Bengal for all four serotypes revealed co-circulation of all four dengue serotypes with major circulating serotypes being DEN2 (73.4%) followed by DEN4 (14.7%), DEN1 (6.9%) and DEN3 (4.9%) (Fig. 8).



Fig. 7: Emergence and dissemination of Polymyxin B sensitive *V. cholerae*O1 strains in different states in India.



Fig. 8: Circulating Dengue Serotypes in 2017 dengue outbreak in West Bengal.

Characterization of HIV for drug resistance mutations among adults in Kolkata at the molecular level indicated the absence of HIV drug resistance mutation (both major and minor) among ART naive HIV infected individuals indicated potential success of 1st line ART.

Surveillance and molecular characterization of enteric viruses among children (<5yr) with acute gastroenteritis showed that 50% of all hospitalized diarrhoeal children were infected with one or more enteric viruses. Rotavirus was the most predominant isolate (35%). Genetic characterization of rotavirus revealed G3P[8] (67%) as the major serotype during this period. Emergence of G3P[8] strains has been observed in Eastern India after more than a decade.

Proteomics tool was utilized to identify novel host determinants which aid rotavirus infection during virus-host cell interaction.

Their potential as anti-viral targets was explored. Antiviral activity of cellular heat shock proteins (Hsp60, Hsp90), Src kinase and PI3K/AKT inhibitors were established (Fig. 9).



Fig. 9: Src kinase inhibitor triggers premature apoptosis resulting in abortive Rotavirus replication.

Studies on genomic variations of hepatitis C virus (HCV) in high risk group population in Eastern India were carried out. HCV RNA positivity varied in different high risk group population, e.g, RNA positivity in thalassemia patients and PWIDs (People Who Inject Drugs) were 65.08% and 88.46% respectively, whereas general population with chronic liver diseases was 70.83%. The

distribution of HCV genotype also varied in different HRG (High Risk Group) populations, e.g., most of the hemodialysis patients infected with HCV genotype 1c (~ 65%) whereas thalassemia patients infected with HCV genotype 3 (~86%). Another study was carried out in West Bengal to understand the genomic variations and distribution of HCV among multi-transfused thalassemia patient. The results revealed that the patients in lower age groups have greater chances to eliminate virus and HCV genotype 3a (~78%) was the major circulating strain within thalassemia patient.

TRADITIONAL MEDICINE

Shorea robusta based herbal formulation, used for skin and intestinal ailments in Indian Traditional medicine, was found to be effective against multidrug resistant wild isolates of *Salmonella* Typhi and mouse virulent S. Typhimurium infections. The anti-typhoid activity has been confirmed by *in-vivo* challenge study in animal models. Thus might be potentially used as a therapeutic agent for multidrug resistant typhoid cases. Further studies are in progress to elucidate the mechanism of antityphoid activity.

Since there are no reports on use of targeted antirotaviral drugs as therapeutic agent, screening of small molecules, the ethnomedicinal product with potential antiviral activity, was performed for its use as adjunct therapy in rotaviral diarrhea. Andrographolide, a diterpene lactone found in leaves and stems of *Andrographis paniculata*, showed potent anti-rotaviral activity *in vitro*. Initiation of an anti-rotaviral therapeutic by targeting critical host determinants to reduce rotavirus disease burden has been undertaken.

CHILD HEALTH

ICMR-NICED scientists investigated the causes of high infant mortality in Saiha district of Mizoram and identified that the consumption of raw areca nuts by mothers during their pregnancy was associated with higher mortality in infants. A project is in progress to study the rates of early initiation of breast feeding (EIBF) and exclusive breast feeding (EBF) up to 42 days of post-partum period and factors associated with failure to early initiation of breast feeding in rural West Bengal. Cultural factors, social norm and knowledge have emerged as major reasons for failure of exclusive breast feeding (EBF) up to 42 days of post-partum period.

The study on Burden of antibiotic resistance in neonates from developing societies (BARNARDS) was carried out by ICMR-NICED and Cardiff University, where the project provided the means, support, network and tools to understand the impact of multidrug resistant Gram negative bacilli on morbidity and mortality among neonatal sepsis cases. Transmission of resistant enteric organisms from mother to child, an important aspect of neonatal sepsis, was determined through this collaborative project.

BIOINFORMATICS

A study described the methodology for developing a research database for zoonotic and emerging infectious diseases in India, using a first-of-its-kind approach in the Indian context, which would help generation of database for important infectious diseases.

A novel pro-apoptotic peptide has been designed to kill the malignant cells, which specifically targets PAR1 receptor over-expressed in cancer cells. (Fig. 10). This has translational potential to be used as anticancer therapy. The study is in progress, to investigate its activity on various cancer cells.



Fig. 10: Effect of the novel pro-apoptotic peptide kills breast (A) and colon (B) cancer cells in mice model.

Computational studies were carried out to decipher host-pathogen interactions, identify drug resistance in pathogens and develop novel therapeutics by targeting pathogen virulence factors and repurposing the existing drugs.

In another computational study, S-adenosylmethionine was identified as an inhibitor for interaction between *Salm*. Typhi E3 ubiquitin ligase with leucine-rich repeats and the host receptors. *In silico* prediction of drug resistance due to a mutation of Influenza H1N1 neuraminidase protein was also made.

NATIONAL INSTITUTE OF MALARIA RESEARCH, NEW DELHI

Comprehensive Case Management programme for control of malaria in Odisha: A pilot project

Comprehensive Case Management Programme (CCMP) for control of malaria was undertaken by National Institute of Malaria Research, Government of Odisha and Medicines for Malaria Venture, Geneva ensuring early diagnosis and treatment, supported by a strong surveillance system in different transmission settings in the state of Odisha.

CCMP approach showed expected results in low endemic block. In other blocks, there has been a significant improvement in surveillance and early diagnosis and treatment which has permitted outbreak control and preventing complications. More than 90% of malaria patients were followed up for complete treatment. Most cases were diagnosed and treated at the ASHA level. The time from onset of fever to treatment decreased with majority of patients receiving treatment within 24 hours of onset of symptoms. In all intervention areas the number of cases detected has increased except in the low endemic block Bolangir which witnessed reduction in incidence. CCMP has led to a significant increase in access to diagnosis and treatment in all intervention areas. Initially there was increase in malaria cases due to improved surveillance, followed by decline due to interventions (Fig. 11).



Fig. 11: Improved surveillance and access to malaria treatment: Significant increase in cases initially followed by a decline.

CLINICAL DEVELOPMENT OF ANTIMALARIALS

A Phase IIIb trial to assess the safety, tolerability and efficacy of dihydroartemisinin/piperaquine (Eurartesim®) in Indian children and adolescent patients with acute uncomplicated *Plasmodium falciparum* malaria

This is a multi-centre, phase IIIb, single arm trial to assess the safety, tolerability and efficacy of Eurartesim oral film coated tablet formulation (160/20 mg or 320/40 mg PQP/DHA) in children and adolescent patients with acute uncomplicated Plasmodium falciparum malaria.

One hundred patients fulfilling screening criteria were enrolled in the study. The PCR-corrected ACPR was reached in 95% of the patients on day 28, in 93% on day 42 and in 92% of the patients on day 63, both in the ITT and mITT populations. A higher significance in PCR corrected ACPR was observed in the PP Population in which 100% of the patients showed a PCR-corrected ACPR on day 28; on day 42, 97.9% of patients still presented PCRcorrected ACPR and finally 96.8 % of them were still showing a PCR-corrected ACPR on day 63.

Thirty-three Adverse Events were reported. No severe adverse event/deaths were reported, indicating that the combination was safe and effective.

MONITORING THE THERAPEUTIC EFFICACY OF ANTIMALARIAL MEDICINES IN INDIA

Therapeutic efficacy studies were carried out in collaboration with NVBDCP for providing updated

information for the National programme. The data generated shows that the prescribed antimalarials, artemisinin based combination therapy (artemether lumefantrine in NE states and artesunate + SP in rest of India) was safe and effective in falciparum malaria; while chloroquine was safe and effective in vivax malaria.

EL NINO SOUTHERN OSCILLATION AND MALARIA OUTBREAKS

Correlation between 'rainfall index' and 'malaria case index' showed that malaria transmission in all geographical regions of India is not equally affected by the Indian Summer Monsoon Rainfall deficit or excess. Correlation between '+winter Ocenic Index(ONI)' and 'malaria case index' was found ranging from -0.5 to + 0.7 (p < 0.05). A positive correlation indicates that increase in El Niño intensity (+ winter ONI) will lead to rise in total malaria cases in the concurrent year in the states of Orissa, Chhattisgarh, Jharkhand, Bihar, Goa, eastern parts of Madhya Pradesh, part of Andhra Pradesh, Uttarakhand and Meghalaya. Whereas, negative correlations were found in the states of Rajasthan, Haryana, Gujarat, part of Tamil Nadu, Manipur, Mizoram and Sikkim indicating the likelihood of outbreaks in La Nina condition. This study can provide plausible guidelines to national programme for planning intervention measures in view of ENSO events.

Health Impact Assessment of Narmada Basin Dams and Resettlement & Rehabilitation Colonies in MP: Phase III

After successful completion of Phase II, the project was extended for a further period of five years (2016-2021) to cover 20 dams and its components as Phase III.

Cross sectional surveys were carried out for fever surveys and malaria positive cases were treated. MHD of the vectors was also recorded. Drinking water samples were tested and positive samples were recommended for chlorination. ASHA workers and Anganwadi workers were trained in preparation of blood smears awareness regarding vector borne diseases, symptoms and control measures. Health camps were organized and villagers were sensitized regarding vector borne diseases and pamphlets were distributed.

On the basis of work done, mitigation measures were suggested to Narmada Valley Development Authority for action (Fig. 12). There was remarkable impact of intervention measures on reduction of malaria.



Fig. 12: Mitigating measures at Dam site (Before and After).

Implications of Insecticide resistance in Malaria vectors: A five year multi-country study in a tribal district Chhattisgarh Study undertaken in Kondagaon (Chhattisgarh) brought out the following outcome

LLINs provided significant protection against malaria infection and disease, even in areas with pyrethroid resistant malaria vector *Anopheles culicifacies*, even with a 13% loss in susceptibility.

LLINs performed neither worse nor better when comparing areas with higher versus areas with lower vector resistance with more than 80% coverage.

Bottle Assay for monitoring of insecticide resistance: A new bottle bioassay technique for monitoring insecticide resistance is being standardized for large scale use. A laboratory study was carried out in five states and 21 districts of the country to assess the feasibility of use of deltamethrin-PBO combination LLIN in areas with variable pyrethroid resistant vectors. The study has shown metabolic resistance as a prime mechanism in *Anopheles culicifacies* and was synergised by PBO. The mortality was in the range of 42 to 99% and the LLIN were found effective in killing resistant mosquitoes and of course the susceptibles.

The studies using innovative ovitraps for surveillance of *Aedes* has shown significant difference (p < 0.05) compared to routine house to house surveillance.

NIMR being a nodal institute for Zika virus screening, around 3500 *Aedes aegypti* mosquitoes in 451 pools were screened from Delhi and 50 from Ahmadabad. None of the samples showed zero positivity.

A synergistic action of mosquito olfactory factors manages blood feeding associated complex behavioral responses

Decoding the genetic relationship of mosquito's sense of smell is central to design new molecular tools to disrupt mosquito-human interaction. But it is not known. how the adult female mosquitoes manage blood feeding associated behavioral responses. The institute's recent findings demonstrated that a synergistic and harmonious action of olfactory encoded unique factors govern the successful 'prior and post' blood feeding associated behavioral complexities. A quick recovery of the actions of odorant binding proteins immediately after blood feeding, and delayed reactivation of olfactory receptor proteins after blood meal digestion completion are unique to manage diverse behavioral responses. A comprehensive blood meal follow up transcriptional profiling further suggests that apart from the innate odor responses, adult female mosquitoes might take an advantage of prior odor (vertebrate) exposure,

> which leads to an exclusive evolutionary specialty, allowing them to learn, experience and adapt as a fast blood feeder in nature (Fig. 13).



Fig. 13: How smart actions of olfactory system manages blood feeding associated odor response: an evolutionary specialty of adult female mosquitoes.

Targeting Protein-Protein Interactions and Unusual Proteases of Parasite; New Tools to Combat Drug Resistance Problem in Malaria

Malarial cysteine proteases are among the critical enzymes required for parasite machinery. Structural and functional analysis of these enzymes showed that they have unique domains for refolding, inhibition and hemoglobin binding. Malarial cysteine proteases are synthesized as inactive zymogens, and hot-spots interactions are required for auto-activation. Although there are very potent inhibitors against active site of these enzymes but they are prone to drug resistance. Therefore, new strategies to develop anti-malarial agents based on hot-spot interactions involved in activation of enzymes were looked into. Targeting protein-protein interactions is a new field to explore in malaria, which might be a better tool to combat drug resistance. The centre has designed small molecules that interfere at the hot-spots residues involved in protein-protein interactions. This study also found unusual cysteine proteases (Metacaspases) as potential targets which are absent in human and act as a potential modulator of programmed cell death in P. falciparum. The study also suggests that Metacaspases -2 inhibitor, specifically affect the growth of parasites in schizont and gametocyte stages, and play a crucial role in programmed cell death by specifically interacting with Tudor Staphylococcal Nuclease domain of parasite. The centre's recent study suggest that K13 (Kelch domain) of *P. falciparum* interacts with some novel uncharacterized proteins. The study of mechanism of interaction and characterization of binding partners will further help to understand the mechanism of drug resistance.

Profiling antifolate resistance and gametocyte prevalence in uncomplicated malaria in field isolates of *Plasmodium falciparum*

Drug resistance in Plasmodium falciparum is a known major hindrance to malaria control and surveillance programmes. The polymorphism in the antifolate genes are associated not only with treatment failure but also with gametocyte carriage. In order to understand the mechanism, blood samples were collected from symptomatic patients from two malaria endemic regions, Ranchi and Raipur and one non-endemic region, Mewat. After confirmed microscopic diagnosis parasite genotyping was carried out for ploymorphic loci viz msp1, msp2, Pfg377 along with drug resistance genes viz, dhfr and dhps by PCR assay, PCR-RFLP and DNA sequencing. The field isolates were culture adapted and were assessed for gametocyte producing ability in vitro. Of the 122 field isolates analysed; 59.5% dhfr mutants, 59.8% dhps mutants were seen and high diversity for *msp1* and *msp2* genes and in Pfg377 gene were also reported. The sequence analysis of Pfg377 gene revealed five types of populations in the field isolates. The occurrence of polymorphisms in drug resistance genes indicates the increasing rate of mutations due to drug pressure in the current ACT therapy. On phylogenetic analysis of the *dhfr* and *dhps* genes in the three regions it was seen that there is no particular pattern for all the mutant alleles of *dhps* and *dhfr* across the country to any particular region.

VECTOR CONTROL RESEARCH CENTRE, PUDUCHERRY

FILARIASIS

A community based study, to compare the safety, efficacy and acceptability of a triple drug regimen (Ivermectin, Diethylcarbamazine and Albendazole) with a two-drug regimen (Diethylcarbamazine and Albendazole) for lymphatic filariasis elimination programme

A community based study (a part of multi-centric study) is carried out with an objective of finding out an alternate and effective drug regimen for Mass Drug Administration to accelerate LF elimination in 'hardcore' districts and achieve the National target for Elamination of Lymphatic Filariasis (ELF) by 2020. The study compared the safety of co-administration of a single dose of ivermectin, diethylcarbamazine and albendazole (IDA) and that of diethylcarbamazine plus albendazole (DA). The study was carried out in villages of Yadgiri district, Karnataka with persistent transmission of lymphatic filariasis (LF) despite twelve rounds of mass drug administration (MDA). Treatment assignment was randomized by blocks of villages and all consenting residents >5 years of age were treated excluding pregnant and sick. Participants were followed actively for 2 days and passively for an additional 5 days post-treatment. A total of 4787 participants were enrolled in IDA arm and 4273 in DA arm. Almost all the treated (DA: 99% and IDA: 98%) participants were monitored for any AE on days 1 or 2 post-treatment for adverse events (AEs). Rates of AEs were 8% after IDA and 6% after DA. Almost 90% of the adverse events were of mild type i.e. grade 1 in both the arms. Only one person in IDA presented with diarrhoea of grade 3 on day 4 post-treatment, and it was resolved by day 6. There were no serious AEs in both the arms. The most common AEs reported were fever, headache, dizziness, nausea and fatigue. All the AEs were self-limiting or resolved fully after treatment and did not require any hospitalization

in both the arms. The AEs were significantly more common in persons with Mf, and also significantly more common after IDA (40%) than after DA in persons with Mf (20%).The 3-drug regimen was found to have no safety concern and acceptable to communities. Reviewing the safety results of this multi-centric study, WHO has conditionally recommended the triple drug regimen to the ELF programme in special epidemiological settings. Studies on the efficacy and effectiveness of the regimens are in progress.

Adaptation, validation and application of LYMFASIM model to predict the risk of resurgence following stopping MDA based on transmission assessment survey (TAS)

LYMFASIM model was used to assess the impact of 3-drug regimen ((ivermectin, DEC & albendazole) over the currently recommended 2-drug regimen used for MDA in the LF elimination programme. The model predictions showed that mass drug administration of 3 drug regimen reduced the number of rounds of mass drug administration needed to reach the target prevalence by one or two rounds, compared with the two-drug regimen in settings with a low baseline prevalence of lymphatic filarial infection (5%). For areas with higher baseline prevalence (10-40%), the tripledrug regimen reduced the number of rounds of mass drug administration needed, by about four or five, but only at moderate-to-high levels of population coverage (>65%) and if systematic non-adherence to mass drug administration was low. The model outcome facilitated recommendation of 3-drug regimen in the LF elimination programme.

Field validation of xenomonitoring of infection in *Culex* vector by PCR as a surveillance tool for lymphatic filariasis elimination programme

A two stage cluster design based vector surveillance strategy (sampling design, gravidtrap, PCR assay) for post-MDA vector surveillance ('xenomonitoring') was developed and validated at district level in one of the evaluation units (EU) in Cuddalore district Tamil Nadu. *Culex*

quinquefasciatus, vector mosquito was sampled from 186 households spread over 30 clusters (villages/wards) using gravid traps. Molecular assay for filarial parasite of the collected mosquitoes in 346 pools of 13771 mosquitoes showed a filarial infection rate of 0.11%. The estimated infection rate is much lower than the critical cut-off of 0.5% for transmission, suggesting that MDA in the EU could be stopped. This decision of stopping MDA, based on Xenomonitoring is in agreement with the decisions based on TAS and Mf survey in the EU. Xenomonitoring strategy is recommended for its adoption as a standardized protocol for global elimination programs (WHO/HTM/NTD/ LF PCT/ 2013.10; NVBDCP National Programme Guidelines, 2016-Draft) for stopping MDA or post-MDA surveillance. The protocol is being validated in 3 districts representing three phases of evaluation (TAS failed, TAS passed once, and twice).

Effectiveness and operational feasibility of mass DEC fortified salt as a supplementary intervention to mass drug administration towards elimination of the lone foci of diurnally sub-periodic *Wuchereria bancrofti* in Andaman & Nicobar Islands

This is a collaborative study with RMRC Port Blair, aiming at assessing the operational feasibility, community acceptance and effectiveness of DEC fortified salt in Nancowry group of 21 islands in Nicobar district as a supplementary strategy for MDA. These islands are the only foci of diurnally sub-periodic Wuchereria bancrofti (DspWb) transmitted by Downsiomyia nivea mosquito. Persistence of infection with more than 1% Mf prevalence was observed in these Islands even after 12 rounds of MDA with DEC and albendazole. One year DEC salt distribution (0.2% w/w) and use by the community could reduce Mf prevalence below 1%, lending interruption of transmission. Incidence of infection was below the threshold in the target (<1%) age class indicating that mass distribution of DEC salt with above 80% coverage could be a

potential and operationally feasible option to hasten the process of elimination, in such situations.

MALARIA AND LEISHMANIASIS

Phase III evaluation of Deltamethrin 62.5 SC-PE long lasting indoor residual spraying against *Anopheles fluviatilis* and *An. culicifacies*, the vectors of malaria in Koraput district of Odisha State, India

Deltamethrin 62.5 polymer-enhanced suspension concentrate (SC-PE) is an adjuvanted aqueous suspension concentrate formulation containing 62.5 g of active ingredient per litre intended for extended residual activity on treated surfaces due to the addition of a specific polymer. The efficacy of Deltamethrin 62.5 SC-PE at 20 mg/m² against the susceptible (to synthetic pyrethroids) population of Anopheles fluviatilis and resistant population of An. culicifacies and its impact on malaria incidence was evaluated in a Plasmodium falciparum endemic area following the common protocol. Indoor residual spraving (IRS) with deltamethrin 62.5 SC-PE was carried out in 7 villages of Keskapadi SC (arm 1) and 6 villages in Kutinga SC (arm 2) received IRS with deltamethrin 2.5%. Spray coverage in HDs was 93.5% and 90.3% in arm 1 and 2, respectively while in cattle sheds the coverage was 100.0% in both the arms. After 4.5 months of spraying, 21% and 60% of the houses were found mud-plastered in arm 1 and 2, respectively.

Relative abundance of *An. culicifacies and An. fluviatilis* resting indoors (Human dwellings + Cattle sheds) and outdoors were significantly reduced in both the arms. In arm1, the parous rate of *An. culicifacies* was reduced from 63.2% (prior to spraying) to 24.1% (after spraying) while it was from 57.5% to 26.1% in arm 2. Cone bioassay showed above 80% up to 135 days post treatment in arm 1 while it was 105 days in arm 2. There was marked reduction in the Monthly Parasite Incidence (MPI) after spraying for 4 months. Deltamethrin 62.5 SC-PE is effective for longer duration compared to deltamethrin 2.5%.

Assessment of development of insecticide resistance in malaria vectors based on the exposure to different insecticides in southern districts of Odisha State

An. culicifacies was tested for its susceptibility/ resistance against DDT 4%, Malathion 5% and deltamethrin 0.05% from April to June 2017 in 10 malaria endemic districts of Odisha. The corrected mortality of this species ranged between 11% (Malkangiri) and 37.5% (Bolangir) against DDT 4 %, 44% (Nabarangpur) and 66% (Koraput) against malathion 5% and 73% (Nabarangpur) and 85% (Nuapada) against deltamethrin 0.05%, indicating development of resistance to the three insecticides in all the 10 districts.

JE, DENGUE AND ZIKA

Vector surveillance for ZIKV in selected high risk areas of India

WHO declared ZIKA outbreak as a global health Emergency during February 2016. This declaration called for all other Countries to be on high alert as well as a look out campaign for ZIKV in Dengue endemic Countries, not affected by ZIKA Virus. As a preparedness measure, vector surveillance of ZIKV was initiated to assess the risk in India since March 2016, by ICMR. As the lead institute of ICMR, VCRC coordinated vector surveillance in 36 districts from 7 states and a total of 9020 adult mosquito specimens comprising Aedes aegypti (n=8196) and Aedes albopictus (n=824) were processed for ZIKAV genome by RT-PCR. None of the samples were found positive for ZIKAV. The surveillance is extended to states and UTs where the ICMR centres/institutes are located.

SCRUB TYPHUS

Prevalence of scrub typhus vectors/rodent hosts and the pathogen, *Orientia tsutsugamushi*, in areas reporting human cases of AES in Gorakhpur district, Uttar Pradesh

Outbreaks of acute encephalitis syndrome (AES) with unknown etiology are reported every year

in Uttar Pradesh, particularly in the Gorakhpur district. Though Japanese encephalitis (JE) has been considered as a major cause of the problem in this region, analysis of AES surveillance data indicated that only 8% of the cases were due to JE. Recent reports, based on serological and molecular results, indicate that about 60% of the AES cases are due to scrub typhus. In view of this, ICMR initiated a comprehensive multi-disciplinary investigation to generate epidemiological, entomological and socio-behavioural evidence on the endemicity of scrub typhus infection in Gorakhpur district. VCRC conducted a study of entomological and zoonotic aspects of scrub typhus transmission in selected villages in this endemic area.

Orientia tsutsugamushi infection was detected both in the animal hosts and the trombiculid mites collected from AES endemic areas of Gorakhpur which confirmed transmission of scrub typhus pathogen. The infestation rate of mite vector, *Leptotrombidium deliense* was well above critical level of 0.69 per animal. Detection of natural infection of *O. tsutsugamushi* in animal and vector host indicates that the people living in the rural villages of Gorakhpur are at high risk of acquiring the disease, which might lead to AES.

MICROBIAL/CHEMICAL AGENTS FOR VECTOR CONTROL

DNA finger printing of *Bacillus thuringiensis* subsp. *israelensis* (VCRC B-17) strain, development of an improved production process/formulation and a real time PCR assay for quantification of delta endotoxin

*Bacillus thuringiensis subsp. israelens*is, an entomopathogenic bacterium is currently used as a public health biolarvicide for the control of vector mosquitoes of various diseases. The production technology related to an Aqueous Suspension (AS) formulation based on an indigenous *Bti* (VCRC-B17) has been patented by VCRC and licensed to 15 commercial firms. In order to develop

genetic marker to detect its presence in the treated habitats, complete nucleotide sequencing was done and taxonomic marker genes such as 16s rRNA, 23s rRNA, gyrA and rpoB and endo-toxin genes, cry4Aa and cry4Ba of Bti have been identified. Of these genes, only RNA Polymerase beta-subunit (rpoB), the house keeping gene, was found to act as a phylogenetic genetic marker for the identification of Bti. A sensitive taqman probe-based real time PCR assay using crystal gene specific primers targeting 439 bp fragment of the VCRC-B17 Cry4Aa gene has been developed This marker can be used as an operational tool to monitor spraying activity. An ELISA has also been developed to estimate crystal toxin content of the formulations for quality assurance and for the purpose of product registration.

VECTOR STUDIES

Faunistic studies on the diversity and distribution of mosquitoes of high altitude Himalayan regions of Himachal Pradesh and Jammu & Kashmir

Surveys were carried out in 230 localities in the Shiwalik, Pir Pangal, Zojila pass, Zanskar, Karakoram and Dhaola Dhar hill ranges of Western Himalayas, covering two states namely, Jammu & Kashmir and Himachal Pradesh to document the species diversity in view of climate change and recent outbreaks of vector borne diseases in the region. Forty-nine species, including Ochlerotatus cataphylla, a new country record was obtained from the Zanskar range at an altitude of 13,823 ft in Jammu & Kashmir. From Himachal Pradesh 42 mosquito species were obtained, of which 16 species were found to be the new record to this area. Ochlerotatus caspius, a Palearctic species was found to be widely distributed in Ladakh division and Oc. sintoni in Kargil region. Aedes aegypti and Aedes albopictus, the vectors of dengue and chikungunya have also been recorded in Jammu Division.

NATIONAL INSTITUTE OF VIROLOGY, PUNE

Influenza surveillance and diagnostic services

A network of laboratories established in the country for surveillance/ investigate outbreaks caused by respiratory viral pathogens. During the year 2188 acute respiratory infections (ARI) and 1533 from Severe Acute Respiratory Illness (SARI) patient's throat/nasal swabs collected from were tested for different respiratory viruses by duplex RT-PCR. About 15% ARI and 36.2% SARI cases were found positive for influenza viruses. Over all 29.8% were positive for different respiratory viruses [Influenza A/H1N1pdm09 (9%), RSV (6%), rhinovirus (4%), PIV (3%), hMPV (3%), adenovirus (3%), influenza B (2%) and H3N2 (1%)].

Institute is also collaborating with World Health Organization on pilot study on Respiratory Syncytial Virus (RSV) surveillance under Global Influenza Surveillance and Response System. During the year, OPD (192) and hospitalized (1092) cases belonging to all age groups were screened for RSV by Real Time PCR that showed 5.14% samples positive (RSV A=1 and RSV B= 65).

Another on-going study to track community mortality due to RSV in infants/children under 2 years of age, in a rural high-risk community in Melghat, Maharashtra (samples were also screened for Influenza and other respiratory viruses) detected an outbreak of human metapneumovirus in September 2017. Screening of 833 samples for RSV yielded 18 RSV B positives. Rhinovirus activity was observed throughout the year, whereas, influenza was detected in August and September 2017.

Similarly, a network of population-based influenza surveillance platforms for elderly persons in India is being developed at Janata Vasahat, an urban slum in Pune with a population of 31,489. Mapping and listing of the study site is done. A cohort of 1009 elderly was recruited and baseline data (Individual and household) of all the participants were recorded. Weekly surveillance of the cohort was started in January 2018. ARI cases were detected during the surveillance and a total of 28 ARI samples were collected by the nurses based on the random roster.

Full genome analysis of representative influenza positive samples from Srinagar, Delhi, Jaipur, Ahmadabad, Rajkot, Maharashtra, Hyderabad, Bhubaneswar, Kolkata, Guwahati, Chennai and Kerala was carried out. Data showed that influenza A/H1N1pdm09 virus HA gene (n=80) grouped in clade 6B.1, which is similar to A/Michigan/45/2015 strain and is the 2018-19 northern hemisphere vaccine component. HA gene (n=39) of influenza A/H3N2 virus grouped in Clade 3C.2a1 similar to A/Singapore/INFIMH-16-0019/2016, which is the 2018-19 northern hemisphere vaccine component. HA gene (n=10) of influenza B isolates showed that both the lineages Victoria and Yamagata are in circulation in India are similar to 2018-19 northern hemisphere vaccine components Colorado/06/2017 and B/Phuket/3073/2013. Suggesting that the currently available quadrivalent vaccine would be effective for influenza prophylaxis in our country.

WHO External Quality Assessment Program (EQAP): Panel number 16 (2017) for influenza A Real Time PCR from WHO, CHP Hong Kong was received; this contained 10 samples of A(H3), A(H5), A(H1)pdm09, influenza B and other Influenza A, the results were 100% concordant. NIV Influenza laboratory is NABL Accredited for influenza virus diagnosis and assessed and accredited the standard ISO/IEC17025:2005 in the discipline of biological testing by National Accreditation Board for Testing and Calibration Laboratories (NABL).

Public health relevance: This Influenza surveillance network is across five different geographic regions of the country: Pune, Delhi, Kolkata, Dibrugarh, Kashmir and Tamil Nadu. Surveillance helps in quickly detecting any antigenic shift or drift in the virus genome. This project also helps in keeping track of current situation on immuno-pathogenesis and antiviral susceptibility of circulating influenza strains. Data also helps in advising for the national policy, rapid intervention with antiviral drugs as well as on vaccine.

Multi-centric study to estimate the seroprevalence of dengue virus infection in India

As a multi-state study, Maharashtra state survey was undertaken during August to December 2017. Four districts in Maharashtra were selected and two urban and two rural enumeration blocks were chosen randomly. Enumeration of households and members was done using Tablet computers and the data were uploaded onto the servers at NIE. The subjects selected for the study were then contacted for consent for data collection and sampling of venous blood specimens. In all the 774 blood samples were collected; sera were separated and aliquoted into two parts. One aliquot was tested for anti-Dengue IgG antibody by indirect MAC ELISA at NIE while the other was used for quality control to be undertaken along with PRNT at NIV Pune. The prevalence of anti-Dengue IgG antibodies was 71.32% (95% CI 68.03%-74.39%). The highest seroprevalence of 90.43% was observed in 18-45 years, followed by 73.76% in 9-17 years and the lowest of 51.91% in 5-8 years. Seroprevalence was significantly higher in females (74.8%) than males (67.8%). Seroprevalence was higher in urban areas (78.00%) as compared to rural areas (65.80%). The highest seroprevalence was observed in Osmanabad district (82.63%) while the lowest was in Pune district (47.45%).

Public health relevance: In India, dengue seroprevalence data is critical for making decision on introduction of dengue vaccine in immunization program. The preliminary data from Maharashtra state indicates that the seroprevalence for dengue is higher in urban areas as compared to rural areas. All age groups have antibodies from previous infections, though seroprevalence is lower among children than adults. The WHO recommends introduction of dengue vaccination if the seroprevalence among children is above 70%.

Resource Centre for Virus Diagnostic Laboratories

Resource Centre for Virus Diagnostic Laboratories providing training on different aspects of biosafety, outbreak investigations, biomedical waste management, ELISA and PCR and Real Time PCR-based viral diagnostic methods for the staff in the VRDL network and conducted quality assurance (QA) and quality control (QC) programs. During the year department also extended scientific and technical expertise for establishing new and existing VRDLs in the country.

Public Health relevance

- This department is providing support to country's VRDL network of DHR. This is also providing support in enhancing laboratory capacity for the preparedness of emerging infections in the country.
- Response to National emergency
- Need-based hands-on training for Zika virus and Influenza virus diagnosis was conducted during the year. This provided basis for establishing countrywide Zika virus surveillance program.

Diagnostic Reagent Facility

During the year 11,106 MAC ELISA kits (JE, Dengue and Chikungunya) were produced and supplied to SSH and 15Apex laboratories under the national program and also to WHO SEAR for onward transmission to neighboring countries. Maximum number of kits was supplied to Karnataka followed by Delhi, West Bengal, Gujarat and Andhra Pradesh. Nagaland, Arunachal Pradesh and Himachal Pradesh received the least number of kits during the year.

Public Health relevance: Country's vector borne diseases surveillance program of NVBDCP, Delhi, is largely dependent on the supply of these kits.

Hospital based surveillance of rotaviruses and strains in children with acute gastroenteritis

Hospital based surveillance of rotavirus disease and strains among children <5 years age for determination of the diseases burden, seasonal distribution and prevalent RV G-P genotypes was undertaken. In the study, 177 faecal specimens collected from children hospitalized with acute gastroenteritis in Pune (Maharashtra) showed Rotavirus positivity in 28.2 % of the cases by ELISA. All positive specimens were subjected to multiplex PCR for RV VP7 (G) and VP4 (P) genotyping. Nearly 96% and 94% of the strains were typed for G and P genotypes respectively while 92% were typed for both. The study showed circulation of G3P[8] (70%), G1P[8] (10%), G1P[6] (2%), G9P[4] (2%), G12P[11] (4%), G10P[8] (2%), GNTP[8] (2%), G3P[NT] (2%), G12P[NT] (2%) and GNTP[NT] (2%) rotavirus strains. Mixed infection of rotavirus genotype G3P[4]P[8] was detected in single specimens.

The study highlights predominance of RV G3P [8] in 70.0% of the strains followed by RVG1P[8] in 10% and unusual RV strains at low level in Pune clinical recruitment site (CRS).

Public health relevance: Rota virus is one of the major cause of hospitalization and leading cause of childhood mortality. ICMR initiated a countrywide network for the surveillance. This project is providing surveillance data from western India. During the year the RV G3P [8] was predominantly found circulating. This can be prevented by the existing Rotavac vaccine.

SURVEILLANCE OF ZIKA VIRUS INFECTIONS IN INDIA

The explosive outbreaks of Zika infection triggered a global alert by the WHO for Zika infections in February 2016. The abundance of the principal Aedes mosquito vectors across the country and extensive global travel connectivity placed India at high-risk for Zika infections. Recognizing this, the ICMR/DHR entrusted the NIV to coordinate nation-wide preparedness to address the risk. In response, the NIV quickly developed in-house conventional PCR and real-time RT-PCR assays for Zika diagnosis. Detailed guidelines were also developed for collection, transport and laboratory testing of clinical specimens for Zika. NIV trained a total of 31 laboratories from different regions of the country. Three ICMR laboratories were specifically trained in molecular detection of Zika virus in mosquito vectors. The RCVRDLs initiated the country-wide surveillance for Zika infections in February 2016. With support from the ICMR, DHR and state governments, the RC-VRDL at NIV conducted three on-site, hands-on training Programs at Govt. BJ Medical College in Ahmedabad, Gujarat (during February 14-16, 2018), PGIMER, Chandigarh, Punjab (March 23, 2018) and SMS Medical College, Jaipur, Rajasthan (March 26-27, 2018). A special training program was also conducted for selected IDSP laboratories in Maharashtra during April 24-26, 2018. Following the heightened surveillance four cases of Zika virus have been detected.

Public health relevance: This project is providing Zika surveillance data for India. The epidemiological patterns of Zika transmission in India, characteristics of Zika strains in circulation, as well as the potential association of Zika with comorbidities need to be explored in detail. There is need to enhance the surveillance among patients with acute febrile illnesses, ante-natal women and especially among babies with congenital microcephaly.

Studies on the vector competence of Indian strain of Aedes aegypti to Zika virus

ZIKV replication in Ae aegypti and transmission to infant mice was confirmed by clinical signs and presence of viral RNA in different organs of mice. Concomitant infection of Ae aegypti mosquitoes with DENV, CHIKV and ZIKV showed simultaneous propagation of all the three viruses. Infection of mosquitoes with CHIKV followed by ZIKV showed 7% dual positivity; 8.3% positivity for ZIKV followed by DENV; DENV followed by ZIKV and 5% positivity for ZIKV followed by CHIKV in individual head squashes. TOT could not be demonstrated for ZIKV in the Indian strain of Ae aegypti mosquitoes. Super-infection experiments showed that ZIKV might have a relative advantage in replication dynamics over DENV.

Public health relevance: Understanding the vector competence of Indian strains of main vector Aedes aegypti to determine the possibility of outbreaks this study was carried out. In India, two other Aedes borne viruses i.e. Chikungunya and Dengue are highly prevalent. The data suggest that despite of the presence of these two viruses, Aedes vector can additionally transmit Zika virus efficiently. For prevention of these diseases, there is need to focus more on the vector control rather other individual disease control strategies.

Viral Hemorrhagic Fever surveillance

A network of six-laboratories established in the country for surveillance/ investigate outbreaks caused by hemorrhagic fever causing viruses. During the year 5839 suspected Viral Hemorrhagic Fever (VHF) cases samples were screened for dengue (DEN), Chikungunya (CHIKV) and Zika virus (ZIKV), and found 811 positives for DEN, 429 for CHIKV, while 166 samples showed positivity for both. None of the samples were found positive for ZIKV.

Public health relevance

- CHIK cases were found throughout the year however samples were referred by treating doctors for Dengue.
- The overall CHIK cases were higher than dengue. This may be because of shorter incubation in Aedes mosquitoes than dengue virus.
- The frontline test IgM followed in the network may not be effective since during acute phase [1-5 POD] the IgM is not detected secondly presence of IgM due to infection occurred

earlier cannot be detected. The molecular tests can provide accurate diagnosis since detect specifically viral RNA in the peripheral blood.

• The season of dengue & Chikungunya also coincides with gastroenteritis and many of the clinical cases are clubbed with dengue.

Seroprevalence of CCHF infection among humans in rural population in Gujarat

A total of 4978 human serum samples from all the 33 districts of Gujarat were screened for anti-CCHFV Human IgG seroprevalence. Twenty-five samples tested positive for CCHF (0.5%, 95%CI 0.3%-0.74%) of which, 17 belonged to category "A" (CCHF affected cases/ close contacts); 5 belonged to category "B" (Neighborhood) and one each from category "C" (Animal Handlers), Category "E" (Farmers) and Category "F" (Abattoir worker).

Public health relevance: The prevalence of this virus has been shown countrywide. This disease has been included by IDSP in the public health priority diseases. During the year attempt was made to understand possibility of using seroprevalence among humans to determine high-risk areas. Data shows that the seroprevalence among domestic animals would be suitable method which can be covered only under "One-Health Program".

Study of Kyasanur Forest Disease (KFD) in patients and disease progression in monkey model

With an intention to develop a diagnostic algorithm for KFDV, a KFD disease progression study was planned in KFD patients in Sindhudurg District. Persistence of KFDV viremia, IgM and IgG antibody kinetics from 72 KFD positive patients were studied over a period of two years. A total of 399 human serum samples were collected at different time-points for 740 days and screened for KFDV viral RNA, anti-KFDV IgM and IgG antibodies with the in-house developed real-time PCR and IgM and IgG ELISA. KFD virus was detected from 1st to 18th post onset day (POD). Anti-KFDV IgM and IgG antibodies were detected as early as 4th and 5th POD and persisted till 122 and 468 PODs respectively. KFDV was detected in human clinical specimens using Real-time RT-PCR [1-3 POD]; anti-KFDV IgM [24-145 POD] and IgG by ELISA [6th POD to at least 2-year post infection].

Public health relevance: KFD is one of the emerging viral infections in India. For nearly forty years it was thought that the disease was confined to Karnataka state but for few years now it has shown its presence in other state as well. The study will help us to understand the natural progression of antibody levels among patients post infection. This will help in proper understanding of the lab results in relevance with the appearance and disappearance of various antibodies levels.

IDENTIFICATION AND CHARACTERIZATION OF NOVEL VIRAL ISOLATES

Isolation and identification of Equine Encephalosis virus, an Arbovirus in horse samples was undertaken. In July 2008, blood and necropsy samples (lung, liver, kidney, and spleen) from a horse suffering from fever, nasal discharge, loss of appetite, and symptoms of weakness, for etiological investigation from a horse farm in Pune, Maharashtra state. RNA and DNA extracted from infected cells were analyzed on an Illumina Miniseq NGS platform machine, and the infectious virus was identified as Equine Encephalosis virus (EEV). The complete genome of the isolate was obtained and phylogenetic analysis of the VP2 gene sequences which, is used for the genotype classification of Reoviruses, revealed that the Indian isolate groups with Bryanston EEV strain belonging to serotype 4.

In addition, the identification and characterization of novel mosquito-borne (Kammavanpettai virus) and tick-borne (Wad Medani) reoviruses isolated in India and the identification and confirmation of Quaranfil virus, an Orthomyxovirus in India was undertaken. Further, the complete genome sequencing of Kaisodi virus (Phlebovirus: Phenuiviridae) was done. **Public health relevance:** EEV infections may take a heavy toll on the animal husbandry. The economic costs associated with such infection can be quite heavy. There has been discovery of novel pathogens in the country; however, its pathogenic significance needs to be understood with help of well-planned scientific studies. In Indian context, their pathogenic and public health significance needs to be explored.

Hepatitis outbreak investigation and diagnosis Collaborative study with RMRC Port Blair

241 samples collected from the tribal population of Andaman and Nicobar were processed for detecting HBsAg and HBsAg positive samples for hepatitis B virus (HBV) DNA detection. Of the 63 HBsAg positive samples, 44 samples were HBV DNA positive. Viral loads in these samples were comparatively low (<104 copies/ml) and all belonged to the genotype D which, is prevalent in the mainland India.

Public health relevance: Present report on HBV infection in Primitive Tribal Group (PTG) of Andaman suggests high transmission of HBV infection in PTGs. It warrants early public health attention in tribal populations vulnerable to HBV infection.

ELIMINATION OF POLIO, MEASLES AND RUBELLA PROGRAM

Under the National Polio Surveillance Project (NPSP), India, ICMR-National Institute of Virology, Mumbai is one of the seven Global Specialized Laboratories (GSL) of Polio Laboratory Network in South East Asia Region (SEAR), World Health Organization. Wild poliovirus has been eradicated from SEAR with the last case detected in India in January 2011. As SEAR region has been certified free of wild poliovirus in 2014, the surveillance has now become more stringent as there is always a risk of importation of wild poliovirus from neighboring polio-endemic countries such as Pakistan and Afghanistan. The objective of this Program is to eradicate wild poliovirus from India and carry out stringent surveillance with continuous monitoring

until global eradication of poliovirus is achieved. During April 2017 to February 2018, the unit tested a total of 5230 stool specimens from AFP cases reported in Maharashtra, Madhya Pradesh, and Goa. A total of 167 isolates Sabin-like (SL) polioviruses (P1SL=49; P3SL=56; P1+P3SL=36 and NPEV growing in L20B = 26) were isolated. Under environmental surveillance, the unit has tested 297 sewage specimens/concentrates and 208 isolations were made. All the isolates were found to be Sabin-like poliovirus type-1 and type-3 (P1SL-26, P3SL-99, P1SL+P3SL-83, and NPEV-88). Wild poliovirus/VDPV/Sabin2 have not been detected in any of the AFP cases/sewage specimens.

Further since 2016, the unit is also involved in the Measles and Rubella Surveillance program in relation to national and global measles and rubella elimination by 2020. The objective of this surveillance program is the elimination of measles and control of rubella.

Public health relevance: The laboratory-based surveillance system is instrumental in generating real time, credible data that helps to identify areas and populations at risk. This will help in developing strategies to ensure high coverage in these high-risk areas. Measles and Rubella Surveillance program assist in developing and sustaining a sensitive and timely case-based measles and rubella surveillance system the country that fulfils recommended surveillance performance indicators.

TECHNOLOGIES DEVELOPED

Indigenously developed ELISA Kits for diseases of public health importance

One of the mandates of National Institute of Virology, Pune is to provide support in the diagnosis for viral diseases of public health importance in the country. The technologies developed will help to provide diagnostic support for implementing rapid public health measures during disease outbreaks as well as to undertake survey to monitor viruses in humans, animals and vectors to understand the prevalence.

INDUSTRIAL PARTNER: M/S ZYDUS CADILA, AHMEDABAD, INDIA

TECHNOLOGY BRIEF: Technology in the form of indigenous kits addresses the need of a rapid diagnostic system to monitor viruses in humans, animals and vectors.

The following kits received approval from Animal husbandry and now these technologies are released on 29-11-2017 by honorable Secretary Health and DG ICMR, Dr. Soumya Swaminathan for marketing in India and at International Market.

CCHF Livestock IgG ELISA

- Crimean-Congo hemorrhagic fever (CCHF) IgG ELISA (Sheep/Goat).
- Crimean-Congo hemorrhagic fever (CCHF) IgG ELISA (Bovine).
 - CCHF virus belongs to family Bunyaviridae and a BSL-4 pathogen.
 - Fatality rate > 50% in humans, > 45 outbreaks recorded from Rajasthan and Gujarat since 2011.
 - High seropositivity is recorded in livestock in 23 states of the country including Gujarat and Rajasthan state which are endemic for this disease.
 - Livestock animals play an important role in natural cycle of virus.
 - Serological screening of ruminants allows CCHF affected areas to be identified.
 - Antibody prevalence in animals is a good indicator of virus circulation.

JE virus antigen capture ELISA for mosquito

- JE is a notifiable disease in India, caused by Flavivirus, affecting all age groups.
- Virus is maintained in nature in a cycle involving pigs, ardeid birds & mosquitoes.
- Antigen capture ELISA is developed to detect JE virus from mosquitoes.

- Assay is highly sensitive & specific due to use of monoclonal antibodies.
- This will help in monitoring virus activity in mosquitoes and also predicting high risk areas.

PUBLIC HEALTH IMPLICATIONS

- Indigenously developed antibody detection kits are cost effective, rapid, sensitive and user friendly.
- Diagnostic ELISAs will help in early disease diagnosis, efficient control and rapid implementation of public health measures.
- The kits for survey help in predicting high risk areas for the disease and timely warning for interventions.

KITS AT THE FINAL STAGES OF COMMERCIALIZATION

Anti KFD human IgM assay

- KFD is a Biosafety level (BSL-3) agents and commercially no assay is available for screening of anti-KFD IgM antibodies. This developed ELISA assay has a gamma inactivated KFD virus antigen, which will be able to diagnose samples in early phase of disease and that information will be helpful in the patients' management as well for the preventive measure in affected area. In this assay patient serum samples can be heat inactivated and used for assay. As a secondary antibody mouse immune serum (anti-KFD IgG antibody) has been used. It was purified by protein G column and biotinylated to increase the sensitivity of the assay. This can be prepared easily in containment laboratory at large scale.
- Due to inactivated nature of antigen, this kit can be used in any laboratory setting across the country. As it is globally accepted that ELISA is 1). Cost effective, 2). Sensitive, 3.) Rapid, user friendly and large number of samples can be tested in any levels of clinical set ups, public health centres and hospitals.

Recombinant protein-based assay for diagnosis of hepatitis E

- Hepatitis is highly endemic in several developing countries of Central and South Asia, North and West Africa, Mexico where inadequate sanitation and supply of unsafe drinking water is very common. In India, more than 50% of reported sporadic acute viral hepatitis cases have been attributed to HEV. Mortality rate in general adult population is 1-3% but a significant mortality (10-30%) is noted in pregnant women in their third trimester.
- Diagnosis of hepatitis E with this kit is optimized to have the highest possible accuracy for detecting infection with human HEV strains circulating in India.
- This is an indirect immunoassay that utilizes open reading frame 2 (ORF2) proteins of HEV. The presence of IgM antibodies in the specimen is detected by mouse monoclonal anti-human IgM antibodies labelled with horseradish peroxidase.

Anti CHPV human IgM assay for detection of anti CHPV antibodies

- Chandipura virus (CHPV) was incriminated as the etiological agent of larger scale outbreaks in children with high case fatality rate in various districts of Andhra Pradesh, Gujrat and Maharashtra indicated its disease-causing potential.
- In order to diagnose CHPV infection in early stage of infection the presence of virus specific IgM in patient's cerebrospinal fluid (CSF)/ serum serves for diagnosing acute encephalitis due to CHPV. The high fatality due to CHPV outbreaks and sporadic cases were reported in the affected regions in India.
- We have developed anti-CHPV IgM ELISA for the detection of virus specific IgM in the encephalitis patient's human serum and CSF samples. This indigenous ELISA uses the inactivated CHPV antigen with monoclonal

antibody-based probe. It can be efficiently used to detect IgM antibody against CHPV. The utility of avidin and anti CHPV biotin labelled antibody in kit indicated higher sensitivity.

• First anti-CHPV IgM antibody detection ELISA assay and cost effective for Indian setting. The kit is developed indigenously for diagnosis of human samples during acute phase of illness with monoclonal antibodybased probe.

NIV'S NEW PRODUCTS/KITS

Detection anti Measles Human IgM ELISA

- The disease ranks at the top for causing deaths of young children in the majority of developing countries. Annually 50 million individuals are affected and almost one million deaths are reported due to measles in developing countries. It is a highly contagious disease, transmitted through aerosol and droplets.
- Indigenously developed ELISA kit which is cost effective.
- It can be efficiently used for qualitative detection of IgM antibody in serum of suspected measles patient.
- Test with sensitivity, specificity and reproducibility.

Anti KFD human IgG ELISA

- Anti-KFD IgG ELISA kit is intended for qualitative detection of IgG antibodies in the serum of patients suspected of KFD. The serological assay is designed for providing the presumptive diagnosis of KFDV in sporadic cases, outbreak investigations and identifying etiological agent causing KFD. It can be used at any level of clinical set up, public health centres and hospitals.
- Currently there is no diagnostic ELISA kit available for detection of anti-KFD IgG antibodies.
- First anti-KFD IgG antibody detection ELISA assay and cost effective for Indian setting. The

kit is developed indigenously for serosurvey in human samples.

Anti-CCHF Human IgM ELISA

- CCHF virus is a BSL-4 level pathogen and can be handled only in BSL-4 laboratory.
- Currently there is only one commercial diagnostic ELISA kit available for detection of anti-CCHF IgM antibodies in Humans from Vector Best (Russia) but it is very expensive for developing countries. Though, many publications on CCHF human IgM ELISA development have been cited but none of them available in the market as commercial product. Indigenous anti-CCHF IgM Human screening ELISA test was developed at CDC,USA but it is not available commercially.
- This is the First indigenous anti-CCHF human IgM antibody detection kit. This assay is costeffective, sensitive, rapid and user friendly.
- Anti-CCHF IgM ELISA kit is intended for qualitative detection of IgM antibodies in human serum samples. This will also help to understand the risk of exposure or likely possibility of any infection in human population.

Anti-CCHF Human IgG ELISA

CCHF virus is a Biosafety level 4 (BSL-4) agent which causes high mortality in humans. Though it is widely spread in many countries, but only few commercial ELISA kits are available for detection of anti-CCHF Human IgM and IgG antibody. A commercial ELISA kit is available for screening of anti-CCHF Human IgG antibodies but it is very expensive for developing countries. Workers involved with livestock sector are in close proximity to animals, at high risk [that includes a larger population from rural areas, since these animals are in close proximity with the human and get infected through the infected tick bites]. Veterinary personnel dealing with these tick-infected domestic animals are also at potential risk.

- We have developed indigenously this ELISA assay which content gamma inactivated CCHF virus antigen, which will able to diagnose anti-CCHF IgG antibodies from human samples. This information will be helpful to take up preventive measure in affected area. In this assay Human serum samples can be heat inactivated or Gamma irradiated before testing to rule out the possibility of infectious virus present in serum samples.
- This kit can be used for the serosurvey studies to understand the prevalence of this disease in any areas to understand the exposure of risk or likely possibility of any infection happening in human population by CCHF virus.

MULTIPLEX REAL TIME RT-PCR FOR DENGUE AND CHIKUNGUNYA VIRUSES

Dengue (DENV) and Chikungunya (CHIKV) are spreading rapidly and invading newer regions in the world. In many regions, the two viruses co-circulate during the same outbreak. The clinical symptoms are similar for DEN/CHIK infections. However, the line of treatment although symptomatic is different for both and therefore, early diagnosis would be important for patient management. Early diagnosis would be desirable for case management. One of the methods for early diagnosis is detection of virus by molecular methods, RT-PCR or real time RT-PCR. In addition, there is the NS1 (viral antigen) detection ELISA for dengue. However, there is no single test that can detect both viruses in a single test which would provide early differential diagnosis of DEN and CHIK. The present DENV/CHIKV qRT-PCR technology provides a single step assay for detection and quantitation of five viruses; all four serotypes of DENV and CHIKV; that co-circulate in India and other parts of the world.

NIV Rota Virus Antigen capture ELISA

Rotavirus is the prime cause of severe gastroenteritis leading to a significant mortality in infants and young children worldwide. Studies conducted on paediatric nosocomial diarrhea have identified rotavirus (RV) A as the major etiological
agent globally. Rotaviruses are excreted into the intestine in large amounts (109-1011 virus particles per g feces). Transmission electron microscopy that needs special facility and technical expertise was in use to detect rotavirus particles in fecal and intestinal samples. Isolation of rotaviruses in cell culture directly from human fecal samples is time consuming and difficult, and hence, rotavirus infections are generally identified by the direct detection of antigen(s) in diarrheal samples by immunoassay methods.

NIV Rotavirus ELISA is a simple, sensitive and specific method for detection of rotavirus antigen(s) in fecal samples from diarrheic patients in acute phase of the disease.

OTHER SIGNIFICANT TECHNOLOGIES DEVELOPED DURING 2017

Viruses Inactivation Technology

Emerging and re-emerging viral infections are important public health concern worldwide. Viruses with outbreak/epidemic potential often take a heavy toll of human and animal life by rapid spread across the borders. In the past, they have emerged globally including India thus imposing a huge burden on healthcare services. India has witnessed several such viral outbreaks of public health importance that remained undiagnosed. Majority of them belong to genera: Flaviviridae, Alphaviridae, Orthomyxoviridae and Bunyaviridae. Outbreaks due to respiratory viruses such as SARS (2003), Avian flu (2005), H1N1 pandemic (2009) and H7N9 (2012) have been experienced. The high-risk associated clinical samples obtained for diagnostics necessitates their handling and processing in containment specialized laboratories. These facilities reduce the occupational exposures to high-risk pathogenic material and ensure safe environment by containing organisms and facilitate early detection of such emerging infections. The containment laboratories are complex, very expensive to operate and needs to be staffed by expert personnel. Further, safe means of transporting samples suspected of containing virulent agents to

specialized high-level containment laboratories for analysis is a major issue that hampers timely diagnosis.

NIV has established a rapid, reliable, and simple method for complete inactivation of various viruses by using combinations of chaotropic agents. Once the blood samples are collected in the vials containing these reagents, the virus(es) thus present in the samples gets inactivated within 10 minutes; therefore, these samples can be subsequently handled in normal BSL-2 laboratories, even at district hospital laboratories for diagnosis, since the Biorisk is mitigated at the time of samples collection itself. Our established inactivation technology will facilitate the diagnostic examination of these emerging and re-emerging viruses by applying standard laboratory conditions at BSL-2 level.

Using this technology medical college level VRDLs can also provide diagnosis for viruses of BSL-3/BSL-4 levels. This will also helpful to provide timely diagnosis of viral infections and save the costs required for transportation.

Technology for drinking water testing for enteric viruses

- Water quality has emerged as a growing concern. Lack of convergence with sanitation compromises water quality.
- Absence of sufficient support structure and professional capacities.
- Lack of sense of ownership in facilities created.
- Waterborne viruses are major causative agents of a wide variety of diseases like diarrhea, gastroenteritis, and hepatitis. These are often found in environmental samples like groundwater, surface water, sewage, costal water, shellfish, and tap water. Every year several disease outbreaks occur because of such viral agents.
- The major difficulty in investigating the waterborne viral disease outbreaks is recovery of small numbers of organisms from

large volumes of water. The main reason is unavailability of user-friendly and costeffective technologies that can concentrate these agents and bring to detectable level by the existing laboratory testing methods.

- Few available methods include filtration method based on adsorption-elution, virus concentration by binding virus onto erythrocytes and filtration-elution and polyethylene glycol (PEG) concentration but which are cumbersome and time-consuming.
- We have indigenously developed a technology, which describes a novel method of concentrating viral particles in the form of precipitates and bringing them up to detection level for existing molecular detection methods.
- This method is sensitive, user-friendly and cost-effective that can be useful for the detection of viruses from water samples drawn from any source.

SALIENT FEATURES

- Indigenous method for testing & screening waterborne viruses.
- Virus could be efficiently sediment and detected from water having 100 particles/ lit.
- Efficiency of sedimentation was comparable for the enteric viruses under study.
- The detection system (PCR) can serve as alarm to identify agent circulating in the region.
- The model is simple, user friendly and hence can be used at water testing laboratories.
- It can be used as screening test for detection of waterborne viruses of public health importance in field settings.

NATIONAL AIDS RESEARCH INSTITUTE, PUNE

UNDERTAKINGS IN COMMUNITY / CLINIC / PROGRAM SETTINGS

In-country Data Validation for the Elimination of Mother-to-Child Transmission of HIV and Syphilis Phase I- Maharashtra has derived duplicationfactor and revised ANC-registration and testing data. Key recommendations to NACO, MoH&FW, for E-MTCT were provided by ICMR-NARI as part of this initiative.

An assessment study was undertaken on feasibility of operationalization of 'Early or Immediate ART' to HIV infected partner as a combination intervention among HIV sero-discordant couples.

Suboptimal counseling and testing of partners of PLHIV as well as training required for care providers regarding partner testing couple counselling and ART for prevention were identified as some of the program issues and requiring urgent attention.

Assessment of Early Infant Diagnosis (EID) OF HIV infection in India was initiated during this period. This study would provide national level data on how the EID program is functioning in the field. Key processes, gaps, and barriers, along with the quality of services and data in the EID program will be identified. Secondary data have been received from NACO for 11 states for pregnant women testing and EID component in this regard.

UNDERTAKINGS IN LABORATORY SETTINGS

In order to achieve viral suppression and strengthen the Anti Retroviral Treatment (ART) roll out, the national ART programme is attempting use of dried blood spot (DBS) based HIV-1 viral load estimation to obviate logistics and the need of cold chain sample transportation. In this context, a study is being conducted to evaluate Abbott HIV-1 DBS viral load kit with paired samples of plasma, DBS finger prick and DBS venous spots.

External quality assurance support for NACO for HIV-1 viral load testing is being provided by ICMR-NARI. The laboratory at ICMR-NARI, has been identified as a Viral Load Proficiency Testing (VLPT) provider for the public sector laboratories. Under this initiative, the technology transfer of a robust and cost effective Dried Tube Specimen (DTS) was initiated with CDC. This included training on the DTS VLPT panel preparation and programme management at CDC, USA and onsite panel development at ICMR-NARI. As an outcome of this exercise, two DTS VLPT panels have been developed successfully which will be distributed to nine public sector laboratories.

Achievements from aforementioned projects

First ever data-validation study, which evaluated program data and collection processes related to ANC registrations and HIV and Syphilis testing in India has been completed successfully. National dissemination has also been carried out.

Synthesis of Inorganic Nanoparticles and its application as Carrier System for Antiviral Agents in HIV-1 Infected Human Cell Lines was initiated during thi reporting period. This study was designed to assess the efficacy of Mesoporous Silica Nanoparticles (MSNPs) as efficient antiretroviral drug (ARV) carriers. The inorganic-Amine terminated MSNPs were synthesized, conjugated with anti HIV-1 drugs and analysed for size, distribution and zeta potential. The MSNPs were characterized by field emission scanning electron microscopy, Bruker transmission electron microscopy, Fourier transform infrared and Thermo-gravimetric analysis.

MAJOR ACHIEVEMENTS HAVING PUBLIC HEALTH IMPORTANCE

Community/Clinic/Program related achievements

Scientists of ICMR-NARI provided evidence for WHO certification of Elimination of Mother to Child Transmission of HIV and Syphilis in India by 2020.

ICMR-NARI undertook implementation research assessing Test and Treat for HIV discordant couples in program setting.

A Study conducted by ICMR-NARI scientists showed that among febrile cases, rickettsioses played the paramount role in Gorakhpur region of Uttar Pradesh. The results also indicated that local clinicians should consider rickettsial infections other than scrub typhus in the differential diagnosis of all fever cases in this region.

LABORATORY BASED ACHIEVEMENTS

Understanding the type and emergence of drug resistant mutations was carried out by sequencing the complete genomes of MDR and XDR *M.tuberculosis* strains through longitudinal follow-up.

ICMR-NARI characterized intratype genomic variants of *Human papillomavirus* type 16: by cervical intraepithelial neoplastic status with functional and evolutionary analysis. The role of capsid and oncogene HPV16 variants with high-grade cervical disease and disease progression was elucidated through this study.

An evaluation was carried out between five rapid diagnostic tests for detection of antibodies to Hepatitis C virus. Anti-HCV rapid screening diagnostic tests with performance characteristics in accordance with Drug Controller General, India have been identified through this assessment.

A pilot study was carried out to determine the levels of Osteopontin (OPV) and galectin-9 in patients with Tuberculosis. OPN and Gal-9 levels were higher in TB and HIV-TB coinfected patients and correlated with TB and HIV disease severity, respectively.

Anti Retroviral Treatment (ART) related drug resistance in HIV infected infants was typed. Samples from 50 HIV infected infants from EID program were tested for HIV drug resistance mutations.

As a part of this work, the NARI-Virology laboratory programme with EQA in maintaining sustainable quality of HIV-1 viral load testing during the countrywide scale up of the HIV-1 viral load across 80 laboratories.

Scientists of ICMR-NARI have identified vaginal lactobacilli with potential probiotic use in Indian women.

HIV Drug resistance survey in India and with the samples received from the neighboring countries

of Nepal and Myanmar have been successfully completed. Data for Primary Drug Resistance (PDR) survey for Myanmar have been published in WHO HIVDR report, 2017.

RAJENDRA MEMORIAL RESEARCH INSTITUTE OF MEDICAL SCIENCES, PATNA

The research outcomes of RMRIMS, Patna has empowered the Kala-azar elimination programme with improved intervention tools in terms of early detection, effective treatment, vector management, supervision & monitoring, capacity building and strengthening partnership apart from high-end basic research.

TREND OF KALA-AZAR CASES IN BIHAR

The retrospective study (year 2001-2017) based on the secondary data revealed a significant decline in Kala-azar (KA) incidence in Bihar (p<0.001). KA incidence of 1.2 per 10000 populations in the year 2001 decreased to 0.3 in 2017.

Majority (62%) of the Kala-azar incidence occurred in only two quarters (Q2: April-June & Q3: July-September) with highest peak in Q2 and lowest incidence in Q4: October-December in almost all the years. Geographical distribution of KA incidence revealed that throughout north zone contributes about 56% of cases followed by east zone (40%) whereas west and south zone had minimal incidence i.e. 1.5% and 2.5% respectively.

Correlation of KA elimination program with disease morbidity revealed that average annual incidence for the pre-intensification period (2001-2008) was higher (2.3/10,000 population, range 1.1-3.9) than post-intensification period (2009-2017) i.e. 1.2/10,000 population, range 0.3-2.4. The overall linear slope of decline in the KA incidence between 2001 and 2008 was considerably flatter than that for 2009–2017. Only 8 districts contributed majority (64%) of the cases, of which 4 were from north zone and 4 from East zone.

Assessment of Safety and efficacy of Liposomal Amphotericin B (AmBisome) Vs Miltefosine 12 weeks therapy in PKDL treatment

A total of 100 confirmed PKDL patients have been enrolled in the study [50 in Group A (AmBisome) and 50 in Group B (miltefosine)]. Altogether 89% of enrolled subjects had a past history of VL. There was mono-morphic lesion (either macular, papular or nodular) in 70% cases whereas 30% had mixed lesions.

All the 50 patients in Group A completed full course of treatment, whereas in Group B only 24 patients have completed the full course. At the end of treatment, in both groups, papular and nodular lesions were found almost disappeared whereas macular lesions got faded without appearance of new lesions. The initial cure rate was 98% (49/50) in group A and 100% (24/24) in group B. qPCR was done to confirm the diagnosis and at the end of treatment in all the patients.

Till date, a total of 41 patients in group A and 28 in group B experienced adverse effects. Vomiting was the predominant adverse effect in miltefosine group. Other A.E. observed in both groups include increased level of hepatic enzymes, serum creatinine, anorexia, abdominal pain, back pain, headache, gastritis, etc. All the A.E.s were either CTC grade I or II and did not require any major intervention or dose modification. None of the patients experienced any serious adverse events.

Screening of ornithine decarboxylase inhibitor along with immunomodulator for their role in immunity and therapeutic implication in visceral leishmaniasis

Centre purified recombinant ornithine decarboxylase from *L. donovani* (r-LdODC) of 77 kDa approx. and examined its effects on immunological responses in peripheral blood mononuclear cells of human VL cases. r-LdODC was found inducing parasite (promastigotes as well as axenic amastigotes) growth. The up-regulated IL-10 production after stimulation of peripheral blood mononuclear cells with r-LdODC and no

effect of its stimulation on IFN-c production from CD4+ T cells in active as well as cured VL cases indicates that r-LdODC has a pivotal role in immune suppression in a susceptible host.

Further *in-vitro* study on role of r-LdODC in immune response and anti-leishmanial macrophage function revealed decreased IL-12 and nitric oxide production, and down-regulation in mean fluorescence intensities of reactive oxygen species. There was little impact of r-LdODC in the killing of *L. donovani* amastigotes in macrophages of visceral leishmaniasis patients.

The effect of cocktail containing ODC inhibitor and CD2 on safety and immunogenicity was evaluated in Balb/c mice in in-vitro condition. The results indicate that cocktail containing ODC inhibitors and CD2 used as immuno-modulator were safe for mononuclear cells and were effective in inducing IFN- γ response concomitant with reduction in parasite load.

Study on modulation of innate immune response and immunopathogenecity in PKDL patients

Skin biopsy samples were collected from the parasitological confirmed PKDL patients were investigated for expression of CD62L, CD11b, CXCL8/IL8, MIP-1 α and its role in signaling during trafficking of innate cells [macrophages and polymorphonuclear neutrophils (PMN)]. In parallel, the production of IFN- γ , TNF- α and IL-10 was also evaluated. It was observed that PMN's in nodular patients displayed more decreased L-selectin (CD62L) level and increased integrin (CD11b) expression than in macular patients.

Further analysis showed that lower extravasations of PMN's in macular patients occurred as a result of an inadequate release of CXCL8/ IL-8 than in dermal lesion of nodular patients. The production of antagonistic cytokines (IFN- γ & TNF- α) was also decreased in macular patients. It was also reflected that interference in extravasations abilities especially of the M ϕ in the dermal lesion of macular patients was due to decreased p38 MAPK pattern and increased ERK1/2 pathways. It was inferred that cytokine and chemokines differentially regulate trafficking of innate immune cells during PKDL infection.

Studies on translation initiation factor 2-alpha (LdeIF2α) of *L. donovani*: its role in survival of parasite under stress conditions

In continuation to previous studies, effect of common anti-leishmanial drugs viz; Sodium Antimony Glucamate (SAG), Amphotericin B (Amp B), miltefosine and paromomycin on phosphorylation status of LdeIF2 α was studied. It was found that ROS generated by all these drugs, except paromomycin, induces LdeIF2 α phosphorylation.

It was inferred that anti-lesihmanial drugs involved in ROS generation can induce LdeIF2 α . Estimation of LD50 values revealed that decreased LD50 values for all ROS generating drugs viz; SAG, amphotericin B and miltefosine. The findings indicate that stress induced phosphorylation of LdeIF2 α plays a crucial role in differentiation and parasite survival under stress with possible involvement in protection against drug induced stress.

Studies on differentially expressed T cells miRNA and their regulatory role in cellular immune responses during *Leishmania donovani* infection

Under the present study, it was observed that in CD4+T cells co-cultured with *L.donovani* infected macrophages, the expression of micro-RNA 150, 155, 146, 210 and 29 was significantly increased as confirmed by RT-PCR. miR-150 was selected for further studies.

Prediction of target gene of miR-150 by online software Target scan revealed that it targets a kinase family MAP3K3. After silencing of miR-150 by antagomir, the p38 signalling protein was found activated. The production of pro-inflammatory cytokines like IFN- γ and Th17 was found significantly up-regulated and anti-inflammatory cytokines IL-4 down-regulated.

Further, studies on evaluation of functional role of miR-150 in pro-inflammatory immune regulation revealed that miR-150 has a key role in pro-inflammatory cytokines production in *Leishmania* infection. Next generation sequencing of miRNA from CD4+ T cells is underway for identification of novel miRNA and its role in immune regulation.

Pathophysiology of lipoproteins in *Leishmania* donovani infection

In continuation of the study, interaction of *L. donovani* with apoA-I was studied in BALB/c mice grouped into fed with sterile commercial diet and cholesterol enriched diet. After *L. donovani* infection, intestine was pooled out and Total RNA were extracted, reverse- transcribed by CDNA kit (Thermoscientific). The resulting cDNA was subjected to PCR amplification with Taq DNA polymerase using the respective primers of ApoA1, ABCA1 and ABCG5 and GAPDH.

It was observed that cholesterol feeding induced a striking elevation in serum total cholesterol (200 mg/dl) compared to normal diet fed BALB/c mice used as controls. The cholesterol enriched fed infected mice exhibited elevated mRNA levels of ABCG5 in the small intestine compared with control mice and furthermore, apoA1, ABCA1 and ABCG5 mRNAs were induced more easily by a cholesterol-enriched diet fed mice than control mice.

Further, elevated Interferon-gamma was also found in cholesterol enriched fed mice as compared to control BALB/c mice. The findings suggest that IFN- γ and cholesterol rich diet plays an important role in inducing hypercholesterolemia in *Leishmania donovani* infected BALB/c mice.

Identification and characterization of secreted/ excreted proteins of Amphotericin B resistant *L*. *donovani* parasite

In continuation of the study, 2-D gel electrophoresis was done to study secreted proteins profiling of Amp-B sensitive (S) and resistant (R) parasites and identify differentially secreted proteins. Out of 6 major spots found in sensitive strain (S) and 4 major spots in resistant isolates (R), two (S5, S6) were present only in sensitive strain. Further, six spots (S1, S2, S3, R1, R2 and R3) were differentially expressed and were excised out for MALDI-TOF-TOF/MS analysis. Raw data of these six spots was searched against *L. donovani* database for protein identification with the help of Mascot search engine. Proteins identified in MALDI analysis were found involved in various processes like parasite survival, cellular trafficking and flagellum integrity.

To identify the major secreted proteins in conditioned media, 2-D gel was run. Out of 6 spots found, 4 spots (P1, P2, P3, P6) of major secreted proteins were excised out for MALDI analysis. Identified proteins were found involved in energy metabolism. LC-MS/MS analysis of the whole secretome of both sensitive (S) and resistant (R) isolates is under progress.

Field evaluation of Alphacypermethrin 5% in Indoor Residual Spray for sand fly control and accessing its impact on reducing Visceral Leishmaniasis cases in endemic district of Bihar, India

Under this NVBDCP supported study, decreased post-IRS (alphacypermethrin) density of parous *P.argentipes* (18.75%) as compared to pre-IRS indicates good impact of Alphacypermethrin in vector control. However, resurgence of vector species after eight weeks of IRS is a matter of concern.

Interview with spray personnel as well village community was conducted to assess operational acceptability of Alphacypermethrin. Primarily, reduction in nuisance of sand flies was reported as benefits of Alphacypermethrine 5% (Synthetic Pyrethroid) by spray personnel as well as village community. Altogether, acceptability was much higher as compared to the DDT. Moreover, disappearance of other insects viz., head lice, ants, cockroaches and house flies were also reported. Overall satisfaction was perceived with the Alphacypermethrine i.e., 100% as compared to the acceptability to DDT (87%).

Susceptibility test against different types of surfaces with alphacypermethrine confirmed maintenance of residual activity of insecticide on the surface over the period of 60 days. Thus, it was inferred that Alphacypermethrine might be very effective in Kala-azar vector control.

Integrated vector management for the VL control

In continuation of this IVM study, household based survey and entomological assessment was performed in the sampled population of the study area (both intervention and control). Feeding success rate in *P. argentipes,* Bioavailability of Insecticide in Intervention (BII) for IRS and ITN, Percent Reduction due to Intervention (% RI) in vector density, Mass acceptability of intervention(s) were assessed.

After the intervention, the lowest numbers of sand flies were collected from villages with the combined approach (IRS plus ITN) as compared to single intervention sites (either IRS or ITN only) or the control site. The reduction of insecticidal content of IRS was faster and more pronounced as compared to ITN over the period of 13 months since intervention. The monthly observation of post-intervention sandfly density revealed the highest % RI (Percent Reduction due to Intervention) at the sites with IRS+ITN as compared to either at the control site or with single intervention of IRS or with ITN.

Studies on community perception on effectiveness and side effects revealed overall satisfaction by community in regards to ITNs (87% acceptability) as compared to IRS as single intervention.

Trial of alternative insecticides for sandfly (*Phlebotomus argentipes*) control by IRS in India

The present study sponsored by Kalacore consortium was undertaken in collaboration with

LSTM, UK to assess efficacy of three insecticides: deltamethrin (K-orthrine), pirimiphos methyl (Actellic) and malathion. Under Phase 1 of this study, initial 'range-finding' and 'log probit' analysis was used to calculate lethal concentrations for each insecticide at time points LC80 and LC100. Test doses obtained for Actellic and K-orthrine was 1-2 g/m² and 40-80 mg/m² respectively. Malathion did not produce reliable killing at recommended WHO dose (2 g/m²) and was dropped from the next phase.

Further, under Phase 2 for evaluation of insecticide residue, Actellic and K-orthrine were coated on tiles at their respective test doses. It was observed that K-orthrine maintained effective mortality for both lime and brick surfaces at high and low dose regimes. Actelic produced more variable results, with clear loss of effective killing power on brick surface.

The study is in progress for validation of laboratory findings in field conditions, molecular analysis including DNA variants (kdr) and gene expression.

Evaluation of active molecule having insecticidal effect to P. argentipes.

Out 97 plants collected from different areas (62 from endemic and 35 from non-endemic areas), PK48 and PK90 (plant code), a common wild perennial herb, was identified having insecticidal effect to *P. argentipes*.

Bio-assay test revealed that methanol phase was more effective (53.02% mortality) than Hexane phase (9.5% mortality) at 100 mg/L concentration. UV-Vis Spectroscopy of fractions of PK90 leaves hexane extract was performed. Hexane extract of PK90 leaves was found non-toxic by Percentage Hemolysis Inhibition Assay having IC₅₀ value of 162.8 mg/L. The 9th fraction was found as pure compound i.e. Clerodolone with LC₅₀ and LC₉₀ being 769.22 mg/L and 10.44 mg/L (95% confidence limit) having potential insecticidal effect. It can be used directly as crystal/powder using water as solvent.

Morphological and molecular taxonomy of the *Phlebotomus argentipes* species complex in relation to transmission of Kala-azar in India

This study under ICMR VBD Science Forum was conducted in 2 Kala-azar endemic villages of north Bihar and 2 non-endemic villages of south Bihar. Altogether, 1761 *P. argentipes* complex were collected (563 from endemic and 1198 from nonendemic). All three sibling species of *P. argentipes* complex i.e. *P. argentipes* ss (45-47%), *P. annandalei* (30-31%) and *P. glaucus* (22-23%) were scrutinized based on 14 morphological features. Out of which five features were found diagnostic at a glance i.e. (i) the ratio of Sensillachaeticum/ A2. (ii) Length of wing (iii) Ratio of A1/A2+3 (iv) Aedegal lateral spine and (v) ratio of gonocoxite/ gonostyle.

It was observed that all three sibling species of *P*. argentipes complex are distributed in the endemic and non-endemic areas of Kala-azar. However, P. argentipes ss were found in larger number in both endemic and non-endemic areas than P. annandalei and P. glaucus. The life cycle and seasonality are almost similar for all sibling species with similar larval morphology. The adult P. glaucus can be distinguished by seeing the external appearance in comparison to P. argentipes ss and P. annandale. The molecular characterization need to be correlated with the morphological findings in terms of infectivity and detection of natural infection to establish the role of sibling species in disease transmission.

Remote sensing and GIS based geospatial risk modeling of kala-azar in endemic foci of Bihar

Village wise Kala-azar incidence of Vaishali district, Bihar for the year 2012-2016 was collected and analyzed in GIS platform for mapping and visualization. Household location of each individual patient was geo-surveyed by a GPS device and a spatio-temporal analysis was performed at GIS platform. Spatial pattern of the disease distribution was found varying during the years and was significantly correlated with case load per village and number of endemic villages reported during the year.

Remotely sensed vegetation proxy normalize difference vegetation index (NDVI) was calculated to quantify the vegetation density in the study villages. NDVI value of study villages ranges between -0.16 to 0.69. The VL cases located between 250 and 500m distance lags were yielded the highest mean of NDVI of 0.44 (95% CI 0.16 -0.67). Whereas, the lowest mean of NDVI of 0.36 (95% CI 0.14 - 0.62) was calculated at less than 250m distance lag. A village level sandflygenic household types based spatial risk map was generated and evaluated with pre and post IRS sandfly abundance. Finally, a district level geospatial risk map was generated to identify the high risk zones for transmitting the disease at high to low level spatial suitability across the district.

Development of software for predicting sand fly density and its correlation with the kala-azar transmission

This ICMR funded translational study was conducted in Muzaffarpur district of Bihar and Deoghar of Jharkhand as endemic and non-endemic sites respectively. In each district 5 blocks and in each block 5 villages were selected for remote sensing and entomological data collection. During the study period, a total of 260 households were surveyed from the 50 villages. Geographic location of sandfly collection sites and coverage area of the study villages were digitized and mapped in a GISshape file. Monthly variation of climatic factors such as relative humidity and temperature were also recorded.

Prediction of sandfly density was evaluated through the software model. Result shows a moderate positive association between field-observed and software-generated sand fly densities. In both the study sites, R^2 values were found at <0.80; the values ranges between 0.35 and 0.68 (R^2 values, endemic sites 95% confidence interval (CI): 0.44 to 0.68 and non-endemic sites 95% CI: 0.44 to 0.59). We also found a non-significant, very low-level relationship (r-<0.10) between sand fly density and kala-azar cases incidences among the study villages of the endemic sites. Results of this study suggest that although the spatial estimation/prediction of sandfly density is possible through remote sensing environmental and climatic observations, but to improve the model accuracy at significant level (<0.05), a real time simulation of environmental changing and tendency of sandfly abundance building is required with a dynamic prediction model.

Discovery of potential inhibitors of an essential RNA-editing ligase to block RNA Editing Activities and Editosome Assembly in *Leishmania donovani*

In-silco computational analysis followed by MD simulations revealed 36 novel compounds. MTT assay revealed six compounds with Asinex code 03013071, 01426145, 00068200, 00201711, 01811599 and 00625189 having significant potential for *in-vitro* inhibition of *L. donovani* promastigote. Out of 6, the best 2 molecules i.e 2-nitro-N-(pyridin-2-ylmethyl) benzenesulfonamide (2NB) and decahydropyrazino[2,3-b] piperazine were further studied.

Treatment of promastigotes with 2NB demonstrated a dose-dependent inhibition of the parasite growth indicating its parasite-killing ability whereas piperazine derivative showed a higher inhibition at low concentration. More interestingly, treatment with 2NB in combination with AmB reversed the resistant property of the AmB-resistant parasites.

Further, peritoneal macrophages were infected with *L. donovani* and treated with different concentrations of 2NB. 2NB was found to inhibit amastigote growth in a dose-dependent manner with an IC50 value of $86.4\pm2.4 \mu g/mL$ and reduced the parasite burden in infected macrophages by >85% (P<0.001) as compared to untreated controls. Both molecules had no toxic effect to the host macrophages. The target protein was cloned, expressed and purified. Study on potential inhibition effect of 2NB as well as piperazine derivative against REL by a radioactive based assay is underway.

Prevalence of Pulmonary tuberculosis and Latent TB Infection amongst the tribal and nontribal population of Bihar

The study was conducted in tribal and non-tribal population of Chakai and Jhajha block of Jamui district of Bihar. Out of 13711 individuals covered in Chakai block, 9208 (5051 tribal and 4157 non-tribal) i.e. 67.16% persons were of age \geq 15 years who were further screened for screening of TB infection.

After screening, 200 tribal (3.96%) and 91 non-tribal (2.19%) individuals were found symptomatic. Two sputum samples - one spot and one overnight – was collected from 291 eligible cases (Symptomatic) and examined for AFB by smear microscopy and culture. Finally, 15 (7.50%) tribal and 5 (5.49%) non-tribal were found positive for acid fast bacilli by ZN microscopy and culture examination.

Drug-susceptibility testing (DST) of 20 culture positive samples revealed that 5 samples (4 from tribal and 1 from non-tribal) were resistant to Rifampicin and Isoniazid. Tribals were found more resistant than that of non-tribals while sensitivity rate was also observed higher in tribal.

Cohort observational study to estimate prevalence of PKDL in VL patients treated with three regimens in Bihar

Under this DNDi sponsored study, an identified cohort of 1622, earlier treated with three different regimens for VL, has been targeted to follow up to detect PKDL manifestation. The three different regimens are: I) Single Dose Ambisome (SDA), II) Combination of Miltefosine and Paromomycin for 10 days (MF+PM), and III) Ambisome and Miltefosine for 8 days (AMB+MF). Post-treatment follow-up of the cohort revealed more PKDL development in patients treated with MF+PM (7.4%) than SDA or AMB+MF (2.9%).

Treatment outcome of VL patients under single dose AmBisome treatment and factors affecting outcome in a highly endemic district of Bihar, India

Under this retrospective cohort study funded by WHO Small Grant, 470 VL cases were recorded and line-listed in Muzaffarpur district across 16 PHCs, during the period July, 2016 to June, 2017. Every line-listed case was followed for treatment outcomes. Majority of VL cases (30%) were from children aged <12 years, followed by 25% from age-group 12-23 years.

Out of 470 VL cases, 426 (91%) were treated with Single Dose Ambisome (SDA). Major treatment outcome of SDA treated cases were cured (94%) after six months follow up. Overall relapse rate was 3.1% and it was higher (5.3%) in females as compared to males (1.3%). There was negligible proportion (<1%) of defaulter, failure, died, Transferred out. Overall treatment success rate (TSR) was consistent across the all age group in a range value of 90.3-100%. Out of 4 death reported, 2 were co-infected with HIV.

Study the impact of ultraviolet (UV) rays penetration on increasing incidence of PKDL in Kala-azar endemic region of Bihar

In this DST-India supported field-based study, the satellite-based UV radiations (UVR) monitoring (in terms of UV index, UV dose, Ozone column, Vitamin-D UV dose etc.) has been initiated since June 2017 in the VL endemic regions in Bihar; in special correspondence with TEMIS team, KNMI, the Netherlands. Apart from daily readings, the average data for week and months are also computed and compared with that of the non-endemic regions (in and outside Bihar).

High UV index (more than 12-14.5) was observed in the VL endemic regions during June to Aug. 2017, whereas it was lower (11 or less) in other non-endemic places in and around Bihar. Moreover, during Oct.- Dec. 2017 the UV index of the corresponding regions has gone significantly down (5-6 or less) along with other UVR parameters like UV dose, Ozone column, Vitamin-D UV dose. In the initial phase of measuring ground-level UVR penetration data by light UV meters, a significant intensity of UV radiation was found higher between 11:00 AM to 3:00 P.M. at different altitude level in Saran, Vaishali and Patna Districts.

Nine different blocks of Bihar has been visited for the actual and comprehensive observations of the key factors viz. Sun light intensity, level of UVR exposure, hygiene and sanitation, living conditions, peripheral surrounding, etc. at and around the places of PKDL patients.

More than hundred persons (PKDL suspected, cured, under treatment) have been surveyed till date. A significant biasness between UVR exposure and complaints of PKDL (or similar) lesions was noticed. Out of 50 blood samples collected from PKDL patients, genomic DNA has been isolated from >20 samples for further investigations. Currently, the fact of increasing UVR exposure is to be significantly validated with the increasing prevalence of PKDL in the endemic regions of Bihar.

SPECIAL ASSIGNMENT

As entrusted by DGHS, RMRI undertook holistic intervention approach in Vaishali district as model for Kala-azar elimination in close collaboration with Care India, MSF, DNDi, Bihar State Health Dept. and NVBDCP. Planning, execution and strict supervision & monitoring of the activities viz. IEC, training & re-orientation, active case detection, treatment with single dose AmBisome, IRS using DDT/Synthetic pyrethroid etc were the key component. The concerted effort leaded to remarkable reduction in kala-azar incidence at block level in Vaishali district.

This successfully developed Vaishali Model is currently being replicated in Saran district of Bihar as suggested by VBDSF and NVBDCP.

PUBLIC HEALTH IMPORTANCE

Successful implementation of Kala-azar elimination program, consisting strategies based on long-term research outcomes, has induced regular decline of Kala-azar incidence at the block level. However, a few blocks are still away from the elimination target. The Institute is striving to develop strategic framework through discussion at national and international platform to bring the entire blocks within the elimination target. The institutes's successfully developed "Vaishali Model" is currently being replicated in Saran, another highly district of Bihar.

Though surveillance system has improved at ground level with involvement of ASHAs and camp approach, a hospital based study conducted in two enedemic areas revealed average duration of fever 16.75 ± 3.64 days at the first contact to hospital.

Single dose AmBisome (SDA) is in the main stay for kala-azar treatment. A cohort follow-up of 426 cases treated with SDA revealed final cure of 94% with 3.1% relapse rate. An another cohort observational study of VL cases treated with three different regimens revealed comparatively high rate of post-treatment manifestation of PKDL in VL patients treated with miltefosine + Paromomycin (7.4%) than SDA and AmBisome + Miltefosine (2.9%). These findings are in favour of the current treatment regimen under elimination program. Further, as compared to 12-weeks long miltefosine regimen for PKDL treatment, AmBisome was observed as safe and effective treatment with shorter duration.

In regards to vector control, field-based evaluation of IRS with alphacypermethrin confirmed its residual efficacy over the period of 60 days with 100% acceptability by community as well as spray personnel. A comparative evaluation of integrated vector management revealed higher reduction in vector density through IRS+ITN as compared to IRS or ITN alone. However, community acceptance was higher for ITN (87%) than IRS. After test dose optimization and residual effect assessment, K-orthrine was found as an alternative insecticide for vector control. Further, Clerodolone, isolated from 9th Fraction of Methanol phase of Hexane extract of leaves of identified plant, was identified as an active compound having insecticidal effect to *P. argentipes*. Remote sensing and GIS based geospatial risk modeling has been developed for mapping of sandflygenic condition and high-risk zone for Kala-azar.

Apart from Kala-azar, RMRI has undertaken research project for estimation of tuberculosis, latent TB infection, and drug resistance in TB cases specifically focused in tribal population of Bihar.

RMRI VDRL is the sole centre in Bihar for diagnosis of H1N1 by RT-PCR and diagnosis of dengue through NS1, IgM and IgG ELISA tests. Altogether 21 viruses, including JE, influenza, Enterovirus, swine flu, HAV, HBV, HCV and HEV, etc., are being diagnosed routinely. During the period, more than 14,000 samples (blood, serum, throat, swab, CSF and stool), obtained from various sources viz. Govt. hospitals, medical colleges, private hospitals, etc. have been tested for viral infection. Moreover, The centre provided investigational support to the state Govt. during various outbreaks of viral disease.

Under capacity building, several rounds of training/ re-orientation program were organized for state medical officers and lab technicians to build up their clinical/ diagnostic skill in regards to VL and PKDL. Besides, extensive training on kala-azar elimination was imparted in collaboration with NVBDCP to Kala-azar technical supervisors and VBD consultants.

Samrat Ashoka Tropical Disease Research Centre, a new establishment, is dedicated to serve people suffering from various diseases.

ICMR-NATIONAL INSTITUTE FOR RESEARCH IN TRIBAL HEALTH (NIRTH), JABALPUR

MOLECULAR SURVEILLANCE OF MALARIA BY PCR DIAGNOSIS

In this study, finger-prick blood samples were collected from 2,333 malaria symptomatic individuals in nine states from 11 geographic locations, covering almost the entire malaria endemic regions of India and performed all the three diagnostic tests (microscopy, RDT and PCR assay) and also have conducted comparative assessment on the performance of the three diagnostic tests. Since PCR assay turned out to be highly sensitive (827 malaria positive cases) among the three types of tests, data from PCR diagnostic assay were utilized for analyses and inferences. The results indicate varied distributional prevalence of P. vivax and P. falciparum according to locations in India, and also the mixed species infection due to these two species. The proportion of P. falciparum to P. vivax was found to be 49:51, and percentage of mixed species infections due to these two parasites was found to be 13% of total infections. Considering India is set for malaria elimination by 2030, the present malaria epidemiological information is of high importance.

Phase III evaluation of Deltamethrin 62.5 SC-PE long lasting indoor residual spraying against *An. culicifacies*, the vector of malaria in India

This study was proposed to evaluate the efficacy of a new insecticide formulation Deltamethrin 62.5 SC-PE in *Plasmodium falciparum* endemic villages of Dindori district against *An. culicifacies*. Susceptibility of *An. culicifacies* to DDT, Malathion, Aplhacypermethrin and Deltamethrin was 31, 67, 93 and 95% respectively. About 90.0 % the houses and rooms were sprayed with new insecticide in one arm and by conventional insecticide in the other arm by State Govt under supervision of ICMR-NIRTH. Mortality of *An. culicifacies* by cone bioassay was only 3.3 and 2.2 in Arm I and II before spray and after spray. Suscepibility was >80% up to 195 days in arm I and up to 45 days in arm II. Vector densities, by hand catch in indoor and by light trap in outdoor during base line survey was 26.0 PMH and 4.5 per light trap catch in arm I. In Arm II, it was 19.6 PMH and 4.7. After spray the vector density reduced in both areas but the reduction rate was much higher in arm I as compared to arm II. Human landing and animal bait collections also showed reducing density in subsequent months. Malaria also declined in both area post spray. However, the reduction rate was very higher in arm I as compared to arm II. Vector incrimination and sibling species identification is in progress.

The results of the study revealed that Deltamethrin 62.5 SC-PE has the longer residual effect on vectors of malaria. These results would facilitate in deciding the possibility of inclusion of Deltamethrin 62.5 SC-PE formulation for indoor residual spraying in malaria control programme.

Bionomics of Malaria Vectors, sibling species composition and to establish their role in malaria transmission in Madhya Pradesh

This study was initiated in May 2017 in 8 villages of different terrains of 2 CHCs of Sidhi district with the overall objective to study the bionomics of prevalent malaria vectors and their role in malaria transmission for development of evidence based sustainable malaria control strategy with special reference to vector control. Monthly entomological surveys revealed average indoor resting anopheline density was 17.5 of which >60 % were vector An. culicifacies and An. fluviatilis. In pyrethrum spray catches and outdoor light trap catches the vector proportion was 45 and 50% respectively. Human landing collections showed vector proportion was more than 83%. Animal bait collection revealed 6.0 per bait density of vectors. A total of 1719 An.culicifacies and 170 An. fluviatilis collected from different collections, for vector incrimination and sibling species determination were stored and the tests are in progress. A total of about 286 samples of An. culicifacies and 11 An. fluviatilis

were stored for blood meal evaluation. Breeding site surveys in different water bodies revealed the 78% emergence in *An. culicifacies* mainly from streams and rocky pits.

The results of this study will provide information on the distribution, prevalence and sporozoite rate of the predominant vector species complexes at sibling species level in the Madhya Pradesh state. The results would facilitate decision on development of evidence based sustainable malaria control strategy with special reference to vector control.

Monitoring of insecticide resistance in malaria vectors in Madhya Pradesh state

The study was proposed to generate data on insecticide resistance in malaria vectors by insecticide susceptibility tests using different insecticide coated papers in 12 districts of MP. The 6 district data revealed that An. culicifacies the main malaria vector was resistant to DDT (4%) and Malathion (5%) in all 6 districts surveyed. The vector was susceptible to Deltamethrin (0.05%)and Aplhacypermethrin (0.1%), in 3 districts. Varying level of resistance was noted in 2 districts. On completion of the study, updated map on resistance of malaria vectors against commonly used insecticides will be available. As the indoor residual spray is the main tool for vector control, therefore data generated will be useful for making evidence based decisions for the selection of effective insecticide.

Malaria Elimination and Demonstration Project (MEDP) Mandla

Malaria Elimination and demonstration project (MEDP) is ongoing in Mandla district with the main objective to demonstrate malaria elimination and prevention of re-establishment of malaria in the district. ICMR-NIRTH is involved in monitoring and supervision of vector control objectives. Susceptibility tests against adult *An. culicifacies* mosquitoes was conducted according to WHO standard guidelines to ascertain the present susceptibility status. It was identified that

An. culicifacies the vector mosquito in Mandla is not resistant to the synthetic pyrethroids used in IRS operation in Mandla. Variable resistance to DDT, Malathion and Alphacypermethrin was found with susceptiblity to Deltamethrin. Percent Anopheles culicifacies was found to be highest in 3 surveys conducted each survey village. An.fluviatilis was also detected in the surveys. Cone bioassays revealed about 98% mortality among An. culicifacies in a single day post spray. However after 30 days only 40% mosquitoes died showing improper spraying. The IEC on use of LLINs and proper coverage of spray essential among the villages. The study will be helpful to elimination and prevention of reintroduction of malaria in Mandla District.

MOLECULAR DIAGNOSIS OF MALARIA PARASITES

The prevalence of malaria in disturbed and conflict affected CHCs (Lanjhigarh) of district Kalahandi, Odisha was recorded by microscopy and polymerase chain reaction (PCR). Microscopically only *P. falciparum and P. vivax* were found, while by PCR 17 % mixed infections were recorded with all four parasite species (*P. falciparum, P. vivax, P. malariae and P. ovale*).

Study on HRP2 and HRP3 gene in *Plasmodium falciparum* parasites from Odisha state, India: A prospective evaluation

The centre evaluated the presence or absence of *pfhrp2* and/or *pfhrp3* gene of *P. falciparum* parasite samples from a malaria-endemic site of Kalahandi district, Odisha, India to guide Malaria Control Programme for procurement and implementation of appropriate malaria rapid diagnostic tests (RDTs). The *pfhrp-2* based RDTs are widely recommended and used for management of *P. falciparum* malaria. However, the sensitivity of various RDTs used for malaria diagnosis varies in the field. The presence of *Pfhrp-2/3*gene deleted *P. falciparum* albeit was found at low frequency (2.2%) in the high malaria endemic area of Odisha.

Molecular characterization and immune response against *Plasmodium falciparum* Apical merozoite protein (Pf34) from Central India

Molecular characterization of Pf34 was aimed to elucidate the potential of *Plasmodium falciparum* Apical merozoite protein (*Pf34*) as a diagnostic biomarker. This protein expresses at all stage of Pf lifecycle with very limited genetic diversity. Characterization of *Pf34* was done with identify genetic diversity, its expression level during erythrocytic cycle and immune response against *P. falciparum Pf34* in the malaria patients. About 10% diversity was noted at DNA level among the isolates. Expression of *Pf34* was found throughout the erythrocytic stage at RNA level.

Efficacy and safety of artemether-lumefantrine (AL) combination therapy for the treatment of uncomplicated *Plasmodium falciparum* malaria in 4 Tribal dominating states in India: Madhya Pradesh, Maharashtra, Chhattisgarh and Odisha

Therapeutic efficacy of ACT was determined in the *P. falciparurm* from Chhattisgarh, Odisha, Madhya Pradesh and Maharashtra and the study showed adequate clinical and parasitological response (98.9%) with four cases (1.1%) of late parasitological failure (LPF). Molecular study revealed that no functional mutation against *K13* was present in the study areas.

An assessment of intervention measures for prevention of malaria in pregnancy. A prospective longitudinal study in Central India

The study was carried out in Meghnagar CHC (symptomatic group) and Ranapur CHC (all pregnant women irrespective of symptoms) of district Jhabua to study the malaria prevalence. During the time of enrollment 81 (3.2%) women were positive for malaria (67 *P. falciparum*, 09 *P. vivax* and 05 mix infection). This study showed that in both the Intermittent Preventive Screening and Treatment (IST) and symptomatic group (SMT), groups the malaria positivity rate was same, therefore screening only symptomatic cases will

reduce the extra burden of the routine ANC test. Also the study provided the data regarding anemia profile of the pregnant women in the area and it indicated that the nutritional status of these women needs serious improvement.

TRIBAL HEALTH RESEARCH UNIT (THRU)

The THRU was established at the Government Medical College & Maharani Hospital, Jagdalpur, Chhattisgarh. A study was designed to identify the prevalence and association of malaria and hemoglobinopathies was carried out. During the report year (April 2017- March 2018), a total of 15769 patients were screened for malaria, among these 685 patients were found positive for malaria with P. falciparum (87.4%) as major infection. Overall, 111 severe malaria (SM) and 64 cerebral malaria (CM) cases were detected and 21 deaths were also recorded among the severe and cerebral malaria cases. Overall 13271 patients were screened for sickle cell anaemia and other hemoglobin variants; out of them 33.0% were found as HbAS trait and only 4.5 % of patients were diseased. The study is in progress.

Bionomics of malaria vector(s), sibling species and to establish their role in transmission in Maharashtra. The study is being carried out in two CHCs of namely Dhanora and Ahiri of District Gadchiroli

The study under taken has significant public health importance. Bionomics of malaria vector is important as Gadchiroli (tribal district) contributes about 60% of the malaria cases and about 85% of *P. falciparum* cases of Maharashtra state. The major malaria vector *An. culicifacies* was found to be resistant to all the major insecticides being used for the control of malaria in the region.

VECTOR SURVEILLANCE FOR ZIKA VIRUS IN SELECTED HIGH RISK AREAS OF INDIA

The study is being carried out in Jabalpur and Narsinghpur districts of Madhya Pradesh. Zika virus is the emerging public health threat and hence entomological surveillance was undertaken in areas where dengue outbreak have been reported earlier and known for prevalence of *Ae. aegypti* mosquitoes. All the mosquitoes tested so far were negative for both Dengue and Zika viruses.

EXTRAMURAL RESEARCH

ANTIMICROBIAL RESISTANCE

- Surveillance: ICMR has initiated the Anti Microbial Resistance Surveillance Network (AMRSN) to enable compilation of Data of AMR from tertiary care hospitals, detailed understanding of underlying mechanisms of resistance and genetic molecular studies. 10 more regional centres were added to the network in the year 2017-18.
- Antimicrobial Stewardship Program: Antibiotic use in hospitals can be achieved through implementation of good Antimicrobial Stewardship Programs, which help clinicians improve the quality of patient care and improve patient safety through increased infection cure rates, reduced treatment failures, and increased frequency of correct prescribing for therapy and prophylaxis. Four workshops were conducted across the country to train teams from 32 hospitals across the country.

MALARIA

- A well developed microscope with camera microscope base, 100 X lens and LED lights and its validation was carried at NIMR, New Delhi for microscopy of malarial parasites, which can produce digital images to be visualized in phones and laptop.
- A study has been has been done at RIMS, Ranchi for delayed hemolysis with intravenous artesunate in severe malaria done in selected tertiary hospital for observing the risks of hemolysis.
- A common standard protocol for monitoring resistance / susceptibility in malaria vectors was prepared and proposals were invited based on it. Resistance was found in DDT (4%) and

Malathion (5%) in the different districts. The vector was found susceptible to Deltamethrin 0.05% and alphamethrin 0.1%.

 Studies on the bionomics of malaria vectors and their sibling species are being carried out in Haryana, Maharashtra, Madhya Pradesh, Odisha, Gujarat, Dibrugarh, and completed in Jharkhand, Chattisgarh two vectors species.

Studies focused on malaria elimination

- Mandla-Malaria Elimination Demonstration Project (M-MEDP) being carried out in a defined area of Jabalpur, Madhya Pradesh, as a public–private partnership between the Sun Pharmaceutical Industries Limited, ICMR, MoH&FW, Govt. of India and Department of Health of the Govt. of Madhya Pradesh.
- "Situation analysis of malaria in the Car Nicobar island of Andaman and Nicobar Archipelago: Pre Elimination phase Study" was carried out by RMRC, Port Blair, which aims to determine the prevalence of Anopheline vectors and the parasites of malaria in Car Nicobar.

DENGUE

ICMR has collaborated with Monash • University; Melbourne, Australia on Wolbachia based Aedes aegypti control strategy. wMel Wolbachia in Ae. aegyptihave been shown to reduce the replication, transmission of dengue virus and recently chikungunya and Zika virus. Wolbachia are maternally transmitted i.e., wMel Aedes aegypti transmits Wolbachia to its progeny. In crosses between wMelAe. aegypti females and wild type Ae. aegyptimales (which do not have natural Wolbachia), the progeny inherits Wolbachia and also the property of not allowing the replication of these viruses.

LEISHMANIASIS

 Setting the Post Elimination Agenda for Kala-Azar in India (SPEAK India) Consortium: ICMR in collaboration with NVBDCP, DNDi, LSHTM and BMGF has launched an Indialed Consortium of national and international

researchers, to develop a post elimination agenda for Kala-Azar in India.

LYMPHATIC FILARIASIS

Tools which may assist accelerated elimination of Lymphatic filariasis

- As a part multi-country study, a *community* based study on the safety and efficacy of a new triple drug regimen (Ivermectin, Diethylcarbamazine and Albendazole) compared with the two-drug regimen (Diethylcarbamazine and Albendazole) for lymphatic filariasis elimination programme is being carried out in Yadgir, Karnataka by VCRC, Puducherry, which shows that the triple drug therapy is safe and could be used for eliminating LF in hard core districts and accelerating the elimination in other endemic districts. The regimen is being introduced in the National Programme.
- An alternative/supplementary tool for LF surveillance: A sampling strategy for molecular xenomonitoring, developed and tested in block and District level, confirmed the decisions based on TAS and Mf-survey for stopping MDA in an evaluation unit. Xenomonitoring could be used as an alternative/supplement to TAS for stopping or post-MDA surveillance.
- Morbidity Management and Disability Prevention (MMDP): Second pillar of LF elimination. Brainstorming Meeting held with NVBDCP, WHO and clinicians to develop National Guidelines on MMDP based on WHO guidelines.

ZOONOSIS

• Task Force studies under the ICMR-ICAR Collaboration were undertaken at MGIMS, Wardha and Central Institute of Medical Sciences, Nagpur. ICAR has simultaneously funded "Niche Area of Excellence" at Nagpur Veterinary College under MAFSU. These studies are being undertaken in close collaboration with each other and close linkages have been established through these studies.

- The project "To determine the molecular • porcine epidemiology of **Trichinellos** and Toxoplasmosis in India" confirms the existence Trichinella spp. and Toxoplasma gondii in slaughter pigs in North India. For the first time, zoonotic nematode larvae of Trichinella species have been isolated and confirmed by PCR and sequencing. High molecular prevalence of Toxoplasma gondii has also been recorded in the slaughter pigs. The detection of antibodies against Trichinella and Toxoplasma among human risk groups also confirmed the human exposure of human population to these zoonotic parasites.
- The results of a surveillance of selected zoonotic diseases carried out in central India showed that about one third of cases of AUF attending tertiary care hospitals are caused by three zoonotic diseases viz. Brucellosis (6.31%), leptosprosis, (12.67%) and scrub typhus (15.79%). Thus paving a way for further studies on control and prevention of these diseases at a community level.

VIRAL INFECTIONS

- A pilot study entitled, "Serotyping RNA virus to study molecular epidemiology of dengue supplementing emergency preparedness and capacity building in metro cities of Karnataka" completed at NIN, Hyderabad comprising of 77 PHCs of urban/metro areas of Bangalore and 585 PHCs of Mangalore helped determine, with great precision, the exact placed where the infection occurred to understand peculiarities of outbreak with factors involved in transmissions.
- The result of a project entitled "Identification of dengue virus NS5 protein region responsible for interleukin-8 transcription and secretion" was recently completed at MAMC, New Delhi confirmed that pntNS5 Dengue Virus region

had no influence on the transcription and expression of IL-8 gene.

- Findings of serosurvey carried out in a study entitled "Seroprevalence and seroincidence of scrub typhus infection during epidemic period in selected blocks of Gorakhpur district in Uttar Pradesh" completed by NARI, Pune during peak period with AES cases have confirmed the endemicity of scrub typhus infection in this area, with overall sero-incidence reported to be 20%. Preliminary data also indicates the presence of rickettsial infections other than scrub typhus in fever cases and warrant the need for further studies to assess their role in acute febrile illness and AES in Gorakhpur.
- "Assessment of risk factors responsible for causation of scrub typhus during 2017", by NIE, Chennai along with other key stakeholders has conducted a study to identify risk factors associated with acquisition of scrub typhus among children in Gorakhpur region, UP and also compare treatment related factors associated with progression of febrile illness due to AES among children in Gorakhpur region, UP. Results of the study have been communicated to the Govt. of UP, with a request to focus the communication messages for the various risk factors determined in the study. A total of 155 cases of Acute Febrile Illness (AFI) and 406 controls were recruited. Significant risk factors were: location of houses within/adjoining fields; storage of firewood inside house/verandah and behavioural issues like open defecation, playing and visiting fields.
- A longitudinal study entitled "Prevalence of scrub typhus vectors/rodent hosts and the pathogen, *Orientia tsutsugamushi*, in areas reporting in human cases of AES in Gorakhpur, Uttar Pradesh" has been carried out by VCRC, Puducherry in eight villages (6 blocks) reporting AES. The results revealed that natural infection of *O. tsutsugamushi* was detected only in *Leptotrombidium deliense*

mite species collected from shrew mouse, *Suncus murinus*, which indicates a possible role of this animal as the maintenance/reservoir host of the pathogen in the study villages.

HIV

• The results of Phase I and II study entitled, *Validation of Immunogenicity of HIV-I Indian subtype c vaccine*' are promising and showed that the candidate vaccine is likely to be efficacious. The animal immunogenicity studies are being confirmed and the industry is being involved for further manufacture of cGMP batch for clinical trials.

LEPROSY

- A pilot proposal on 'Programmatic implementation & comparison of MIP vaccine immunoprophylaxis & Rifampicin chemoprophylaxis-under NLEP in high endemic settings' was successfully launched by honorable HFM in Rajkot, Gujarat on 7th May, 2017. A total of 152 contacts have been vaccinated successfully. The vaccination of leprosy contacts in Gujarat would be completed soon.
- Another project on profile of deformity in new leprosy cases, their predictive risk factors in the development and progression of the disability was initiated, which would help in identifying the early factors for development of leprosy disability, thus helping in initiating preventive therapy.

TUBERCULOSIS

SFC for 'India TB Research consortium' was approved with a total budget of Rs. 139.40 Cr. upto FY 2020. For undertaking TB research and to develop new tools / interventions in 4 thematic areas of diagnostics, therapeutics, vaccines and implementation research, major projects were initiated include the following studies:

- Clinical trials on host directed therapy with Metformin as an adjunct therapy to ATT for drug sensitive TB.
- High dose rifampicin for better efficacious regimen for DS-TB.
- TB detect an improved microscopy validation test for TB diagnosis.
- TruNat validation for detection of EPTB
- TruNat validation for detection of paediatric TB.
- Rifapentine as preventive therapy and capacity building for the preventive vaccine trial.
- Animal studies on inhalational INH and Rifabutin for TB/MDR-TB.
- Capacity building for undertaking Prevention of Disease trial for TB in HHC of TB patients.
- Another project on development of new therapeutic molecule bacteriocins from marine lactic acid bacteria against drug resistance and latent tuberculosis has been initiated.
- Proposal on Tuberculosis among homeless persons, Chennai City has been initiated to find out the risk of TB in this group.

PARA TUBERCULOSIS

• A multicentric multidisciplinary project (with *Clinicians, Microbiologists from human & veterinary side*) on: "Association of MAP with Crohns disease" was initiated at 18 centers across 8 states in India with veterinary and human components. In animal component, the results showed MAP in animal flock & its products; which is being confirmed by other centers. In human component, association of AP with Crohn's disease is being established. The project will help to develop guidelines for diagnosis, treatment and prevention of Crohns disease & MAP.

DIARRHOEAL DISEASES

• A study entitled "Colonization factor analysis and molecular epidemiology of enterotoxigenic *E. Coli* (ETEC)" was carried out by PGIMER, Chandigarh concluded that ETEC are not only causes of diarrhea in children but equally common in adults. Majority of the ETEC had severe diarrhea, while 23% had moderate diarrhea.

Till now, the study has been able to analyse data of 45 strains of which 32 appear to be novel MLST types. The study demonstrates the need for constant surveillance in developing countries to prevent the spread of these multi-resistant isolates. The study highlights the colonisation factors across a large region of India to be included for potential vaccines.

OTHER MICROBIAL INFECTIONS (OMIS)

- The findings of a study on "In-vitro study synergistic, additive, indifferent or of antagonistic effects of various antimicrobial combinations in multi-drug and extensivelydrug resistant Neisseria gonorrhea strains" carried out at VMMC & Safdarjung Hospital, New Delhi suggest 5 potential new combinations (gentamicin+ertapenem, moxifloxacin+ertapenem, spectinomycin+ertapenem, azithromycin+ moxifloxacin, cefixime+gentamicin) which had highest synergistic or additive effect without any antagonistic effect. Antagonism was observed for 10 combinations.
- A promising antibiofilm activity shown by nanoparticles and nanoparticle-antibiotic formulations imply their immense medical application as effective antibiotics delivery system against CoNS shown in a study entitled, "Molecular studies on biofilms formation in coagulase negative Staphylococci" conducted at Mahatma Gandhi University, Kerala can be used as an effective treatment strategy to control the CoNS implantation failures.
- In a study entitled, "Analysis of antimicrobial gene expression pattern in model organism,

Caenorhabditis elegans" completed at Alagappa University, Karaikudi, the host immune responses were found to be highly specific to the type of infection and it is greatly influenced by the type of microorganism. The antimicrobial fingerprinting (expression profiles) clearly suggested that there are few selective regulatory genes appear to play important roles in extending the host's fight against the interacting pathogens.

study entitled, "Development А and of multiplex real-time evaluation PCR gonorrhoeae, Chlamydia for Neisseria *Mycoplasma* gentitalium, trachomatis. Ureaplasma urealyticum and Mycoplasma hominis detected from patients of cervicitis and infertility" carried out at PGIMER, Chandigarh demonstrated the high prevalence of C. trachomatis infection in infertile patients. In addition, the in-house developed Taqman probe based multiplex real- time PCR assay for simultaneous detection of three STIs i.e., C. trachomatis, N. gonorrhoease and M. genitalium with high sensitivity and specificity (93.91% and 100% respectively) facilitates the opportunity to be used as new rapid diagnostic method in low resource settings.

RESEARCH ACTIVITIES IN NORTH EAST

- The phylogenetic tree constructed from 2 samples from Pasighat and 4 samples from Guwahati in a study entitled, "Surveillance of Chikungunya virus activity in Assam and Meghalaya, revealed that the virus circulating in this region belongs to East Central South African genotype.
- From another concluded investigation entitled, "Efficacy and predation of certain indigenous larvivorous fishes against the vector of malaria in and around coal mining areas of Garohills, Meghalaya, the efficacy and predation against the vector of malaria was observed to be much more efficient in some small indigenous and native species of torrential hill streams and

rivers as compared to the exotic species like *Guppy* and *Gambusia* species. The study further observed that the numbers of mosquito larvae were found minimum from the water bodies of the study area from where the species was collected.

 In another recently completed project entitled, "Evaluation of loop mediated isothermal amplification and polymerase chain reaction in clinically suspected and radiologically confirmed neurocysticercosis (NCC) patients". LAMP and PCR assays were found suitable for a rapid, sensitive and specific diagnosis of NCC. The objective detection of *T. solium* DNA in serum samples can be considered to have the potential to be included in the parasitological diagnostic criteria of NCC.

TRIBAL HEALTH RESEARCH (TRIBAL SUB-PLAN)

- A study entitled "Prevalence and gene typing of beta thalassemia, sickle cell anemia traits and G6PD deficiency among tribal school children of Mysore District, Karnataka" carried out by JSS Medical College, Mysore, revealed high prevalence of all the above hemoglobinopathies in the tribal areas of Karnataka.
- A multicentric study entitled "Establishment of prenatal diagnosis of β-thalassemia syndromes and sickle cell disorders in Madhya Pradesh and Assam" was undertaken under the coordination of NIIH, Mumbai to establish centres for molecular analysis and prenatal diagnosis for hemoglobinopathies in the two states, which will directly benefit the community as it will enable couples at-risk of having an affected child to opt for prenatal intervention in their vicinity without having to travel hundreds of miles.
- A project entitled, "Improving health of under five children in Rayagada district, Odisha" completed by RMRC, Bhubaneswar was planned in context of the MOA signed between

Government of Odisha and ICMR to improve the health parameters of under 5 children. Assessment after 2 years of implementation of the activity has revealed significant increase in the perception of the community on child health, rate of immunization, rate of use of ORS and Zn in treatment of diarrhea, proportion of children/adult habituated to hand-wash practice and safe drinking water. Overall, the morbidity due to malaria, diarrhea and acute respiratory infections (ARI) has been significantly reduced in the study area compared to control area.

- Likewise, another project entitled, "Improving Health of under five children in Kalahandi Dist, Odisha" also carried out by RMRC, Bhubaneswar looked into the baseline under five morbidity and maternal health care in the Kalahandi district of Orissa state covering 2882 under five children from both low and high tribal density blocks. Deficiency was noted in the knowledge in case of IMNCI illnesses at village health worker level. Alternated media like school children were shown to be a feasible way to transmit health promotion messages to the community.
- The phase I of a multicentric study entitled "Estimate the burden of TB among the tribal population and develop an innovative health system model to strengthen TB control in the tribal areas" has been successfully completed under the coordination of NIRT, Chennai along with six other centres. The prevalence of TB among the tribal population calls for focused active case finding among this population, to help in early detection and treatment and prevent TB transmission. The findings point to the need for community engagement and TB community sensitization programmes, which are tribal friendly and acceptable. The findings also reflect on the need for health system strengthening so that those who seek care are ensured quality health services. The study is further expanded to Phase - II, and 4 more sites have been initiated during 2017-2018.

PUBLIC HEALTH IMPORTANCE

- A collaborative multi-site epidemiological and virological survey of Nipah Virus (NiV) with special emphasis in the North-eastern Region of India has recently completed, wherein a survey was conducted to determine the circulation of Nipah virus among Pteropus giganteus bats from West Bengal and Assam states of Northeast region of India and also to understand the activity of NiV in archived / hospitalized AES (Japanese encephalitis negative) cases hailing from North Eastern border areas especially in Dhubri District of Assam. During the survey, presence of Nipah virus was observed for the first time from Dhubri district, Assam State with the circulation of Nipah in West Bengal State. Simultaneously, Tioman virus (TioV), a new member of the Paramyxoviridae family was also isolated from tissues of *Pteropus* giganteus bats for the first time in India.
- A survey to assess the infectious reservoir of Plasmodium infections and to monitor the efficacy of antimalarial medicines has been recently completed in East Garo hills district, Meghalaya and Udalguri district, Assam. During monitoring the therapeutic efficacy of recommended antimalarial medicines (Artemether-lumefantrine, AL) tablets in the East Garo Hills district, Meghalaya and Udalguri district, Assam, 4 cases of treatment failure (3.3%) showing true recrudescence were observed. Overall prevalence of asymptomatic malaria combining both the districts was 6% using RDT kit with 15.5% in East Garo Hills district and 1.2% in Udalguri district.
- Establishing transmission of Zika virus disease in India: Through intensified surveillance in India at 25 sites, local transmission of Zika virus disease was established. A total of 4 cases were detected till May 2017.
- Establishing the risk factors for scrub typhus Acute Encephalitis Syndrome in Gorakhpur:

Major risk factors were seen to be open defecation, storage of firewood in verandah and playing in field for long hours.

- Influenza testing sites: Operationalizing Influenza testing facilities at 41 Virus Research & Diagnostic Networks in India.
- Setting up CRS surveillance in India.
- Completion of sample collection for Nationwide Dengue serosurvey.
- A study "To determine the molecular epidemiology of porcine *Trichinellos* and *Toxoplasmosis* in India" confirms the existence *Trichinella* spp. and *Toxoplasma gondii* in slaughter pigs in North India.
- Phase I of study on '*Validation of Immunogenicity* of *HIV-I Indian subtype c vaccine*' and vaccine constructs have been revived successfully. Preclinical safety evaluation is also completed and

encouraging results have been seen in in-vitro efficacy study. The immunogenicity results are also encouraging which indicate that the vaccine is likely to be effective.

- An ELISA based liquid hybridization assay for simultaneous detection of gene amplification products of HIV-1 & 2 RNA/ HCV RNA/HBV DNA in plasma samples has been developed.
- A new molecular test TruNat (*M.TB & Rif.*) has been validated and found to be at par with gene Xpert for detection of TB and MDR-TB. The test is about one third the cost of Xpert and can be placed at PHC level. The recommendations for use of TruNat under RNTCP have been forwarded to MOH&FW.
- Successful introduction of MIP vaccine to contacts of leprosy patients for prevention of leprosy has been initiated in Gujarat state.

REPRODUCTIVE HEALTH

CMR is undertaking research in the field of reproductive health through two of its research institutions viz, (i) National Institute of Research in Reproductive Health, Mumbai and (ii) Genetic Research Centre, Mumbai as well as extramural research projects. These studies are aimed to protect and enhance the reproductive health of people through research and development of technologies and programmes for field applications which can be incorporated into National Programmes.

INTRAMURAL RESEARCH

NATIONAL INSTITUTE FOR RESEARCH IN REPRODUCTIVE HEALTH, MUMBAI

FEMALE INFERTILITY AND ASSOCIATED REPRODUCTIVE DISORDERS

PON1 Expression, Activity and its Relationship with Oocyte and Embryo Quality in Women with PCOS Undergoing Assisted Reproductive Technique

Redox status in the oocyte microenvironment is a critical factor for oocyte development. Reactive oxygen species (ROS) can negatively affect oocyte quality. Paraoxonase 1 (PON1), along with other antioxidants, plays major role in maintaining redox homeostasis. PON1 protein is downregulated in women with PCOS. Total antioxidant capacity was not significantly different but total thiol levels were significantly lower in follicular fluid from PCOS women compared to controls. Glutathione

Peroxidase activity was comparable between PCOS and control group. Glucose is important metabolite for follicle development and PON1 is reported to influence glucose uptake in hepatocytes. Glucose uptake by granulosa cells was estimated in presence of different concentrations of PON1. In granulosa cells, the glucose uptake is enhanced with increase in PON1 concentration but this effect was more prominent in controls, compared to PCOS women.

Deciphering the Putative Epigenetic Mechanisms Pertaining to Polycystic Ovary Syndrome (PCOS)

Apart from genetic predisposition, epigenetic modifications including DNA methylation and histone modifications are crucial mediators of gene regulation and expression. Collateral epigenetic repercussions and changing lifestyles are said to have a substantial impact on PCOS development. The present study lays emphasis on plausible epigenetic transitions occurring in cumulus granulosa cells (CGCs) of women with PCOS. To investigate altered genome-wide DNA methylation profiles associated with PCOS, 'methyl-capture sequencing (MC-Seq)' based whole DNA methylome profiling was carried out to identify locus-specific alterations in methyl-CpG signatures of CGCs of 3 women with PCOS, compared to 3 age-BMI matched, regularly menstruating controls. A total of 6486 CpG sites associated with 3840 genes linked with Wnt signaling, integrin and endothelin signalling, G-protein receptor signaling, angiogenesis and chemokine/ cytokine mediated inflammation pathways are differentially

methylated in PCOS. Of these, a total of 3509 CpGsites representing 1777 genes were found to be hypomethylated while 2977 CpGs associated with 2063 genes were identified as hypermethylated in PCOS. Altered methylation was also noted in several non-coding RNAs regulating vital ovarian functions that are impaired in PCOS. Also, apart from transcript levels of DNA methyltransferases (DNMTs) that bring about de novo and maintenance DNA methylation, transcripts of Ten-eleven translocation enzyme coding genes i.e. TETs were also found to be altered in CGCs of women with PCOS. These findings suggest that alterations in gene DNA methylation could play a crucial role in the etiopathogenesis of this complex disorder.

Understanding Follicular Angiogenesis in Women with Polycystic Ovary Syndrome (PCOS)

Angiogenesis plays an important role in oocyte development. Proteomics study on follicular fluid of control and women with PCOS showed differential expression of many proteins related to angiogenesis, indicating this process may be dysregulated. The mural granulosa cells (MGCs) are also involved in vasculature development of growing follicle. We observed altered expression of genes of major pro-angiogenic and ECM factors which assist in angiogenesis like VEGFA, HSPG2, SPARC, STC, SCUBE, HIF1A, ADAMTS1, and bFGF in women with PCOS. SERPINA1, an antiangiogenic protein, was found to be upregulated in follicular fluid and MGCs obtained from PCOS compared to controls. This suggests that MGCs and FF both contribute towards follicular angiogenesis. Also, in women with PCOS their potential to support angiogenesis in follicles may be compromised and this may lead to pathophysiology of PCOS.

Implementation of Multidisciplinary Model of Care for Women with Polycystic Ovary Syndrome (PCOS): Developing a Cohort of Adolescent and Infertile Women for Research in PCOS at NIRRH

A multidisciplinary model of care for women with PCOS to address most concerns of women with PCOS was initiated at the institute in 2016 with a team of IVF specialist, endocrinologist, dermatologist, dietician and yoga expert. Physical, hormonal, biochemical, ultrasound and emotional health parameters of the women with PCOS will be studied over a period of time. Data was analysed to study the metabolic complications among 120 women with PCOS attending NIRRH Multidisciplinary PCOS clinic. To estimate the burden of metabolic syndrome among women with PCOS, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) criteria were used. Metabolic syndrome was found among 34.2% women with PCOS. Moderate to severe insulin resistance was found in 68% of women with PCOS. Fatty Liver was seen in 20.6% of women with PCOS. This further emphasises the need for holistic management of PCOS and lifestyle management with diet and exercise at an early age to reduce metabolic complications.

Pathways to Oncogenesis in the Pathophysiology of Endometriosis

Endometriosis shares certain characteristics with cancerous cells such as local and distant adhesion, metastasis, adhesion to heterotypic tissues, invasion and angiogenesis. This raises a possibility of oncogenesis-associated pathways being of relevance in the pathophysiology of endometriosis. This possibility is strengthened by the existing evidences indicating demonstration of common Loss of heterozygosity (LOH) events in chromosomal loci as well as missense mutations and deletions in PTEN gene in solitary ovarian endometriotic cysts. The present study was undertaken to identify whether eutopic endometrium of women with endometriosis shows differential expression of oncogenesis-associated genes. Analysis of RNA Seq data using mid-proliferative phase eutopic endometrial samples from women with and without endometriosis revealed differential expression of 66 oncogenes and 76 tumor suppressors in eutopic endometrium of women with endometriosis. Geneannotation enrichment analysis demonstrated dysregulation of pathways in cancer etc. as a major

pathway in the eutopic endometrium of women with endometriosis. Validation of these results is ongoing.

The Factors of Relevance in Endometrial Adhesiveness to Embryonic Cells

Optimal expression of Cell Adhesion Molecules (CAMs) in the luminal epithelium of the endometrium during the receptive phase is reported to be essential for initiation of pregnancy. However, the mechanisms involved in the distribution of CAMs to the cell surface of endometrial epithelium remain elusive. Surface abundance of CAMs may be regulated by the intracellular trafficking mediated by Rab GTPases. Rab11a (a marker of recycling endosomes), a GTPax is known to be involved in the recycling and exocytosis of cell surface proteins. The present study has been undertaken to elucidate the role of Rab11a in the intracellular trafficking of CAMs such as integrins and E-cadherin, reported to be of significance in embryo-endometrial interactions.

The previous results demonstrated a decrease in E-cadherin expression and an increase in migratory property in Rab11a deficient cells. Studies conducted during the reporting year demonstrated that the levels of E-cadherin transcripts remain unaltered in Rab11a deficient cells. However, Golgi as well as lysosomal protein extracts showed reduced levels of E-cadherin implying the role of Rab11a in the trafficking of E-cadherin to Golgi as well as lysosomal compartments.

iTRAQ approach employed to generate a surface proteome has led to the identification of a number of surface proteins trafficked by Rab11a. Investigations are underway to validate the significance of these cell surface proteins, presumably transported by Rab11a, in endometrial receptivity.

Effect of Uterine Fibroids on Endometrial Receptivity

Uterine fibroids, originating from myometrium of the uterus, are the most common benign tumors of the pelvis. Fibroids affect 20 - 50% of women in their reproductive age group and are characterized by pain and abnormal uterine bleeding. There exist data to suggest that submucous or intramural fibroids protruding into the endometrial cavity are associated with decrease in implantation and pregnancy rates, whereas subserosal fibroids are inconsequential. However, there is no consensus on the impact of small sized (<6.0 cm) intramural fibroids, which do not affect the endometrial cavity, on reproductive outcome. The present study aims to investigate whether the small sized intramural uterine fibroids alter the endometrial receptivity pattern. The previous studies demonstrated higher expression of immunoreactive ER α and ER β in the endometrial glands as well as stroma of infertile women with fibroids as compared to other groups. Endometrial PCNA was also found to be higher in infertile women with fibroids as compared to fertile women with and without fibroids. However, fibroids appear to have no significant impact on the endometrial expression of integrin αv . Transcriptome profiling of endometrial samples from women with fibroids is underway.

Effect of Metformin on Hormonal, Metabolic and Endometrial Profiles in Obese Bonnet Monkeys (*Macaca Radiata*)

Metformin, an anti-diabetic agent, is in use for its benefits in reproductive disorders like PCOS. The current study was undertaken to evaluate the direct effects of metformin on endometrium. The study have previously reported effects of low dose metformin on proliferation of Ishikawa cells. In addition to this, low dose metformin was seen to upregulate the expression of integrin $\alpha\nu\beta3$ and SIRT1. In the reporting year, the effect of metformin was studied on a less adhesive endometrial cancer line HEC-1A. The effects on proliferation of HEC-1A at low dose metformin were found to be similar to that observed for Ishikawa. At low dosages, metformin was found to induce proliferation of HEC-1A. In brief, the study demonstrates endometrial epithelial cells as a target of metformin action.

MALE INFERTILITY AND ASSOCIATED REPRODUCTIVE DISORDERS

Investigations on Obesity Induced Epigenetic Changes in Germ Line of Adult Male Rats

Obesity, a global health concern, is associated with severe reproductive complications which affects both males and females of different age groups. Several studies have shown that obesity can affect sperm parameters, spermatogenesis and hormonal profiles in males and also affect the hypothalamuspituitary-gonad (HPG) axis. It has also been found that obesity can affect the subsequent generations thereby showing transgenerational inheritance in the offspring. Obesity is multifactorial with predominantly genetic or environmental causes. Studies were done to delineate effects of genetically inherited and high fat diet induced obesity on fertility and spermatogenesis using two Wistar rat models: Genetically Inherited Obese (GIO): WNIN/Ob of ICMR-NCLAS, NIN, Hyderabad; and Diet Induced Obese (DIO): High fat diet. The body weights were similar in both GIO and DIO groups, but there was a significant difference in metabolic and hormone profile between the two groups. Fertility assessment revealed significant decrease in litter size due to increased pre- and postimplantation loss in DIO group, while GIO group were infertile due to reduced potency. Significant decrease in sperm counts was observed in GIO but not in DIO group despite body weights being comparable in both groups. To study the effect of obesity on spermatogenesis, enumeration of testicular cells based on ploidy and cell type specific expression markers revealed that both GIO and DIO affects mitosis but differentially alters meiosis and spermiogenesis. Gene expression studies in testis showed differential expression of genes involved in leptin signaling, cytokines and cell cycle. The results indicate that differential effects of GIO and DIO on fertility and spermatogenesis could be due to the significant difference in the white adipose tissue accumulation between the groups. The differential effects of obesity suggest that male obesity induced infertility observed in

humans could be a combination of both genetic and environmental factors.

RTI/ STIS/HIV/ MICROBICIDES

Variants of Human Leukocyte Antigen (HLA) and Their Possible Association with HIV Transmission

The analysis in Indian population highlighted anti-retroviral therapy failure in HIV-1 positive pregnant women (22%) and its risk with high rate of transmission to the neonates. It was found that 45.45% women with high viral load (VL) transmitted the infection as compared to 2.56% those with low VL. HLA-C analysis indicated HLA-C in HIV-1 positive individuals drastically different from healthy controls. As much as five alleles reached statistical significance (p<0.01), when HIV-1 positive patients were compared with healthy controls data. To centre's knowledge, this is the first study from India, which has documented the HLA-C diversity in an HIV-1 infected cohort.

Identification, Isolation and Characterization of Naturally Occurring Antimicrobial Proteins/ Peptides (AMPs) for the Prevention of Sexually Transmitted Infections including HIV/AIDs

One of the objectives of this study is to determine the role of autophagy in host immune response during vaginal candidiasis. During the current year, the study evaluated the role of autophagy in the clearance of *C. albicans* after vaginal infection by developing mice with conditional knockout of autophagy gene, ATG5 in vaginal cells. The results revealed that infection intensity was significantly higher and pathogen clearance severely delayed in the knockout mice (PR-ATG5-KO).

Studies on the Modulation of Vaginal Immunity during Host-Pathogen Interactions in Response to Microbicide

MicroRNA - let-7f is one of the key regulators of TLR mediated immunity in human endocervical epithelial cells (End1/E6E7). The study identified the targets of let-7f in these cells and found that

the transcription factor, C/EBP β is involved in the transcription of let-7f. The signalling pathway(s) downstream of TLR that modulate let-7f expression are not known. Hence, this study investigated the role of MAPK and NF- κ B in the transcription of let-7f. The results demonstrate that activation of let-7f transcription via TLR3 is mediated through JNK and p38 pathway by C/EBP β .

Enhanced, Deep Sequencing Based Detection of Putative ART Resistance in Therapy Failing HIV-1C Infected Individuals

Using a combination of next generation and sanger sequencing, primary (uncultured circulating and arhchival) sequence data from 20 HIV-1C infected individuals encompassing full length pol gene has been generated. This data provides critically needed information including: i) Drug Resistant Mutations (DRM) for Protease, Integrase and Reverse Transcriptase genes, that are in circulation in PLHIV in India. ii) Analysis of drug resistant mutations associated with current anti-retroviral therapy (ART) regimens in co-evolution and prediction of acquired resistance enabling optimal management of ART. iii) Evidence for integrase inhibitor resistance in individuals with no prior history of therapy.

T Cell Dynamics in HIV-1 Clade C Infected Non-Progressors with High Viremia

Studying T cell homeostasis and dysregulation in these individuals may provide insights into immune compensatory mechanisms employed to cope with viral pathogenesis. The cross-sectional study of Viremic Non Progressors (VNPs, N=19) and Putative Progressors (PPs, N=14) has shown that i) Viremic non-progressors (VNPs) compared to Putative Progressors (PPs) with similar levels of viremia and CD4 depletion retain key homeostatic mechanisms such as activation driven expansion of Tregs and ii) CD4+ Central memory T cell preservation as well as differential CD4 and CD8 memory pool expansion is evident in VNPs compared to PPs. This study thus delineates potentially actionable T cell homeostatic signatures for ameliorating HIV pathogenesis and enhancing anti-retroviral therapy mediated immune restoration.

Identification of the factors associated with susceptibility/resistance to heterosexual HIV transmission among serodiscordant couples using proteomics

Existence of HIV-1 exposed sero-negative (ESN) individuals in serodiscordant couples suggests that mucosal factors in the genital tract can prevent viral transmission. Identifying such naturally occurring anti-HIV factors is critical for the development of effective preventative strategies. The centre attempted mapping of genital mucosal proteomes of HIV serodiscordant couples and compared them with the HIV infected and Control groups in a cohort of 112 study participants visiting HIV clinic, Department of Microbiology, KEM Hospital, Mumbai were recruited in three groups. Quantitative iTRAQ analyses was carried out on Cervicovaginal lavage (CVL) and seminal plasma (SP). A total of 1163 non redundant proteins with 39,083 PSMs were identified from the CVL and 432 proteins were differentially expressed. Major functional categories of differentially expressed proteins in the CVL were proteases and protease inhibitors, cytoskeletal proteins of mucosal epithelial barrier, inflammation associated molecules, and virus neutralising proteins. Importantly, upregulated levels of two of the protease inhibitors, Elafin and Cystatin B, in the CVL of serodiscordant females were validated by ELISA (Figure 1A and B). A total of 1477 non redundant proteins with 71,561 PSMs were identified from the SP and 387 proteins were differentially expressed. Major functional categories of differentially expressed proteins in the SP were proteasome complexes, cytokine signaling, lysozyme activity, complement pathway, and neutrophil degranulation. Some of these potential candidates are being validated and may be explored further for development of comprehensive vaginal/rectal microbicide gels.



Fig. 1: Elafin (A) and Cystatin (B) concentration were significantly upregulated in vaginal lavage samples of HIV serodiscordant women (n= 17) in comparison with HIV infected (n=30) and Healthy Control women (n=10). Commercial ELISA kits were used for the analysis. The graph represents Mean±SD of triplicate values for each sample. The concentration was determined by 4P-Logistic Regression analyses, and the differences in the groups were statistically analysed using Graph pad Prism based Mann Whitney, U test. A p value <0.05 was considered significant. *p<0.05 and ** p<0.005.

MENOPAUSE AND OSTEOPOROSIS

Molecular markers of bone metabolism are novel tools, which detect the dynamics of bone remodeling with respect to bone formation and resorption. The availability of reliable, cost-effective, sensitive, and specific assays for bone turnover markers (BTMs) may complement the measurement of BMD in the management of osteoporosis. Key reagents were generated for the prominent serum markers Osteocalcin (OC), Procollagen Type I N-terminal propeptide (PINP), C-terminal Telopeptide type 1 collagen (CTX) and deoxypyridinoline (DPD) with an aim to develop individual assays and validate them and later to multiplex them in an ELISA array for the assessment of bone health. Sandwich ELISAs were optimised for the individual markers. A common protocol with the in-house reagents was used in the development of assays. Initially a sensitive and specific Sandwich ELISA for OC was developed and validated with samples received from the neighbouring hospitals in Mumbai.

Second party validation of OC as a bone turnover marker in the diagnosis and management of osteoporosis was carried out at the Institute with 370 coded samples from the participating centres. The diagnostic potential of OC assay developed in the laboratory was assessed in screening women with varying BMD. The serum OC levels obtained by in house developed assay were correlated with the bone mineral density measurements (BMD), a commercial ELISA kit and clinical history of the participants

The women classified on the basis of T-scores and categorized into pre and postmenopause showed significantly different OC levels (p<0.0001). High OC levels indicated an increased bone turnover in postmenopausal women. The OC levels correlated well with the commercial kit (n=237, r=0.498, p=0.001) from Ray Biotech, USA. The diagnostic potential of the OC assay was evaluated based on cut off limits reported earlier (OC level of >11.9 ng/ml for osteopenia and osteoporosis >14.9 ng/ ml) and it had a sensitivity of 89.6%, specificity of 86.7% and accuracy of 90.6%. The developed prototype for serum osteocalcin can be thus used for screening of women at the risk of osteoporosis who can be further assessed by DEXA scan if required.

MATERNAL AND CHILD HEALTH

Analysis of the Gut Microbiome and Immune Signatures of Cytomegalovirus (CMV) Infection in Pregnancy and Infancy

Human cytomegalovirus (HCMV) is a leading cause of congenital viral infections worldwide and is associated with life threatening sequelae in a subset of infected infants. An understanding of host factors such as the gut microbiome and viral immunity would provide much needed insight into the pathogenesis of this infection. Following evaluation of HCMV infection/exposure using the TORCH (Toxoplasma, Rubella, CMV and Herpes) assay as well as a PCR matrix, characterization of both gut microbiome and immune profiles was carried out in infants. NGS based amplicon sequencing (N=8) of bacterial 16S rRNA revealed gut dysbiosis in HCMV infected infants compared to uninfected infants. This microbiome signature was characterized by an increase in proteobacteria and a reciprocal reduction in firmicutes. Also, immune analysis from 19 infants resulted in the delineation of both innate (NK cell) and adaptive (CD4+ and CD8+ T cell) cellular signatures specific to different stages of infection. NK cell frequency

was down regulated in infected infants compared to uninfected infants. Also, Treg frequency was reduced with a concomitant increase in effector CD4+T cells and cytotoxic CD8+T cells in infected infants. These results indicate clear dysbiotic and altered immune signatures (increased activation, reduced Treg activity) that may be interdependent and predict both susceptibility as well as outcome of HCMV infection/exposure in infants.

To Assess Magnitude and Factors Associated with Vitamin D Deficiency in Children between 1 to 5 years

Despite of ample sunshine, vitamin D deficiency (VDD) prevails in 50 to 90 % of Indian subcontinent. The current study was aimed to assess magnitude and factors responsible for VDD in 1-5 year age group. Apparently, healthy children in a community surrounding Family Welfare Clinic at Abhyudaya Nagar, were included. Information on Socio Demographic, Physical activity, Dietary, Clinical and biochemical profile (25(OH) D, PTH, Calcium, Alkaline phosphatase, Phosphorus, Vitamin D binding protein) was collected. Total 501 children were screened and 332 children were enrolled in the study in 2017-2018.

Preliminary analysis of 201 children showed the prevalence of 74.6% of VDD. The outdoor activities and sun exposure had significant association with vitamin D status (p=0.04). Majority of children had normal PTH levels despite of VDD and a negative correlation between 25(OH) D and PTH. The study endorses importance of sun exposure and highlights the need of defining cutoffs of 25(OH) D for VDD among underfive children in India.

Reversal of Lactation Associated Bone Loss in Women Belonging to Low Socio Economic Strata: A Pilot Study

The study intended to assess the recovery of bone mineral density among lactating women irrespective of supplementation from low socio economic strata and assess the role of traditional food items in reversal of bone mineral density among low income lactating mothers. Traditional dietary foods are an excellent option for lactating women and they should continue these foods until the complete breastfeeding period of 6 months post-partum. Severe Vitamin D deficiency (less than 10 ngm/ml) in nearly half of the young population warrants urgent attention. Vitamin D deficiency and no sunlight exposure signifies the need to supplement lactating women with vitamin D supplements.

There is a need for intensive IEC program targeting the lactating women, need to promote traditional diet practices to increase their macro and micronutrient intakes and help recovery of bone mineral status at the earliest among the low income lactating women. This could be one of the reasons why women have low peak bone mass among Indian women and needs further study in larger population.

Improving Health and Nutritional Status of Vulnerable Segment of Population by Implementing Multi-Component Health and Nutrition Education Intervention as a Sustainable Model of Intervention

The study is being conducted in two blocks, namely Dahanu and Palghar in Palghar district of Maharashtra. Baseline survey was completed during April 2015-August 2016 in ten villages (five in Palghar and five in Dahanu block). Household interviews, diet surveys, interviews of study participants, anthropometric and clinical examination including hemoglobin estimation was done among the study participants. (Pregnant women and adolescents 240 each and under fives 480. At the end of baseline survey, the data was analyzed to identify the gaps in implementation and monitoring of the current national/ state level nutrition programmes and promote inter-sectoral convergence for its effective implementation.

Intervention activities were initiated in September 2016 and completed in February 2018. Intervention plan was implemented via three approaches-Household visits, Mass approach and through phone calls/sms in each of the ten villages. Demonstration of low cost nutrition recipes was done in the

villages by nutritionist. Post intervention survey was initiated in March 2018; three villages were covered. The post intervention survey will indicate the impact of interventions in the selected villages in the district.

A Survey of What Information Research Participants Would Like to Know in Informed Consent Forms in Biomedical Research - A Multicentre study by ICMR

The objective of this study was to identify the elements and the extent of information in Informed Consent Forms that research participants in biomedical and health research would like to know. An anonymous, paper-based, validated, structured and self-administered questionnaire developed and reviewed by a group of professionals in FERCAP was used.

The participants were asked to complete the questionnaire at any time and return it to the collection box located at participating centres. Total of 93 questionnaires were collected from the participants. This study provided basic information regarding the importance for different elements in perspective of the research participants. This study concludes that participants are interested to know about almost all aspects of research especially the benefits the research will provide for the society and for them.

GENETIC RESEARCH CENTRE

Identification of Genetic Aberrations in Ion Channel Genes in Epileptic Syndrome and Channelopathies

Inherited epileptic syndromes are associated with mutations in genes encoding for ion channels (channelopathies). These group of disorders are the major concern to the clinician for development of drug resistance. Therefore, molecular diagnosis is the utmost importance for management of these disorders. In this project, the centre has identified 5 novel and 8 known mutations in SCN1A gene in cases of Dravet Syndrome. *In-silico* analysis showed that these novel mutations are found to be pathogenic. In another case of Heriditary Neuralgic

Plexitis, a known mutation has been identified in SEPT9 gene. The same gene analysis showed the presence of same mutation in all the affected members of that family.

Functional Study of Voltage-Gated Calcium Channel Gene Mutations in Schizophrenia Using Induced Pluripotent Stem Cells (IPSCs): A New Approach for Developing A Cellular Model

Schizophrenia is known to be a multifactorial disorder, however, heritability estimated was found to be almost 80% in familial cases of Schizophrenia. Therefore, the centre intent to identify genetic factors associated with the causation of this disorder. On next generation sequencing analysis of two familial case of Schizophrenia, the centre identified 20 various variants that are associated with the disorder. Out of all 20, one missense mutation in CACNA1G gene was found to have a strong genetic link in causation of this disorder.

Cytogenetic Abnormalities in Cases of Disorders of Sex Development

This project has been carried out as a part of centre's routine cytogenetic diagnostic services offered at this department. The centre has analysed 12 cases of primary amenorrhoea cases. Two of them were found to have 46,XY karyotype. Karyotype abnormality (translocation) has also been identified in one bad obstetric history (BOH) case. The centre has also identified one complete androgen insensitive syndrome, in which the testicles were found to be located at the labial fold. Upon analysis of androgen receptor gene, one splice site mutation was identified. The patient was given proper genetic counselling. She was suggested to remove the testicles to prevent the chances of the development of gonadal tumour

STRUCTURAL BIOLOGY AND BIOINFORMATICS

Design of Two Novel Potent Antimicrobial Peptides with Very Low Haemolytic Activity

Two novel antimicrobial peptides CP and MAPCON have been rationally designed using

family signatures of myeloid antimicrobial peptide (MAP) family. The peptides were tested for their antimicrobial activity against various Gram positive and negative bacterial strains. The haemolytic activity of MAPCON was found to be absent at the highest tested peptide concentration and CP exhibited very low haemolytic activity of 0.2%.

Discovery of a Small Drug-Like Molecule with Human FSHR Modulatory Activity

Using a combination of *in silico* methods such as homology modeling, virtual screening, machine learning and MD simulations few novel small-drug like molecules have been predicted to demonstrate good binding affinity to human follicle stimulating hormone receptor (hFSHR) and one of these molecules have been experimentally validated by *in vitro* methods such as radio receptor assay and cAMP assays.

Developing a Database on Genes Associated with Infertility

A manually curated database, Female Infertility Knowledgebase (FIK) on genes associated with infertility has been developed. The database holds information on 1318 genes, associated pathways, diseases etc. The database also incorporates tools which help in gene-based analysis. This resource would help in gaining a better understanding of genetic aetiology of reproductive diseases associated with infertility.

Multiple Genes Involved in Controlled Ovarian Hyperstimulation: Applications in Predicting Prognostic Biomarkers

A database of the genes associated with FSH signaling pathways and the key genes associated with ovarian response is being developed. This database will help to select genes, which need to be screened as prognostic markers for predicting ovarian response during IVF. The knowledgebase would be of importance to clinicians, as it could be used to improve the understanding of the ovarian response during controlled ovarian hyperstimulation.

STEM CELL BIOLOGY

Studies Using In-house Derived Human Embryonic Stem Cell Lines: Profiling Epigenetic Regulators during hES Cells Differentiation

In-house derived human embryonic stem cells (KIND1) were used as an in vitro model to understand global genetic and epigenetic mechanisms regulating early development. During differentiation of hES cells into cardiac lineage, OCT4A was found to be repressed by NR2F2 via a polycomb group member EZH2 (Fig. 2A). Also a crucial role of DOT1L (H3K79me2 methyltransferase) in the activation of master cardiac transcription factor NKX2.5 (Fig. 2B) was uncovered for the first time.



Fig. 2: A. Schematic representation of OCT4 repression by cooperative actions of transcription factor NR2F2 and histone modifier EZH2. B. Crucial role of DOT1L in the activation of master cardiac specific transcription factor NKX2.5 during cardiac differentiation of hES cells.

NATIONAL CENTRE FOR PRECLINICAL REPRODUCTIVE AND GENETIC TOXICOLOGY

MicroRNA Regulation in Prostate and Ovary upon Exposure to Endocrine Disruptors

Bisphenol A (BPA), a weak estrogenic endocrine disruptor, is present ubiquitously in the environment and in human tissues. Since, BPA exhibits weak estrogenic activity it could affect cell proliferation, migration thereby contributing to cancer. Using a perinatal mice model, effect of exposure of BPA on miRNA expression was studied in prostate tissue of F1 animals. Considering the importance of let7 family miRNA's in prostate cancer (PCa); coexpression of let-7a and let-7b and their target genes was studied. Down regulation of let-7b in BPA exposed (25µg/kg bw) F1 male rats was observed. Expression of miRNA let-7b and its target gene Vimentin (VIM) was found to be upregulated. This over-expression of vimentin in the prostate tissue of perinatally exposed BPA F1 male rats can be correlated with increased tumour growth, invasion and poor prognosis. In addition, TAGLN (Transgelin) tumor suppressive actin binding protein stabilize actin filaments was upregulated. Centre's preliminary results demonstrate BPA can induce prostate cancer in perinatally exposed F1 male rats. miRNA regulation plays a key role in regulating prostate cancer in F1 male rats; with an upregulation of let-7a and down regulation of let-7b genes in prostate cancer. BPA exposure during critical windows of development can disrupt the oncogenesis pathways and may induce prostate cancer.

Deciphering the Molecular Mechanism of Triclosan on Hypothalamus Pituitary Gonadal Axis

Triclosan (TCS), a broad-spectrum antimicrobial agent, is extensively used in household products and consumer products such as toothpaste, mouth wash, hand wash, soaps, toys, surgical cleaning treatments. Human body is exposed to TCS directly or through food chain. Recently, several reports have demonstrated the endocrine disruptive action of triclosan on the testicular steroidogenesis. However, the impact of triclosan on F1 progeny has not been studied in-depth. The present study was undertaken to decipher the molecular mechanism of Triclosan on hypothalamus pituitary gonadal axis. A significant decrease in body weight was observed in the triclosan treated (F0) dams group as compared to vehicle control. There was increase in %pre-implantation loss (PIL) along with decreased litter size as compared to the vehicle control. The mean fetal weight and crown-rump length (CRL) of F1 male fetuses was found decreased in treatment groups. Further, decrease in serum testosterone level was observed in all groups of triclosan treated

animals, albeit statistically significant in higher dose group. Decrease in sperm count and sperm motility was observed in triclosan treated groups of F1 male.

Deciphering the Effects and Mechanism of Action of Butyl Paraben on Fertility

Paraben esters (methyl- to benzyl-); are used as an antimicrobial preservative in various pharmaceutical, medicinal and food products. Amongst the commonly used esters of parabens; butyl paraben has been recently added to the list of endocrine disruptors. Butylparaben is reported to possess a weak estrogenic/anti-androgenic property based on various in-vivo or in-vitro assays. Exposure to n-butyl paraben has been reported to affect steroidogenesis and spermatogenesis/ folliculogenesis in the animal models. Hence, the present study has been undertaken to decipher the effects of perinatal exposure to n-butyl paraben on sexual maturation and fertility of F1 generation male and female rats and understand its mechanism of action. A significant perturbation was observed in the expression of steroid responsive genes in ovary of F1 female rats. Increased expression of estrogen receptor-alpha (ER-a) and beta and STAR genes was observed in butylparaben treated group in the ovary of F1 female rats. The study demonstrates that exposure to n-butylparaben alter the expression levels of steroid responsive genes at molecular level.

Cellular and Molecular Effects of Cypermethrin on Reproductive Functions of Male and Female Rats

Cypermethrin (CYP) is a widely used synthetic pyrethroid insecticide and a known endocrine disruptor. CYP exposure may pose a risk to human health including adverse effects on their reproductive functions. Previously, the study observed that perinatal exposure (GD 6 to PND 22) of pregnant rats to CYP (0, 10, 25 mg/kg BW/ day) through oral route affects fertility of F1 male progeny and induced developmental defects in F2 foetuses. Further centre studied the expression of steroidogenesis pathway genes (StAR, P450c17,

P450scc and Aromatase) in perinatally CYP exposed adult F1 testis. The expression levels of StAR, P450scc, Aromatase and P450c17 mRNA in the testis were altered in CYP exposed F1 offspring as compared to control group. An increase was observed in the expression of StAR and proteins in CYP exposed groups. Aromatase expression in treated group was comparable with control group. These observations indicate that maternal CYP exposure during the perinatal period impairs testicular steroidogenesis in F1 male offspring.

REPRODUCTIVE CANCERS

Evaluating the Potential of Trop2 as Immunotherapeutic Target for Ovarian Cancer

Anti-peptide antibodies raised in centre's laboratory against Trop2 (Trophoblast Protein 2) could detect the recombinant human Trop2 protein by ELISA and Western blotting but could not detect endogenous Trop2 expressed by ovarian cancer cell lines. Ectopic expression of Trop2 in ovarian cell lines and control HEK293 cells followed by probing with anti-peptide antibodies resulted in Trop2 protein detection only in HEK293 cells but not in ovarian cancer cells. This indicated a possible ovarian cancer cell specific post-translational modification of Trop2. The protein is also known to undergo proteolytic cleavage. Site-directed mutagenesis approach was employed to identify the key amino acids regulating the proteolytic cleavage and post-translational modifications.

Immune Response Genes: Variants and its Association with Cervical Cancer

The comparative analysis on HPV infected women with or without cervical cancer and uninfected healthy women suggests a possible association of polymorphism in IL-6-174 GG gene with cervical cancer.

IdentificationandCharacterizationofMembraneBoundEstrogenBindingProteins in Prostate Cancer Cell Lines

The objective of the study had been been to delineate the contribution of non-genomic

estrogenic signaling to the pathogenesis of prostate cancer. Towards this, the presence of estrogen binding proteins on the plasma membrane of nontumorigenic and tumorigenic prostate epithelial cells and their immunological similarity to conventional nuclear estrogen receptors was demonstrated. The studies also demonstrated the role of non-genomic signaling in modulation of cytoskeletal proteins in prostate cancer cells. Further, activation of cell surface estrogen receptors in response to cell impermeable estrogen led to epithelial-mesenchymal transition. Data generated during this year showed the involvement of kinases, reported to mediate cell migration, in nongenomic estrogen signalling. GSK38 was found to be phosphorylated at S9 residue within 5 minutes of activation of cell surface estrogen receptors. Studies are under progress to determine whether GSK phosphorylation (inactivation) or activation is of significance in migration induced by nongenomic estrogen signaling in PCa cells. Silencing of the expression of GPR30, a protein reported to mediate non-genomic estrogen signaling, did not significantly alter the binding of cell impermeable estradiol to the surface of LNCaP cells was also demonstrated

NATIONAL ANIMAL RESOURCE FACILITY FOR BIOMEDICAL RESEARCH, HYDERABAD

MAIN OBJECTIVES

- To pursue and support basic biomedical and clinical research utilizing laboratory animals with emphasis in the areas of developmental biology, reproductive biology, cardiovascular physiology, stem cell, molecular cell biology, neurobiology, behavioral sciences, development of animal models, immunology, virology especially AIDS-related research etc.
- To create resources of Specific Pathogen Free (SPF) quality large and small experimental animals for research & affiliate programs

complying with all applicable regulations of ethics and rehabilitation by breeding them in barrier and natural habitat environment.

- To meet the demands especially the requirements of academic institutions, universities, research institutions, biotech, biopharma and biomedical research organizations for developing diagnostics, new therapeutics for human and animal health with its state of the art infrastructural facilities.
- То provide comprehensive worldwide bibliographic information on all laboratory that enable investigators animals to communicate information on research findings, availability of animals, tissues, blood and specimens throughout the world.
- To provide and expand access to the resources by way of undertaking collaboration with universities, National and International institutions.
- To function as testing and authorizing body of drugs, devices and products prior to human clinical trials and for further submissions.
- To serve as a Regional Reference Centre of ICLAS and WHO for all aspects of Laboratory Animal Sciences.

MAJOR RESEARCH AREAS

Use of innovative methods for testing of new molecular entities and modern medical devices, development of alternatives and validated testing approaches for treatment of human and animal diseases.

SERVICES

• Breeding and supply of quality laboratory animals

During the period a total 16,459 animals were bred and out of which 9,998 animals were supplied to various outside institutions and 1,732 animals supplied within the institute. An amount of Rs.39,41,544/- (Rupees thirty nine lakhs forty one thousand five hundred and forty four only) has been generated.

Supply of Animal Feed

a. Stock Animal Feed

The stock feed of 43,860 Kgs was prepared during the period. Out of this, a total of 15,190 Kgs feed was supplied to outside institutions generating an amount of Rs.27,04,695/-(Rupees twenty seven lakhs four thousand six hundred and ninety five only). An additional 28,433 Kgs of feed was also supplied within the institute. A quantity of 600kg of 27% Protein diet for Gerbils was also formulated and supplied in the institute.

b. Experimental Animal Feed

Institute also prepared 879 Kgs of custom made experimental animal feed. An amount of Rs.8,31,960/- (Rupees eight lakhs thirty one thousand nine hundred and sixty only) was generated. In addition, a quantity of 707 kgs special diet was also supplied to different scientists within the institute.

Blood and Blood Products

During the period, a total of 625ml of Blood and blood products have been supplied to different institutions and also service of image scanning extended and generated an amount of Rs.2,30,750/- (Rupees two lakh thirty thousand seven hundred and fifty only).

Human Resource Development

During this period in the junior level Laboratory Animal Technicians Training Course (LATTC), 12 participants underwent training in Laboratory Animal Sciences. In the senior level Laboratory Animal Supervisors Training Course (LASTC) 6 candidates were trained. In the Ad-hoc training course 26 candidates from different organizations were trained for a period of one week.

The Institute commemorated "World Laboratory Animal Day" on 24th April 2017

in association with ICMR and Committee for the Purpose of Control and Supervision of Experimentation on Animals (CPCSEA). On this day, a one day seminar on "Laboratory Animal Health and Quality Improvement through improvised sanitation, hygiene and sterilization procedures" was conducted. More than 180 delegates from private and Government Organizations have participated including CPCSEA nominees of IAEC from various institutions. During these celebrations some of the retired staff of the NCLAS were also felicitated. Apart from these members from local animal welfare organizations have been felicitated.

| Table 1: Training Courses | | | | | | | |
|---------------------------|---|---|----------|---------------------|---------------------|---------------------|--------------|
| SI. No | Type of Course and current number | Qualification & eligibility criteria | Duration | Fee | | | No. of |
| | | | | Govt. | Pvt | Fresh | Participants |
| 1 | 49 th Laboratory Animal Technicians Training Course (LATTC) 15 th June - 28 th July 2017 | Undergraduate with knowledge of English read and write | 6 weeks | 5000 | 8000 | 3000 | 12 |
| 2 | 37 th Laboratory Animal Supervisors Training Course (LASTC) 1 st Sept -30 th Nov 2017 | Graduation in Life sciences , Medical & Veterinary sciences | 3 months | 10000 | 16000 | 4000 | 6 |
| 3 | Ad hoc / Modular Training Course – open throughout the year for National, International & WHO Sponsored candidates | Sponsorship from the Head of the institution | 1 week | 1000 per week | 5000 per week | 5000 per week | 26 |

Training Courses conducted during the year

RESEARCH OUTCOME

- Anti-obesity, anti-arthritis effect of nutraceuticals developed from sea weeds on genetically inherited WNIN obese rats.
- In vivo anti-tumor activity of the organometallic ruthenium(II) polypyridyl complexes
- Studies on host-genotype impact on the bacterial community in the GI tract and host lipid and glucose metabolism and phenotype

- Basil seed (*Ocimum basilicum*L) supplementation modulates metabolic syndrome / obesity.
- The effect of dietary clarified butter oil (ghee) on inflammation and insulin sensitivity in diet induced insulin resistant and diabetic murine models.
- Development of Multiplex-PCR for rapid detection of important Respiratory bacterial pathogens of rat/mice.
- Evaluation of Anti diabetic activity of methanolic extract of Costuspictus in STZ induced diabetic Sprague Dawley rats.(16 NC 01).

AWARDS

Shri K.Prathap Reddy Received young scientist award for the work entitled "Restoration of reproductive potential by ficusracemosa bark extraction in WNIN/GR-Ob rats: role of hesperidin and chlorogenic phenolic compounds" in annual conference of Nutrition Society of India, held at Jorhat, Assam, from 2nd to 4th November 2017.

EXTRAMURAL RESEARCH

FERTILITY REGULATION

Phase-III Clinical Trial with an Intravasal Injectable Male Contraceptive – RISUG[®]

To study the safety and efficacy of once injectable non-hormonal intravasal male contraceptive RISUG (Reversible Inhibition of Sperm under Guidance), a prospective straight multi-centre clinical trial was conducted at five centres in the country. Healthy subjects of age 25 to 40 years are being recruited from the male family planning unit/urology/surgery OPDs who are visiting for the vasectomy/NSV methods. The presence of the inclusion criteria and the absence of the exclusion criteria have been documented. The RISUG injection was given to 315 subjects at all five centres and out of that 5 subjects were lost to follow up and 7 subjects reported protocol violation. Hence the data of 303 subjects (both husband and wife) are being obtained on demographic, life style, contraceptive use, clinical and reproductive. Data from all the enrolled subjects (both husband and wife) are being obtained on ultrasound of scrotum and vital organs in case of male and of lower abdomen and vital organs in case of female, chest x-ray, blood and urine examinations etc. a semen sample is being obtained from all the enrolled male subjects. Testicular size was measured of all enrolled subjects using an orchidometer.

General examination of the subjects and their wives are being undertaken to establish a set of 'normal' characters and values for the individual so that any changes in the health status later on can be properly assessed. A general physical as well as a gynecological examination of the female partners of volunteers has also been undertaken. Hemogram, liver function test (LFT) and kidney function tests were performed on the blood samples of all the enrolled subjects by the standard routine methods. Semen samples were analyzed as per the WHO method manual and pre-injection semen data on sperm count, sperm density, sperm morphology, sperm motility and viability were obtained.

Following a three finger technique 120 μ l of RISUG[®] in both the vas, one by one was injected.



Fig. 3: Photograph illustrating the RISUG injection procedure in a subject.

The post injection follow up at 3rd, 7th and 21st days were carried out and all the important parameters like pyrexia, local infection, infection in reproductive and urinary system, persistent pain and swelling in scrotum etc. were monitored.

The subjects were also examined for urethritis, vesiculitis, cystitis, prostatitis, epididimitis and orchitis post RISUG injection. The subject were followed after $1\frac{1}{2}$ months $2\frac{1}{2}$ months, 4 months, 5 months and 6 months post injection and all clinical and laboratory examinations were conducted on each visit on each subject to ascertain any physiological changes related to contraceptive agent. First semen sample was obtained on 3rd week after injection and second semen sample was obtained on 6th week post injection. Later on the semen samples were obtained on $2\frac{1}{2}$ months, 4 months, 5 months, 6 months and then every after six months till five years of post RISUG injection.

The salient features of data analysis of the Phase-III clinical trial indicate that the people from all major religion (i.e. Hindu 81.6%, Muslim 8.9% and Sikh 8.9%) have accepted the RISUG injection. People from all major caste (SC 43.3%, General 33.8%, OBC 16.2% and ST 6.7%) have accepted the RISUG injection. Majority of the RISUG subjects injected were having either primary education (43.2%) or Graduation (29.5%). Even few subjects were having post graduate degree and were professional. Even the wives of these subjects were also having the similar trend so far their education is concern. The data clearly indicate that testicular size of the subjects enrolled under the study varied from State to State. No adverse side effect was reported and observed on clinical evaluation of these subjects even up to 7 years of post RISUG injection. No adverse trend were observed in any parameter related to haemogram, liver function test (LFT), kidney function test (KFT), blood sugar, urine examination of the subjects up to 7 years post RISUG injection. Over all data indicates that 92.7% subjects achieved azoospermia at 2¹/₂ month post injection and it increased 97.2% at 6th month and then reached to highest level (97.3%) during sub-sequent follow up visits post RISUG injection. 0.3% method failure was observed. Over all failure of the drug RISUG was 0.98%. Hence over all contraceptive efficacy of the drug RISUG was 97.6%. However, efficacy of drug RISUG as per achievement of pregnancy is 99.02%. Number of

subjects lost to follow up was 5 and the reasons of dropout were:- personal reasons, subjects got transferred, family problem, residence shifted away from the participating center and subjects could not be located.

The data analysis clearly indicates that RISUG is a safe and effective male contraceptive and has been accepted by people of all religion.



Fig. 4: Visits wise overall efficacy of RISUG.

NATIONAL REGISTRY OF ART CLINICS AND BANKS IN INDIA

Around 1789 ART Clinics and Banks have been identified and out of that, 1198 ART Clinics and 196 ART Banks have confirmed their contact details. Out of 1198 ART clinics 396 ART clinics have been enrolled after successful submission of enrolment proforma. But out of 396 enrolled ART clinics complaints were received against 2 ART clinics which are located in Haryana & Gujarat. On investigations it was found that these two clinics were violating the provisions of ICMR guidelines and notifications issued by the Government of India time to time. Therefore the enrolments of these two ART clinics were cancelled. Out of 1198 ART clinics, 802 ART clinics are under process and complete information from 544 ART clinics have been received on the minimum infrastructure facility, trained manpower and procedures being under taken at the respective ART Clinic whereas 258 ART clinics have not submitted their duly filled prescribed proforma. The contact details of the enrolled ART clinics are available on ICMR website under the National Registry of ART Clinics and Banks in India of ICMR. On the other hand 395 ART clinics have not yet responded. The requests from 196 ART banks have also been received but in the absence of proper guidelines for ART banks

these request have not been processed. However ICMR is in process of finalizing the National Guidelines for Accreditation, Supervision and Regulation of ART Banks in India.

The data analysis of the registry indicated that out of 396 approved ART clinics 7 ART clinics performing IUI whereas out of 544 under process ART clinics, 27 ART clinics were performing IUI. Only two ART clinics from Govt. sector and 7 ART clinics from Charitable Trust were approved in comparison 6 ART clinics from Govt. Sector and 8 from Charitable Trust in under process category respectively. All ART clinics were allopathic in approved category whereas 18 ART clinics did not provide any information about their nature of clinic in under process category. Eighty ART clinics, out of enrolled ART clinics, were registered under Clinical Establishment Act. All approved ART clinics were registered under PCPNDT Act whereas out of under process ART clinics, 360 ART clinics were registered under PCPNDT Act. Whereas 28 ART clinics did not provide any information about their registration and 19 ART clinics were not registered under PCPNDT Act. Out of enrolled ART clinics, 29 ART clinics were sub-clinics of main ART clinic. Under enrolled ART clinics category, all gynaecologists were specialized in Obst. & Gyn. whereas in under process category, 2 ART clinics did not have the qualified gynecologist and 22 ART clinics did not provide any information about their qualification. Similarly all enrolled ART clinics were having andrologists and 169 were on regular basis whereas in under process category, 21 ART clinics did not have any andrologists. All enrolled ART clinics were having clinical embryologist and 71.7% were on regular basis whereas in under process category, 36 ART clinics did not have qualified embryologist. All the enrolled ART clinics were having regular counselor whereas in under process category, 14 ART clinics did not have counselor and 125 ART clinics did not have regular counselor. All the enrolled ART clinics were having sterile area whereas 5 ART clinics in under process category did not have sterile area. All the enrolled ART clinics were having semen processing lab and
clean room for IUI. In under process ART clinics, 14 ART clinics did not have Operation Theater for carrying out surgical endoscopy and vaginal ovum pickup. Information regarding ART procedures being undertaken by the ART clinics, 7 ART clinics did not provide any information in under process category. In enrolled ART clinics, 389 ART clinics were doing IVF-ET whereas in under process ART clinics, 357 ART clinics were doing IVF-ET. Under enrolled ART clinics, 314 ART clinics were undertaking surrogacy whereas in under process ART clinics, 232 ART clinics were undertaking surrogacy. In enrolled ART clinics, 203 ART clinics were not doing cryo-preservation of ovarian tissue. The state-wise distribution of ART Clinics and Banks is given in table below.

Development of non surgical Contraception using Synthetic Peptide of 80kDa HSA.

Initially 80kDa Human Sperm Antigen (80kDa HSA) has been identified using serum of an immune

infertile woman. Serum of an immune infertile female specifically reacted with sperm protein of molecular size of 80kDa. By Western blot analysis of human sperm extract showed specific reactivity of 80kDa HSA protein band and not with any other protein with serum of immune infertile woman suggesting that antibodies developed against this protein may be responsible for infertility and this female was healthy. Further it was found that 80kDa HSA is sperm specific protein and does not have identity with other proteins. Partial N-terminal amino acid sequence of 80kDa HSA (Peptide NT) and its peptides (Peptide 1, 2, 3 and 4) obtained by enzymatic digestion did not show homology with any of the known protein in gene bank. Chemically synthesized Peptides NT, 1, 2 and 4 were found to mimic immunobiological activity of native protein. Extensive research was conducted with this peptide on various animal models and the results of these studies are summarized below.

| Table 2: State-wise distribution of ART Clinics and Banks | | | | | | | | | | | |
|--|------------------------------|-----------------|--------------------------------|-------------------------|--------------------------|-------------------------|--|-------------|--|--|--|
| Status of Assisted Reproductive Technology (ART) Clinics and Banks In India under National Registry of ART Clinics and Banks in India Indian Council of Medical Research (ICMR) Ansari Nagar, New Delhi-110029 (India) | | | | | | | | | | | |
| S. | States/UTs | ART Clinics | | | | ART Banks | ART Clinics & | Grand Total | | | |
| No | | Enrolled (A) | Enrollment cancelled (B) | Under Process (C) | Total (D)= (A+B+C) | Under Process (E) | Banks identified by ICMR, yet no response received from them (F) | G=(D+E+F) | | | |
| 1* | Andaman & Nicobar Islands | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | |
| 2 | Andhra Pradesh | 11 | 0 | 21 | 32 | 1 | 12 | 45 | | | |
| 3 | Arunachal Pradesh | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | |
| 4 | Assam | 4 | 0 | 3 | 7 | 0 | 0 | 7 | | | |
| 5 | Bihar | 0 | 0 | 8 | 8 | 0 | 3 | 11 | | | |
| 6* | Chandigarh | 4 | 0 | 7 | 11 | 3 | 3 | 17 | | | |
| 7 | Chhattisgarh | 5 | 0 | 13 | 18 | 1 | 2 | 21 | | | |
| 8* | Dadra & Nagar Haveli | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | |
| 9* | Daman and Diu | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | |

| 10* | Delhi | 51 | 0 | 56 | 107 | 38 | 35 | 180 |
|-------|------------------|-----|---|-----|------|-----|-----|------|
| 11 | Goa | 0 | 0 | 2 | 2 | 0 | 1 | 3 |
| 12 | Gujarat | 23 | 1 | 54 | 78 | 11 | 30 | 119 |
| 13 | Haryana | 25 | 1 | 33 | 59 | 11 | 8 | 78 |
| 14 | Himachal Pradesh | 0 | 0 | 1 | 1 | 0 | 1 | 2 |
| 15 | Jammu & Kashmir | 1 | 0 | 2 | 3 | 0 | 1 | 4 |
| 16 | Jharkhand | 0 | 0 | 6 | 6 | 0 | 1 | 7 |
| 17 | Karnataka | 32 | 0 | 65 | 97 | 18 | 26 | 141 |
| 18 | Kerala | 11 | 0 | 30 | 41 | 11 | 40 | 92 |
| 19* | Lakshadweep | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 20 | Madhya Pradesh | 6 | 0 | 27 | 33 | 7 | 14 | 54 |
| 21 | Maharashtra | 97 | 0 | 159 | 256 | 36 | 70 | 362 |
| 22 | Manipur | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 23 | Meghalaya | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| 24 | Mizoram | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 25 | Nagaland | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| 26 | Odisha | 2 | 0 | 10 | 12 | 2 | 2 | 16 |
| 27* | Puducherry | 0 | 0 | 2 | 2 | 0 | 2 | 4 |
| 28 | Punjab | 25 | 0 | 35 | 60 | 9 | 12 | 81 |
| 29 | Rajasthan | 15 | 0 | 37 | 52 | 3 | 5 | 60 |
| 30 | Sikkim | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 31 | Tamil Nadu | 41 | 0 | 110 | 151 | 14 | 53 | 218 |
| 32 | Telangana | 15 | 0 | 26 | 41 | 7 | 20 | 68 |
| 33 | Tripura | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 34 | Uttar Pradesh | 19 | 0 | 67 | 86 | 19 | 33 | 138 |
| 35 | Uttarakhand | 2 | 0 | 11 | 13 | 0 | 1 | 14 |
| 36 | West Bengal | 5 | 0 | 15 | 20 | 5 | 20 | 45 |
| Total | | 394 | 2 | 802 | 1198 | 196 | 395 | 1789 |

Active immunization with Synthetic Peptide 1 of 80 kDa HSA elicited gradual increase in antibody titer and induced immunological infertility in male rats, rabbits and marmosets.

- Active immunization of normal fertile male bonnet monkeys with synthetic Peptide1 of 80kDa HSA using Muramyl Dipeptide (MDP) as an adjuvant emulsified with squalene and arlacel elicited gradual increase in antipeptide antibody titer.
- Animals failed to impregnate normal fertile females and regain of fertility with decline in antibody titer after about six months.
- Active Immunization of normal healthy females bonnet monkeys with synthetic peptide also elicited gradual increase in antibody titer and found to remain infertile for more than 10 months.
- No effect on biochemical and hematological parameter and animals were found normal healthy.

- Synthetic Peptide1 of 80kDa HSA is being further investigated for preclinical toxicity in collaboration with National Institute for Nutrition (NIN), Hyderabad following regulatory guidelines of DCGI.
- Acute toxicity was evaluated using 30 (15Male and 15Female) *Swiss albino mice*. The animals have been divided into three equal groups viz., 10X, 20X, & 50X. The test compound in various dosage concentrations has been administered by subcutaneous route The synthetic Peptide 1 of 80kDa HSA was found to be safe following acute toxicity studies using mice.
- Acute toxicity study has also been conducted in 5 (3M & 2F) New Zealand White Rabbits. The animals were administered with 500µl of test compound (400µg/kg) through subcutaneous route. This is followed by monitoring the activity and mortality initially at every 30mins for four hours and every day for fourteen days. In addition, body weight was recorded biweekly and Cage-side, neurological activity was also monitored daily. At the end of the study, all animals were euthanized, and gross necropsy of the major organs was performed along with weighing of the organs (liver, heart, lungs). Rabbits administered with 10X dose of 80 kDa HSA peptide were normal throughout the observation period. The body weight gain, clinical signs, behavioral activity, Hematological profile and gross necropsy of vital organs were normal.
- Sub Chronic Toxicity and Acute Toxicity in mice and rabbits with 1X. 5X and 10X TD. The study involves monitoring physical, physiological examinations, Hematology, clinical chemistry, immunology, gross necropsy and histopathology of all vital organs.
- Sub chronic toxicity study conducted in 48 (24M & 24F) Sprague dawley rats at the dose level of 15.3µg, 38.25µg, 76.5µg. Three booster

doses with same dosage were administered at 4 weeks intervals. Subcutaneously administered Sprague dawley rats with KLH conjugated Peptide1 of 80kDa HSA at the dose level of $15.3\mu g$, $38.25\mu g$, $76.5\mu g/0.1ml$ PBS found to be normal profile. There was no mortality in the rats exposed to test compound.

- Sub chronic toxicity study conducted in rabbits with normal health report at the dose level TD 60µg / 0.5ml, 2.5XTD 150 µg / 0.5ml and 5XTD 300µg / 0.5ml by subcutaneous route in 3 Booster doses at 4 weeks interval. The total volume of administration is 0.5ml / animal/dose.
- There was no mortality in the rabbits exposed to test compound. The gain in body weights was not significantly different from control group. The food intake, clinical signs, behavioral activity etc was normal throughout study period in all groups. The clinical chemistry and hematological profile were within normal range. There were no significant changes in organ weights. No gross changes were observed in any of the organs examined during necropsy. The histopathological observations of all organs were not significant and cannot attribute to the test item administered at respective doses and duration of the study.

The clinical signs, behavioral activity etc was normal throughout the study period in all groups. The clinical chemistry and hematological profile were within normal range. There were no significant changes in organ weights. No gross changes were observed in any of the organs examined during necropsy. The histopathological observations of all organs studied did not show any abnormalities attributed to the exposure of test compound. Synthetic Peptide1 of 80kDa HSA may be the potential candidate for fertility regulation which may prevent the use of condom and the surgical procedure for fertility regulation. The synthetic peptide of 80kDa HSA need to be further evaluated for human

clinical trials. The synthetic peptide may also be useful for control of stray dog population which need be investigate

CENTRE FOR DRUG DISCOVERY AND DEVELOPMENT IN REPRODUCTIVE HEALTH.

ICMR provided the financial support to the Centre for Drug Discovery and Development in Reproductive Health at CDRI, Lucknow. Numbers of projects were undertaken and the highlights of the results of these projects are given below.

Preclinical development of orally active, rapid fracture healing agent (CDRI-S007-1500)

The accidental bone fracture rates in India are one of the highest in world. Over the past 30 years' bone fractures have gone up threefold in Asia, with India and China topping the charts. 50 per cent of the world's fractures are expected to occur in this region by 2050. More serious is the fact that Indians are prone to fractures and have about 15 per cent lower bone density than their Western counterparts. Currently, no orally active rapid fracture repairing agent is available nationally and internationally. In the absence of oral drug, patients require several months before a fracture achieves complete return to mechanical stability. Recombinant human BMP2 (INFUSE® Bone Graft) has been approved for open tibial fractures by FDA. However, the use of BMP2 is hampered by numerous clinical complications which include postoperative inflammation, cyst-like bone formation and life-threatening cervical swelling. Thus, there is a need for agents that aim towards enhancing bone regeneration and repair and are cost effective. The study has demonstrated that synthetic pterocarpan, CDRI-S007-1500 enhances new bone formation and regeneration. CDRI S007-1500 is an orally active fracture repairing drug candidate, which has shown approx. 40% fast recovery of bone fractures at 1 mg/kg dose in animal models. CDRI-S007-1500 was found to stimulate bone healing by activation of BMP/ Smad signaling pathway. CDRI-S007-1500 was found to reduce inflammatory markers like TNF- α and IL-17 and suppressed the levels of oxidative stress at injury site. Bioavailability of S007-1500 was found to be optimal and drug interaction or CYP inhibition profile was minimal. More importantly, S007-1500 has been found to be safe in toxicity and safety pharmacology studies. The studies strongly suggest the potential of S007-1500 as an orally active fracture healing agent.

• Preclinical development of Kaempferol with enhanced drug delivery for superior osteogenic activity

flavonoid Kaempferol (K), а dietary found in fruits and vegetables has been reported to reverse osteopenic condition in ovariectomized rats. Since K is endowed with osteogenic activity, centre hypothesized that it may have beneficial effect on glucocorticoid (GC) induced bone-loss. Adult female rats were divided into five groups as control, GC (animals injected with methylprednisolone MP) to induce bone loss, GC+K (MP along with oral K), GC+PTH (MP with PTH s.c.) and treated for 4 weeks. To study the antagonizing effect of K on GC induced inhibition of fracture healing, drill hole injury was performed on control and GC treated rats. Oral dose of K was given for 14 days to observe effect on callus formation at the site of injury. After treatment, bones were collected for further analysis. Bone architecture was studied through micro-CT to assess the reversing effect on Kaempferol on osteoporotic animals induced as result of glucocorticoids. Further, bone strength, histomorphometric study, transcriptional analysis was performed from excised bones. Bone marrow cells from treated animals were differentiated to investigate theosteogenic potential of precursor cells in bone microenvirnment.

After establishing the invivo effect, invitro activity on osteoblast cells cultured in coated plastic plates was investigated to determine the pathway modulated by Kaempferol in the presence of dexamethasone (glucocorticoid). Anti-apoptotic activity was assessed by flow cytometry. Transcriptional analysis and protein studies were performed with primers and antibodies respectively to decipher the mechanism of action of Kaempferol. GC was associated with a decreased bone mineral density (BMD) and impaired bone microarchitecture parameters. Consumption of K induced bone-sparing effects in GC induced osteopenic condition. In addition, improved callus formation at site of drill injury in femur diaphysis was observed with K consumption in animals on GC. Consistent with the in vivo data K elicited a higher expression of osteogenic markers in vitro and antagonized the apoptotic effect of dexamethasone on calvarial osteoblasts. These results suggest that K reduced GC-induced bone loss and enhanced bone regeneration at fractured site, thus emphasizing on the positive role of flavonoid on bone health.

• Designed synthesis, evaluation and identification of novel, dually-effective spermicidal agents with antiTrichomonas activity for prophylactic contraception

Sexual transmission of fertile spermatozoa and sexually transmitted infections during intercourse often leads to unwanted pregnancies and frequent STDs. Globally, an estimated, 25-40% pregnancies are unintended, and, amongst curable STDs, Trichomoniasis has the highest incidence. While the former leads to unplanned families, overpopulation, poverty, increased abortion rates and maternal deaths: the latter increases the risk of low birth weight, pre-term delivery, viral STDs and HIV. Hence, development of novel, dually active compounds for prophylactic contraception is highly desirable. It is pertinent to note that the marketed spermicide Nonoxynol-9 (N-9)

is a potent detergent whose surfactant action has been shown to cause vaginal lesions in long-term use resulting in increased incidence of STDs and HIV. Centre's past effort to target both sperm and Trichomonas vaginalis simultaneously with novel molecules has discovered some potent pharmacophores. Hybridization is a rational approach to get new therapeutically important compound by joining two active pharmacophores. Carbodithioic acid group is a valuable pharmacophore, which exhibits spermicidal activity while thiourea and fluoxetine moieties have shown antiSTD potential. With the aim to synthesize dually active, non-detergent compounds it was decided to introduce thiourea and fluoxetine carbodithioic moieties to acid group. Accordingly eighty new compounds belonging to four different structural series of hybrid molecules viz. disubstituted piperazine-1, 4-bis(carbodithioate): dithiocarbamatethiourea hybrids; N-substituted-4-(3phenyl-3-(4-(trifluoromethyl)propyl) piperazine-1-carbothioamide, and substituted 4-(3-phenyl-3-(4-(trifluoromethyl)phenoxy) propyl) piperazine-1- carbodithioate, were designed and comprehensively evaluated for all the required biological activities. At least 5 dually active, lead molecules were identified with the desired spermicidal and anti-STI activities. These molecules were non-detergent in nature and had specific, mechanism-based action against the targets. They were devoid of general cyto-toxic nature of surfactants and thus appeared safer than the marketed detergent spermicide nonoxynol-9 (N-9). The anti-Trichomonal activity of these molecules was more than metronidazole against drug-resistant strain of Trichomonas vaginalis, in vitro. This project also helped in scaling up the synthesis of a novel series of dually active molecules identified earlier and at least one promising molecule was taken up for preliminary in vitro and in vivo toxicity in cell lines and animal models. A comprehensive formulation strategy was also evolved for

vaginal application of this novel molecule and its in vivo efficacy was evaluated in animal model. The project has identified a few lead molecules for further development as anti-STD vaginal contraceptives, and has provided useful data for development of a locally acting contraceptive molecule.

• Studying mechanism of pro-fertility activity of Mucuna pruriens, Withania somnifera and Asparagus racemosus in spermatogenically compromised rat model and identification of active phytoconstituents

Mucuna pruriens, Withania somnifera and Asapragus racemosus were studied for their prospermatogenic effects. SD rats with spermatogenesis compromised as a result of ethinly estradiol administration were used as animal models. Seed powder of Mucuna and root powder of Withania somnifera and Asaparagus racemosus were tested for 14, 28 and 42 days. All three plant products tested in this study improved spermatogenesis with significant improvement in sperm count or motility. Among these, Mucuna pruriens showed the highest pro-spermatogenic potency, followed by Withania somnifera and Asparagus racemosus. Withania somnifera had effect in particular on sperm motility, but sperm count did not change significantly. All three plants showed general anti-oxidant and adaptogenic properties as evidenced by reduction in ROS, DNA damage and improvement in cell cycle mitochondrial membrane and potential. Mechanism of action studies suggested that Mucuna pruriens acted via the central and peripheral nervous systems. At the CNS level, Mucuna improved the dopamine signaling, resulting in balancing of the reproductive hormones and hence improvement in spermatogenesis. Among various extracts of Mucuna pruriens, methanolic extract was the most effective. A large fraction of the activity of Withania somnifera was accounted by withaferin A, a pure compound isolated from

the root powder. Regarding the mechanism of action of Withania somnifera, it is largely an anti-oxidant and adaptogen, which scavenges ROS and reduces oxidative stress. Asaparagus racemosus also showed marginal activity in improving seminal parameters, but the effect was only peripheral. Since the reproductive hormones are centrally regulated, the central action of a male infertility therapeutic is desired and most effective. Therefore, among the three plants evaluated in this study, Mucuna pruriens appears to be the most effective in treating male infertility. Mucuna pruriens has highly significant promise for development as a pro-speromatogenic therapy for the treatment of male infertility.

• Validation of wnt pathway modulation and efficacy study in primary osteoporosis, fracture healing and secondary osteoporosis models for repositioning of clofazimine

Clofazimine (CFZ) is used for treating leprosy and is also being actively considered for the treatment of multi-drug resistant tuberculosis. Bone loss is reported in both leprosy and tuberculosis patients. Team studied the effect of CFZ in bone regeneration following injury in rats. Bone regeneration is critically dependent on the function of MSC and found that CFZ potently suppressed the viability of MSC from bone marrow (IC50, 640nM). At sub-lethal concentrations, the drug induced differentiation of MSC to adipocyte at the expense of osteoblasts. The adipogenic stimulation of CFZ is specific for bone marrow MSC as it had no such effect on adipose tissue-derived MSC. CFZ treated rats had reduced ability to heal bone injury due to diminished bone formation and increased adipocyte formation at the injury site. The call us at the injury site expressed higher inflammatory cytokines (IL-6, TNFa and MCP-1) and adipokines (adiponectin and leptin) in CFZ treated rats over control. In CFZ treated rats, upon transplantation, homing of both rat and human MSC to the injury site was

significantly reduced. Further, bone marrow of CFZ treated rats had much higher adipocytes than control. In MSC, CFZ strongly induced expression of PPARg that was similar to that caused by rosiglitazone. GW966, an antagonist of PPARg completely blocked the adipogenic effect of CFZ in vitro and in vivo. CFZ also resulted in femur osteonecrosis evident from empty lacunae and pyknotic nuclei containing osteocytes. Unlike glucocorticoids, CFZ does not cause insulin resistance, hypertension and sarcopenia, CFZ-induced osteonecrosis of femur appears better than that caused by glucocorticoids. Team concluded that bone regeneration is impaired by CFZ due to loss of MSC viability and increased adipogenic differentiation, resulting in osteonecrosis.

• Lead identification of non-steroidal molecule with anti-proliferative activity for management of endometrial hyperplasia

Endometrial hyperplasia is a precursor to the most common gynecologic cancer diagnosed in women. Apart from estrogenic induction, aberrant activation of the Wnt/b-catenin signal is well known to correlate with endometrial hyperplasia and its carcinoma. The benzopyran compound 2-(piperidinoethoxyphenyl)-3-(4hydroxyphenyl)-2H-benzo (b) pyran(K-1), a potent antiestrogenic agent, has been shown to have apoptosis-inducing activity in rat uterine hyperplasia. The study demonstrated that the compound K-1 suppressed the growth of human primary endometrial hyperplasial cells through discontinued Wnt/β-catenin signaling and suppressed PI3K/Akt survival pathway. The effect of K-1 on uterine histomorphometric parameters and subsequently investigated the role of Hh signaling in vivo in rat uterine hyperplasial model by demonstrating the expression profile of Hh signaling molecules including Ihh, Shh and Gli1. Hitomorphometric analysis revealed that compound K1 (400µg/kg) caused a decrease in estradiol induced-cellular parameters significantly

(36d regimen). These effects were highly significant in K1 administered rats (400µg/kg. p.o.) as compared to MPA administered rats (25mg/kg, p.o.). Further study was undertaken to explore the functional involvement of Hh signaling (the downstream to Wnt pathway) and its regulatory mechanism in endometrial hyperplasia. Differential expression of Hh signaling molecules i.e., Ihh, Shh, Gli1 or Gsk3ß was observed in endometrial hyperplasial (EH) cells as compared to normal endometrial cells. Estradiol induced the expression of Hh signaling molecules and attenuated the expression of Gsk3ß whereas antiestrogen (K1) or progestin (MPA) suppressed these effects in EH cells. Cyclopamine treatment or Gli1 siRNA knockdown suppressed the growth of EH cells and reduced the expression of proliferative markers. Estradiol also induced the nuclear translocation of Gli1 which was suppressed by both MPA and K1 in EH cells. While exploring non-canonical mechanism, LY- 294002 (Gsk3ß activator) caused a decrease in Gli1 expression indicating the involvement of Gsk3ß in Gli1 regulation. Similar attenuation of Hh signaling molecules was observed in rats with uterine hyperplasia undergoing anti-estrogen (K1) treatment. Overall, study revealed that anti-estrogenic agent (K1) modulates Wnt /Hh signaling that plays significant role in progression as well as protection of endometrial hyperplasia. The study also suggested that Hh/Gli1 cascade (canonical pathway) as well as Gsk3β-Gli1 crosstalk (non-canonical pathway) play crucial role in estrogen-dependent cell proliferation in endometrial hyperplasia which is significantly suppressed by benzopyran derivative K1. Therefore, targeting Hh signaling could hold promising effect in inhibition of endometrial hyperplasia formation, making this pathway an attractive and alternative potential target for drug development. This study revealed that benzopyran compound K-1 can potentially target Hh pathway and suppress endometrial hyperplasia progression.

• Studies on effects of obesogens in male germ cells: An exploratory study

Identification of Obesogens and their effects on male reproductive health is of paramount importance. In the first year of this project, centre has successfully identified a novel obesogen, Imidacloprid and studied its mechanisms of action in male germ cells. The results have confirmed that Imidacloprid induced the obesogenic inflammatory effects as indicated by the modulation of the miR185/SCOS3/STAT-3 pathway critical for the differentiation of male germ cells. Furthermore, centre has established a mice mesenchymal stem cell line that could be useful in screening of obesogenic compounds.

Localization and expression of orexin A (OXA) and its receptor during postnatal development in mouse testis, and role of OXA in testicular functions

In the present study, localization and expression of OXA and OX1R in Parkes (P) strain mouse testis during different stages of postnatal development were investigated. The results of immunohistochemistry demonstrate the localization of OXA and OX1R in both interstitial and tubular compartments of the testis throughout the period of postnatal development. Further, semiquantitative RT-PCR and immunoblot analyses showed that OXA and OX1R were expressed in testis both at mRNA and protein levels during different stages of postnatal development. The expression of OXA and OX1R increased progressively from day of birth (0 dpp) until adulthood (90 dpp), with their maximal expression at 90 dpp. The results suggest that OXA and OX1R are expressed in the testis and that they may help in proliferation and development of germ cells, Leydig and Sertoli cells until prepubertal period, and may also participate in regulation of steroidogenesis and spermatogenesis during adult stage.

Also, the role of OXA and OX1R in testis of adult mouse by blocking the binding of the ligand

to the receptor, using an OX1R antagonist, SB-334867, was investigated under in vivo and in vitro conditions. For in vivo study, adult male P strain mice were given a single bilateral intratesticular injection of the antagonist dissolved in vehicle at doses of 4 and 12µg/animal. Further, the mice in control group were injected with vehicle only. All animals were sacrificed 24 h post-injection. The antagonist treatment caused degenerative changes in the seminiferous tubules in the testis and also interfered with steroidogenesis, with a concomitant decrease in the level of testosterone (T) and an increase in level of $17-\beta$ estradiol (E2) in serum and in the testis in P mice. Further, expressions of SF1, StAR, P450scc and 17β-HSD were downregulated, while the expressions of 3B-HSD and P450arom were upregulated in antagonisttreated mice compared to controls. Also, sperm count was decreased, and oxidative stress was elevated in treated mice compared to controls. The antagonist treatment also caused a significant downregulation in expressions of OX1R, GLUT 3 and WT1 in testis at both the doses in comparison to controls. The level of glucose and activity of lactate dehydrogenase (LDH) in the testis were also significantly decreased in treated mice compared to controls. There was a marked increase in the number of TUNEL-positive cells and a decrease in the number of PCNA-positive cells in testis of treated animals; likewise, a marked increase in expression of caspase-3 and a decrease in expression of PCNA were noted in treated mice. In in vitro study, the antagonist treatment to the testis caused a marked reduction in the levels of T and an elevation in E2 levels in the media, accompanied with downregulation in expressions of SF1, StAR, P450scc and 17β-HSD and an upregulation in expressions of 3β-HSD and P450arom, indicating a direct role of OXA in regulation of testicular steroidogenesis. The observations of in vitro study supported the findings of in vivo experiments. The results suggest the potential involvement of OXA and OX1R in regulation of steroidogenesis, glucose homeostasis and spermatogenesis in the testis of adult P mice.

Further, in order to understand the role of OXA and OX1R in testicular development, an in vitro study was performed. The binding of OXA to OX1R in the testis of neonatal mice (5 days postpartum, dpp) was blocked by using an antagonist of OX1R (SB-334867) under in vitro conditions. Male mice (5 dpp) were sacrificed and their testes were cultured in complete media containing vehicle and two doses (0.1 and 4.0 µg/ml media) of SB-334867 for 72 h in CO2 incubator at 37°C. At the end of the culture, a marked increase in the expression of SF1 and a decrease in the expression of WT1 at both mRNA and protein levels were noted. However, a significant decrease in the expressions of SCF and MIS at mRNA level at both doses of the antagonist was also observed in comparison to vehicle treated controls. The results suggest that interference in binding of OXA to OX1R in testis of neonatal mice alters the expression of various markers involved in the testis development. Further, decrease in the expressions of OXA, OX1R and GLUT 3 in testis in response to both the doses of the antagonist points to their downregulation causing inefficient uptake of glucose by the testicular cells, thereby affecting gonadal development. In conclusion, the results suggest that the binding of OXA to OX1R is important for the development of the testis.

Furthermore, the role of OXA and OX1R in regulation of testicular functions in adult mice during alloxan-induced type 1 diabetes mellitus (T1DM) was also explored. Adult (age: 12-14 weeks) male mice were allocated to two groups, each comprising fifteen individuals. After overnight fasting, animals were weighed and those in Group I were injected (i.p.) with normal saline, while mice in Group II received alloxan (i.p., 175 mg/ kg BW) dissolved in normal saline. After thirty days of alloxan treatment, blood glucose level was increased in treated mice indicating diabetic condition. A significant decrease was noted in body weight of alloxan-treated mice compared to controls. Testis weight was also significantly decreased in alloxan-treated mice in comparison to controls, while the blood glucose level was markedly increased in treated animals. Further,

serum and intratesticular level of testosterone, activities of testicular steroidogenic enzymes (3β- and 17β- HSD) and expressions of various steroidogenic markers (SF1, StAR, P450scc, 17β-HSD and P450arom) were also markedly decreased in treated mice. In addition, expressions of OX1R, GLUT 3 and WT1 were significantly decreased in testes of diabetic mice compared to controls. The levels of glucose, activity of lactate dehydrogenase and lactate concentration in testes of diabetic mice were markedly decreased. A significant rise in the number of TUNEL-positive cells with a concomitant increase in the expression of caspase-3 was also observed in testis of alloxantreated animals. Furthermore, a significant decline in PCNA-positive cells and downregulation in expression of PCNA in testis of diabetic mice was also noted compared to controls. The results thus suggest that the expression of testicular OX1R was downregulated in type 1 DM, which may prevent binding of OXA to OX1R and arrest OXA/OX1R signaling cascade, leading to an impairment in testosterone biosynthesis and in SCs glucose homeostasis; this may result into an imbalance between germ cell survival and germ cell proliferation. The hyperglycemia may disrupt testicular OXA/OX1R signaling cascade, leading to impairment in steroidogenic activity and SCs glucose homeostasis.

The results of the present study help us understand the physiological role of OXA in regulation of testicular functions in adult mouse. Further, the study also strengthens the knowledge as to how the orexin system (OXA and its receptor, OX1R) plays a role in regulation of testicular steroid biosynthesis, and in glucose homeostasis in the testis. The study helps us understand the role of OXA and OX1R in development of the male gonad. Besides, this study also enhances the understanding of the role of OXA and OX1R in regulation of testicular functions during various metabolic disorders such diabetes mellitus. The overall results of the present study help us advance the knowledge of the role of OXA and OX1R in testicular physiology.

MATERNAL HEALTH

Evaluation of immunological & pro-thrombotic/ pro-inflammatory alteration in antiphospholipid antibody mediated & idiopathic recurrent miscarriage in women & role of Coenzyme Q_{10} in its modulation

The prevalence of recurrent pregnancy loss (RPL) is about 1-3 percent. There are various reasons for RPL like genetic abnormalities, uterine or endocrine abnormalities, etc. but about 50% of the cases are idiopathic. Oxidative stress plays a major role in the development and perpetuation of inflammation. Many studies have reported the effect of oxidative pregnancy outcome. Considering stress on inflammation caused due to increased oxidative stress may be a cause of fetal loss in idiopathic RPL females, the effect of an antioxidant, Coenzyme Q_{10} on the immune cells and on the prothrombotic markers in healthy females and in females with idiopathic miscarriage and due to the presence of antiphospholipid syndrome (APS) was studied. A total of 82 women, aged 18-35 years who had experienced two or more consecutive miscarriages before 16 weeks of gestation were screened. Of these, sixteen women fulfilling the classification criteria for anti-phospholoipid syndrome (APS) with a verified history of thrombosis along with a history of recurrent miscarriage were enrolled for the study. The results indicated that CoQ₁₀ may have an effect on the IFN- γ -producing T cells by reducing their proportion and Th1-type cytokine levels, on the contrary, this drug has limited effect on the Th17 cells in the females with a history of RPL and APS. Although, CoQ_{10} was found to be ineffective in changing the proportion of Th2 type cells, it had efficiently enhanced the proportion of regulatory T and regulatory B cells in RPL females during pregnancy. CoQ_{10} induced the production of TGF- β in regulatory T cells and IL-10 in regulatory B cells in RPL pregnant females. Thus, making the cytokine milieu, favourable for the tolerance of the fetus. This increased anti-inflammatory cytokines may be counteracting the enhanced effect of proinflammatory cytokines that was observed

in RPL women during pregnancy. Although, the pathway through which this drug is inducing the effect has to be deduced in the further study, this drug can be beneficial for enhancing the Treg cells in RPL females. CoQ₁₀ treatment ameliorates mitochondrial dysfunction and thus reduces oxidative stress, as mitochondria are the major source of ROS production in the cell and CoQ₁₀ is present inside mitochondria. This eventually reduces the expression of prothrombotic markers. Hence, CoQ₁₀ can be considered for therapeutic purpose for the treatment of APS and idiopathic RPL pregnant females, however, to confirm the profound effect of the drug, in vivo studies need to be done so as to provide a therapeutic option for the patients suffering from RPL. Therefore, further studies may be undertaken to study the effect of CoQ₁₀ in-vivo on the disordered balance of the immune system in idiopathic cases and altered antioxidant enzymes & pro-thrombotic/ pro-inflammatory markers.

Effect of Maternal Bidi Rolling on Fetal Growth and Pregnancy Outcome by Serial Fetal Biometry and Serum Cotinine Assays: A Cohort Study

Bidi rolling by pregnant women exposes them to nicotine through dermal absorption. Nicotine affects placental vasculature resulting in fetal hypoxia and growth restriction. Maternal cotinine assay reflects exposure. A study was carried out to assess effect of tobacco handling on maternal health and fetal growth by serial clinical, fetal biometry and cotinine assays using a prospective cohort study design in antenatal and birthing units of a teaching hospital over a period of three years. Pregnant bidi-rollers at 18-22 weeks of gestation and women matched for parity with no history of tobacco handing constituted exposed (n=178) and unexposed (n=356) groups respectively. Both groups were followed up with serial fetal biometry for intra-uterine growth and serum cotinine assays by ELISA for nicotine exposure. Pregnancy outcome and neonatal anthropometry were documented. Cotinine values >15ng/ml corresponded to active exposure, 2-15 passive and <2 non-exposure. Adjusted Odds ratio with confidence interval (aOR; CI) and adjusted mean differences were derived for pregnancy outcome. Results indicated that bidi rolling was equivalent to passive exposure in 28.1% and active exposure in 9.5% and positivity related to primiparity [OR 3.11(1.31,7.35); p=0.010]. Significant outcomes directly related to tobacco exposure (aOR) included gestational hypertension [3.74(1.37,10.23); p=0.010], small for gestational age [1.78(1.13,2.81); p=0.012] and an overall adverse outcome [1.98(1.27,3.10); p=0.003]. Intra uterine growth restriction [OR 2.27(1.07,4.81); p=0.03] and sonogram abnormalities [OR 1.85(1.25,2.73); p=0.002] were significant. Though crude OR [2.30(1.03,5.15); p=0.038) was significant, adjusted [1.76(0.73,4.19); p=0.205] was not for prematurity. Mean gestational ages were 38.15±2.06 and 38.47±1.13 weeks (p=0.050) in the two groups respectively and BW 2824.14±510.33 and 2991.76±462.3g (p<0.001). Adjusted mean difference showed decrement of 104g (-177,-32; p=0.005) in birth weight, 0.5cm (-0.8,0.15; p=0.004) in length and 0.4cm (-0.6,-0.15; p=0.001) in head circumference. A stratified decremented response was seen for cotinine positivity. Overall occupational handling was equivalent to passive tobacco exposure in the mother and fetus by assay but the birth outcome was comparable to moderate to light maternal active smoking. The study concluded that occupational tobacco exposure through bidi-rolling results in nicotine exposure with significant detrimental effect on maternal health and fetal growth.

Regional differences in neurotrophin regulation of vascularization in preeclamptic placentae

Preeclampsia is a major cause of maternal and fetal morbidity and mortality. During pregnancy, neurotrophins, angiogenic factors and matrix metalloproteinases (MMPs) play an important role in angiogenesis, trophoblastic invasion and placental development. It is likely that the placental architecture, oxygen availability and oxidative stress indices that vary across the placenta may lead to regional differences in the expression of neurotrophins, MMPs and angiogenic factors. A study was carried out to examine regional differences in the placental neurotrophins-,nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), VEGF receptor 1 (VEGFR1), matrix metalloproteinases (MMP) MMP-2 and MMP-9 MMPs and their association with birth outcome, blood pressure and ultrasonography measures in 52 normotensive control (NC) women and 43 women with preeclampsia [18 delivered term (\geq 37 weeks) (T-PE) and 25 delivered preterm (<37 weeks) (PT-PE)].

Results indicated a higher BDNF and VEGF levels in central chorionic -fetal (CF) region as compared to central basal -maternal (CM), peripheral basal - maternal (PM) and peripheral chorionic-fetal (PF) regions of the placenta in the normotensive control (NC) group. VEGFR1 levels were lower in the CF and PF regions as compared to CM region in NC group. Higher VEGF levels in CF region as compared to other regions were also observed in preeclampsia group. MMP-9 expression was higher in the CM region in the normotensive control and Term preeclampsia (T-PE) group but not in Preterm preeclampsia (PT-PE) group. VEGF levels were lower in all regions of PE, T-PE and PT-PE groups as compared to their respective regions in NC group. In contrast VEGFR1 and MMP-2 levels were higher in all the placental regions from PT-PE group as compared to the respective regions from the NC group. There was a positive association of placental NGF levels in all four regions with systolic blood pressure. Negative association of NGF levels in CM, CF and PM regions with baby weight, whereas there was a positive association of VEGF levels in the PF region with baby weight and placental weight was observed. This study, for the first time, documents different protein and mRNA levels of important growth factors like neurotrophins, angiogenic factors and MMPs in different regions of the placenta. Results clearly show that preterm preeclampsia has a severe pathophysiology as compared to term preeclampsia. Angiogenesis differs in different regions of the

placenta particularly in the central fetal region in response to hypoxic conditions prevailing in the placenta. Further, most of the differences found were in the central region of the placenta suggesting that the central region has a critical role and any alterations in this particular region may influence the growth and development of the placenta. There is a need for early first trimester color Doppler and ultrasonography (USG) assessments in pregnant women. This along with longitudinal studies on biochemical parameters like growth factors may help in early prediction and management of preeclampsia.

Non-invasive Prenatal Diagnosis (NIPD) of RHD Genotyping with cell Free Fetal DNA (cffDNA) in Maternal Plasma

Non-invasive prenatal diagnosis of RhD genotype using cffDNA is extensively used in many modern countries. The present study evaluated the performance of non-invasive fetal RhD genotyping using cell-free DNA by real-time polymerase chain reaction. The aim of this study was to evaluate the performance of non-invasive fetal Rhesus D genotyping in a cohort of 140 subjects, by realtime polymerase chain reaction utilizing the cellfree DNA of maternal plasma. DNA was extracted from maternal plasma of both non-alloimmunized and alloimmunized women between 7 and 34 weeks of gestation. RHD sequence was determined by quantitative PCR, with the amplification of RHD gene. Final results were compared with RhD phenotype obtained from cord blood sampling of neonates. A total of 140 samples from RhDnegative pregnant women were collected during the course of study. The fetal RHD status was conclusive in all 140 (100%) cases. The overall sensitivity and specificity of the test were 98.39% (95% CI: 94.30%–99.80%) and 75.00% (95%) CI: 47.62%–92.73%) respectively. The negative and positive predictive values were 96.83% (95% CI: 92.88.15%-98.68%) and 85.71% (95% CI: 59.08%–96.07%) respectively. The highest number of cases genotyped were reported from Punjab (39.2%) followed by Haryana (25.0%), Himachal

Pradesh (16.4%), and Chandigarh union territory (12.8%). Non-invasive fetal RHD determination by single or multiple-exon quantitative PCR exhibits high accuracy and enables its implementation into clinical routine. Results indicate that non-invasive RHD genotyping in early antenatal care appears ideal, since this approach could be included in a systematic screening program, thus avoiding further visits or additional investigations in the event of fetal D-negative status. Consequently, this approach will obviate the need of anti-D prophylaxis to all RhD-negative pregnant women during antenatal care. Given that unnoticed alloimmunization would bear ill consequences on women's pregnancy outcome, this test needs to be highly sensitive and robust. RHD determination through single or multiple-exon analysis may prove cost-effective and safe if performed in replicates. While larger and confirmatory studies are warranted, our data present a convincing view that NIPD testing may be assimilated into a routine clinical diagnostic algorithm for managing Rh pregnancies, who are at risk of alloimmunization.

Effect of oxygen inhalation on maternal and foetal free radical activity during elective and emergency caesarean section under regional anaesthesia

The influence of supplemental oxygen inhalation on free radical activity and total antioxidant status (TAS) during caesarean section (CS) has not been fully evaluated. The aim of this study was to compare oxidant and TAS of mother and foetus during CS under subarachnoid block (SAB) with and without supplemental oxygen inhalation. Using a prospective study design sixty pregnant women undergoing elective CS (ELCS) were randomized to inhale 50% oxygen vs air following SAB till delivery (n=30 each). Similarly, sixty pregnant women undergoing emergency CS (EMCS) were randomized to inhale 50% oxygen vs air following SAB till delivery (n=30 each). Arterial blood samples of mothers were collected at baseline and then every 5 min until delivery. Umbilical artery and vein samples were collected at delivery. All

the blood samples were evaluated for arterial blood gases, malondialdehyde (MDA) and TAS. Results indicated that 50% oxygen inhalation to mothers during ELCS or EMCS under SAB did not result in significant difference in foetal MDA and TAS as compared to air. At delivery, mothers undergoing ELCS receiving 50% oxygen had significantly higher maternal PaO, as compared to air [136.83±24.11 vs 181.93±36.00 mmHg,(P=0.00)]. In EMCS, mothers receiving 50% oxygen had also significantly higher maternal PaO, as compared to air [136.88±24.46 vs 171.06±33.76 mmHg, (P=0.00)] at the time of delivery. During ELCS, mothers inhaling 50% oxygen had higher MDA levels at delivery as compared to baseline [5.42±2.63 vs $6.25\pm3.43 \text{ }\mu\text{mol } 1^{-1}, (P=0.04)$]. In EMCS, mothers inhaling 50% oxygen had lower TAS levels at 10 min as compared to air, [0.98±0.13 vs 1.40±0.20 m mol 1^{-1} , (P=0.01)]. The study concluded that maternal hyperoxia did not concomitantly change foetal MDA and TAS levels following ELCS or EMCS under SAB as the average duration of oxygen supplementation was only (~10.3 min) in ELCS and (~7.4 min) in EMCS in this study. Further studies are needed to examine the effect of prolonged oxygen supplementation on mother and foetus during CS under SAB. Rationalization of oxygen inhalation for increased duration is required during CS under SAB.

Fetal movement awareness in pregnancy utility, compliance and outcomes in pregnancy

Feasibility and acceptability of using 2 types of fetal movement charts in 60 pregnant women beyond 28 weeks of pregnancy by giving them a choice of selecting either count to 10 ten or Sadovsky type of fetal movement chart was done in a tertiary care hospital. Count to 10 chart records time taken to count 10 movements once a day, whereas Sadovsky notes the movements for 20-30 minutes 3 times in a day. Both the groups of women in the study had similar demographic profile. Though more women (53%) selected the count to 10 type of chart, compliance was greater (63%) in the Sadovsky group. Reason of noncompliance was either the women were too busy or they forgot to document or they were not interested in counting fetal movements as there was low risk perception. Nearly 96% were satisfied with the Sadovsky method as compared to 63.3% in the count to 10 group. More than 80% were willing to recommend or use this method in the future and their was no difference between the groups. There were 4 incidences of decreased fetal movement in the count to 10 group whereas only 1 incident of decreased fetal movement in the Sadovsky group. NST done in all the cases was reactive. All but one had a normal fetal outcome. The women in the Sadovsky group failed to document the chart but immediately contacted the hospital when the fetal movement was less. The study indicated that awareness regarding fetal movement counting increased among the enrolled women. Since results are equivocal in the both the groups and there was no statistical difference, the feasibility and acceptability of these two charts warrants a study on a larger group to verify the results.

Acceptability of Pre-Exposure Prophylaxis for prevention of HIV among Men who have sex with Men in India

Under HIV prevention technologies, an ICMR task force study was conducted using formative qualitative research methodology. Focused Group Discussions and In-depth interviews were undertaken at two sites; Bengaluru (KHPT), Delhi (NaZ Foundation) among MSMs during July 2017-June 2018. Respondents who met study inclusion criteria were selected purposively with the help of targeted intervention teams and interviewed at CBOs/KHPT offices in their preferred languages - either Kannada Hindi or in English. A total of 12 Focussed Group Discussions and 11 indepth-Interviews involving 141 participants were conducted. All interviews were transcribed and translated into English. Software Nvivo was used for coding & data management. Spreadsheets were maintained to not lose track from the context of each individual cases. Study indicated that many participants were not aware of PrEP, in these situations the interviewer provided information so that participants could properly answer the questions being asked. Concerns were raised regarding side

effects associated with PrEP and long-term damage that the medication may cause. Concerns such as Counter indications PrEP may have with other medications, illnesses, or alcohol; PrEP being mistaken for ART and users facing additional stigma and discrimination; The 6 day period needed for PrEP to be effective was concerning to most given the unpredictable nature of their sexual encounters. Many participants participated in sex work to fulfill their financial needs. Though they understand they are at increased risk to contract HIV, the potential cost associated with using PrEP was identified as a possible deterrent Participants were also concerned that the costs of taking additional lab tests to initiate PrEP would be exorbitant and beyond their means. A few suggested that PrEP should be subsidized by the government and offered for 3-5 rupees per tablet. This low cost will ensure that some do not abuse or throw away tablets. This low cost will ensure that some do not abuse or throw away tablets. Most of the participants suggested that PrEP be offered for free. Much like the condoms the government offers for free, PrEP should also be offered for free since this is a government initiative to encourage PrEP use with MSM/TG. Preparation of the final report and dissemination meetings to share the result with NACO and policy makers are planned in the next few months.

CHILD HEALTH

Estimating the burden of pediatric HIV in a "A" category district in India: Phase II (Cohort study of children (0-14 yrs.) exposed to maternal HIV)

The Phase 1 of the research study had identified around 238 exposed and infected, and 1184 exposed-but-uninfected children of age 0-14 years. In Phase 2, the cohort of these children (all willing children from Strategy 1 & 2, all willing positive children and their siblings, if any from Strategy 3) was followed up to explore health and life outcomes among the maternal HIV exposed children, and differentially between the infected and uninfected. Exposed infants born during the course of the post-Phase 1 (Jun 2013 to Nov 2014) and Phase 2 (Dec 2014 - Nov 2017) study, and their siblings, were also recruited and followed up, in addition to the orphans and their siblings identified in Phase 1. Data was captured periodically based on the age of the children and/or status of pregnancy: For children: once in a week for neonates, once in a month in post-neonatal infancy, once in two months during age 1-5 years, once in three months during age >5-<15 years; For pregnant mothers: Once in first trimester, twice in second trimester, monthly in third trimester till 36 weeks of pregnancy and once biweekly thereafter till delivery. The patterns of growth and development of these children in terms of clinical and nutritional profiles, morbidity/ mortality events, natural course of infection, and prophylaxis or treatment status, will be described, compared and correlated with other socio-economic, demographic and health status related variables. Early case detection among exposed infants was attempted through a cord blood sample, wherever possible, since the phase 1 study showed a high mortality among maternal HIV exposed children less than 6 weeks of age. DBS DNA PCR testing of cord blood samples was planned to be implemented in case of positive deliveries happening during the study period, but was not very fruitful. All blood tests were synchronized with the national protocols and existing systems, and results were gathered.

- All the 291 health care facilities had been revisited periodically and data on positive pregnant women has been gathered, post Phase 1 Strategy 1 recruitment. 551 positive pregnancies have been thus include in the Strategy 1 that had been continued through Phase 2. Database completed, cleaned and locked. Analysis underway.
- From the cumulative list of households drawn from Phase 1 Strategy 1, Strategy 2, Strategy 3 (Households with a positive child), Orphans and Post Phase 1 Pregnant Positive Women reported, 985 households were recruited in Phase 2, till the end of the study. This included a child universe of 2211, from among which 1779 children participated in the study. There were about 10758 successful follow-ups

conducted for the children, during the course of the study. Database completed, cleaned and locked. Analysis underway.

- Basic information for non-recruited participants: So as to facilitate comparison between the participants and non-participants in the Phase 2 study, basic information sheet (G2 form) was successfully attempted for 213 (out of 286) participants who were trace-able and willing to share one-time data, as they were reluctant to join the cohort study.
- Verbal and Social autopsy: For children of any age dead on or after 01 Jan 2011, VSA was attempted. For this three forms (VSA-N, VSA-P and VSA-C) were used. Of the 171 child deaths, 104 VSAs have been completed, first and second reading completed. Analysis is underway.
- Case-studies (9 Nos.) have been conducted to look into the reasons for HIV sero-conversions identified in >18-month age children.

An explorative study of determinants of occupational injuries in child and adolescent workers and development of a suitable intervention approach

A cross sectional study addressing occupational injury was carried out in Kolkata, involving 250 child and adolescent workers of four major informal sectors with intervention approach to identify human and workplace factors as well as to undertake intervention through health education. About 20% of study subjects were of less than 16 years age and 67% workers were working in present job for more than one year. Back pain, joint pain and headache during or after work were major work related morbidity in study subjects. Not only more than 50% workers felt pain-discomfort at work, but also similar percentage of subjects perceived their workload to be moderate to heavy. This study examined the occurrence of injuries in last lyr period. About 58% of workers reported injuries in last one year. Most of the workers affected by

injuries had single injuries in this one year period. It was observed that in about 75% injuries limbs were affected. Superficial injuries/ fracture/ dislocation (55.7%) and sprain/strain (32.8%) were the major effect of such injuries. As far as causation is concerned fall of object (27.3%) and wrong movements (66.7%) was major concern. So far as involvement of equipments/agencies is concerned, in most of injuries (87%), involvement of small tools was observed. The observation highlights that lack of job training, lack of safety training, lack of protective devices, lack of expertise to deal with small tools are major predictors of the injuries of the study subjects. While examining heat exposure of study subjects at work, it was found that moderate level heat stress was present in most of the work places, hence contribution of such heat stress in injury occurrence may not be ruled out. Injury occurrence is multifactorial in causation, hence multivariate analysis was sought for better understanding the role of different individual variables. Habit of workers (OR 2.383, 95% CI 1.315 - 4.319) and perception of pain and discomfort (OR 1.825, 95 % CI 1.015 - 3.281) was the significant predictors of such injuries in totality. In brickfield workers, persons having perception of pain and discomfort (OR 10.262, 95 % CI 1.236 – 85.226) were at significant risk. In construction workers, age of the subject (OR 1.503, 95 % CI 1.00 - 2.260) was found to be a significant risk factor. In farming sector, centre found that perception of pain or discomfort (OR 6.034, 95 % CI 1.314 – 27.707) was a significant risk. Postural analysis was carried out by OWAS, REBA, RULA techniques. Working postures adopted in most occassions are not ergonomically optimum. Work postural stress combined with unskilled use of tools has been the cause of injuries in many occasions. An assessment of knowledge of participants (pre and post intervention) was undertaken by interviewer administered questionnaire. Enhancement of knowledge following awareness activity was evident. As far as intervention is concerned, majority of participants liked the method 'showing on hand how to perform safe practices on job' the most.

Cluster Randomized Trial of a mHealth Intervention "ImTeCHO" to Improve Delivery of Proven Maternal, Neonatal and Child Care Interventions through Community Based Accredited Social Health Activists (ASHAs) by Enhancing Their Motivation and Strengthening Supervision in Tribal Areas of Gujarat, India

In this two-arm, stratified, cluster randomized trial over 36 months, an innovative intervention based on mobile-phone technology (mHealth) to improve performance of ASHAs through better supervision and support in predominantly tribal and rural communities of Gujarat was implemented and evaluated. There were eleven PHCs in each arm. The intervention was a job-aid in form of a newlybuilt mobile-phone and web application used by ASHAs and PHC staff to improve (1) Coverage of MNCH services (2) Coverage of care among complicated cases (3) Supervision and support to the ASHA program. Primary outcome measures were a composite coverage index and proportion of neonates who were visited by ASHAs at home within the first week of birth. Outcomes were measured by conducting household surveys at baseline, and post-intervention. Baseline characteristic were similar in both arms. 6,493 respondents were interviewed during household endline survey; 85% of study population was tribal. Primary outcomes: 1. Coverage of home visits within first week of birth and 2. Modified ASHA centric composite index (MACCI) was 10.2% (CI: 6.4, 14.0) and 4.9% (CI: 0.2, 9.5) higher in the intervention arm compared to the control arm. There was significant improvement in coverage and quality of home visits by ASHA during antenatal period (15.7%, (CI: 11.0-20.4)), home based newborn care (6.4% (CI: 3.2-9.6)), early initiation of breast feeding (7.8% (CI: 4.2-11.4)), and exclusive breast feeding (10.3% (CI: 5.9-14.7)). The average login rate was 85% and task completion rate was 74% indicating high level of uptake of the intervention. Use of mHealth intervention might be effective toward improving of coverage and quality of MNCH services in hard to reach areas and could be considered for scale up.



Fig. 5: Photograph illustrating use of mobile-phone technology (mHealth) by ASHA worker.

Participatory health facilitation intervention to promote maternal health, feeding attitude and adherence to recommended IYCF practices in tribal Gujarat

Nutrition in the first 1000 days of life after conception has implications not only for the growth of child but also development of cognitive abilities and executive function. This interventional experiment was carried out in the tribal region of Dahod, Gujarat to assess key determinants of infant and young child feeding practices in the tribal blocks of Dahod district and to design and develop evidence-based, contextually relevant and culturally sensitive health promotion intervention to facilitate IYCF practices as well as to extend lactation management support through trained lactation counsellors. After a needs assessment of 1239 mothers. Dahod block was selected as a control-arm and Jhalod block as an interventionarm in consultation with Chief District Health Officer. Mothers were recruited in two cohorts accounting for high migration in the region: (i) mothers in their third trimester; (ii) mothers having infant <4 months of age. In intervention-arm mothers received counselling after questionnaire Age-appropriate and assessment. culturally acceptable IYCF counselling messages were developed and pre-tested in presence of FHSs and CHWs. In addition, audio-visual counselling show cased Gujarati videos relevant to tribal context from YouTube channel Health Phone (developed by Indian Academy of Pediatrics and partners). The videos were shown using 8 inch tablet devices. Additionally, group counselling and recipe demonstration was also conducted at all anganwadi centers in the intervention villages by the study team members trained by the PI. The BCC intervention helped improve breastfeeding practices in terms of early initiation of breastfeeding and colostrum feeding. It also helped improve timely introduction of complementary feeding in 6-9 month agegroup. However, the intervention did not show any significant impact in improving minimum meal frequency, minimum dietary diversity and minimum acceptable diet. The simplicity of this contextual intervention enhances its ability to be replicated by leveraging the existing healthcare system. Given the low literacy, poverty, limited livelihood opportunities and high out-migration, complementary feeding practices need further exploration to understand social determinants of health.

Randomized controlled trial to compare the efficacy and safety of mycophenolate mofetil versus levamisole in children with frequently relapsing and steroid dependent nephrotic syndrome

In this prospective randomized, open label parallel group single centre trial efficacy of therapy with oral levamisole on alternate days to daily therapy with MMF was compared in decreasing the frequency of relapses in patients with frequently relapsing or steroid dependent nephrotic syndrome. Of 207 patients screened for eligibility between August 2012 and December 2014, 149 were randomized. Baseline characteristics were similar in patients allocated to receive MMF (n=76) or levamisole (n=73). The annual frequency of relapses was comparable between patients treated with MMF and levamisole (mean difference in incidence of relapses -0.29; 95% confidence interval -0.65, 0.08; P=0.12) and declined significantly from baseline for both groups. Similar and high proportions of patients in both groups showed sustained remission (40.8% vs. 34.2%; P=0.42), while comparable but small proportions developed frequent relapses (14.5% vs. 16.4%; P=0.75) or treatment failure, a

composite of frequent relapses, steroid resistance and significant corticosteroid toxicity (15.8% vs. 20.6%; P=0.46). The two groups were comparable in the time to first relapse (6.8 vs. 8.8 months; log rank P=0.25), frequent relapses (P=0.72) or treatment failure (P=0.22); these results were sustained during clinic follow up beyond study period. Both groups of patients showed similar and significant improvements in anthropometry and blood pressure and low rates of minor and serious adverse effects. Serial evaluation of B and T lymphocyte subsets in a subset of 31 patients consecutively randomized to receive MMF (n=17) or levamisole (n=15) showed similar proportions of B cells and CD4+, CD8+, T helper (Th)1, Th2, Th17 and T regulatory cells at randomization and 3 monthly follow up; patients in relapse showed significantly decreased Th1/Th2 and Treg/Th17 ratios compared to those in remission.

Subgroup analysis did not show significant differences in relative relapse rate or hazards ratio (HR) of frequent relapses or treatment failure between subgroups of patients categorized by sex, age or disease severity, and adjusted analysis failed to find independent predictors for these outcomes. The risk of first relapse was reduced for patients treated with MMF compared to levamisole in patients younger than 7.5 years (HR 0.48, 95% CI 0.65, 0.93; P=0.027) and steroid dependence at randomization (HR 0.59, 95% CI 0.27 0.71; P=0.006). Steroid dependence (adjusted HR 1.73; 95% CI 1.09, 2.73; P=0.019), and neither therapy nor age, was an independent predictor of risk of first relapse. The study concluded that therapy with MMF and levamisole are associated with comparable and satisfactory reduction in frequency of relapses, high likelihood of sustained remission, significant corticosteroid sparing and improvements in blood pressure and anthropometry in children 6-18 years old with frequently relapsing or steroid dependant nephrotic syndrome. These findings have implications for offering a choice of safe and effective therapies in patients with steroid sensitive nephrotic syndrome.

Plasma proteome profiling in children with Kawasaki Disease

Kawasaki Disease (KD) is the commonest cause of acquired heart disease in the developing world, and its incidence is progressively increasing in developing countries including India. The diagnosis of KD is based on clinical criteria laid down by the American Heart Association. There is no pathognomonic laboratory test for the diagnosis of KD. Two-dimensional electrophoresis followed by mass spectrometry is an unbiased approach for biomarker discovery. Ten children diagnosed with KD and 10 acute febrile controls were enrolled for the study at PGIMER Chandigarh. EDTA and serum samples were collected in the acute phase and one week after intravenous immunoglobulin (IVIg) administration. Mean age at diagnosis was four years. Male: female ratio was 1.6: 1. Twodimensional gel electrophoresis (2 DGE) was performed on patient and control samples after removal of abundant proteins by Proteominer columns. Isoelectric focusing was performed on using Ettan IPGphor protean IEF Cell (GE Health Care Biosciences) using 11cm IPG strips (pH 3 to 10). The second dimensional electrophoresis was performed on 12% SDS-PAGE using Tris-glycine buffer (250mM Tris, 1.92M glycine, 1% SDS) at 20mA for 4-5h. The 2D images were analyzed by the Image Platinum 2D software characterization of the differentially expressed proteins by peptide mass fingerprinting using mass spectrometry. Two differentially expressed proteins spots were found in a patient compared to control by 2DGE. These proteins were further characterized by MS. Peptides 1362, 1928 and 2211 from spot 1 and peptides 1340, 1928 and 2211 from spot 2 were further analyzed by using MS-MS mode. Spectra showed the closest match with Human peptidyl-propyl cistrans isomerise (FKBP9) and Kinesin-like protein 1A. For validation of these proteins, an enzyme linked immunosorbent assay was performed in serum samples of 15 patients with active disease before and after IVIg adminstration. However, the levels of Kinesin like protein 1A was not found to be elevated in patients during active disease.

Validation of Comprehensive Intelligent ARI monitor for early detection of Pneumonia in rural children aged less than 5 years in Madchal Mandal, A.P. (Phase 1)

Pneumonia among children aged under five years continues to remain a major killer. The diagnosis rests on IMNCI guidelines in rural areas. Peripheral health workers may make early referrals if supported by technology for accurately diagnosing a sick child. In this validity and reliability of a Comprehensive Intelligent ARI monitor to correctly record four parameters- heart rate, temperature, SpO2 and Respiratory rate among infants and under five children suffering with respiratory symptoms attending paediatric outpatient department or admitted to the paediatric ward of Mediciti Institute of Medical Sciences, Medchal mandal, AP was tested. The prototype, developed at BITS Hyderabad campus, operated using three probesan accelerometer probe for respiratory rate, and a temperature sensor. Additionally, a commercially available probe using optical sensor was used for SpO2 and heart rate. These parameters were then transferred to smartphone application via wired or wireless connection. Smartphone application analysed the physiological parameters together with other parameters in the algorithm such as age, gender etc. to show if the child had signs of serious illness.

The initial testing of children done using the prototype device showed some problems with capturing data related to respiratory rate and SpO2. The problems were identified. This calibration process is extremely time consuming and thus may require more time to realize an accurate ARI monitor.

Health Account Scheme-HAS empowering people for healthcare through Multi-Sector coordination-An Operational evaluation

Under this study 7484 individuals of all ages and genders from 500 households at rural Hardoi, 500 from urban Hardoi, Uttar Pradesh and 500 Households from Tribal zone adjacent to Itanagar, Arunachal Pradesh have been enrolled. One slum site at Kalyan Puri, Delhi is updating the health status of 500 Households. Individual are given health diary with self carbonized sheet and place to write health problem, treatment, expense, experience and needs. Monthly updating of the diary involved interaction with the enrolled participants and transfer of sheet online for updating. This work was undertaken largely by project staff and health volunteers identified by the investigators from the community since anticipated grass root health workers were unable of doing monthly updating. A shift in disease paradigm was observed i.e. decreased in prevalence of communicable diseases by 1-4% and addiction by 8% in comparison to base line data. Increase in non-communicable diseases by 12% was observed due to diagnosis of hidden cases during updating of the diary on monthly basis. The data also indicated increased diagnosis of the previously undiagnosed non-communicable diseases like hypertension (11%), diabetes (6%), and anemia (7%).

Majority of the participants (98%) accepted keeping one health diary and allowed its monthly updating for 12 months. However 89% participants expressed their opinion to link the health diary with existing health services. It was also observed that the health programs could have been reached to the community in a better way if local health system could have participate actively or would have been cooperative. Only education, counseling and some emergency care could be extended to the community during monthly health diary updating. At the end term survey in 3rd year, majority of the participants wished to continue with the scheme and expressed if health service/ medicines delivery can be linked with it.

It was also observed that unmet needs are existing in the community and the major reasons of unmet needs are lack of health related education and information; weak linkages among system as well as with community which can be strengthened by setting up reliable feedback mechanism as undertaken under Health Account Scheme which is involving empowering the community to overcome suboptimal implementation of health programs and health care delivery.

EMF HEALTH

Effect of Non-ionizing Electro Magnetic Field (EMF) on Human Health

This is an ongoing prospective multi disciplinary cohort study with the primary objective of finding effects, if any, of radio frequency radiations (RFR) emitted from cell phone on human health with special reference to ENT, Neurological, Cardiological, Reproduction, Oncological, Biochemical and Hematological disorders. The associated objectives of the study are also to find out the physical characters of the RFR emitted both from cell phone and cell phone towers and to find out health related problems and complaints reported by the peoples residing near cell phone towers at various distances.

The required sample size of the study is 4500 healthy male and female volunteers (18-45 years) under six study groups. Currently 3215 male and female subjects have been enrolled after fulfilling exclusion and inclusion criteria's under various study groups and out of that 2868 enrolled subjects have been followed for their clinical and laboratory examinations. The salient findings of the interim data analysis are as follows.

- The increasing trend in air conduction, bone conduction and speech recognition threshold indicates that the sensitivity of hearing is decreasing gradually during the consecutive follow up visits which indicate the possibility of gradual sensory neural hearing loss in exposed groups. The Data Safety Management Board (DSMB) and Experts Committee formed the opinion that overall cell phone use has the effect of progressively increasing adverse effect on auditory system which needs to be followed for longer duration.
- The decline in levels of testosterone have been noticed in exposed groups therefore majority

of androgen dependent parameters like sexual desire & sexual activity, sperm count, sperm motility, percentage of live sperm, percentage of morphological normal sperm etc. are decreasing in male subjects of exposed groups during the consecutive follow up visits. The Data Safety Management Board (DSMB) and Experts Committee formed the opinion that use of cell phone has progressively increasing adverse effect on sperm morphology and seminal plasma. This trend needs to be follow to draw the conclusion whether these changes are resulting in infertility.

- Increase incidence of irregular menstrual cycle and decrease in sexual desire and frequency in female subjects of exposed groups were noticed during the consecutive follow up visits.
- Memory, fluency, visuospatial-abilities and overall Addrenbrooke's Cognitive Examinations-Revised Score (ACE-R) were reduced significantly in highly exposed and moderately exposed male and female groups during consecutive follow-up visits.
- Epworth Sleepiness Scale Score & Diagnostic and Statistical Manual of Mental Disorders, IV Edition (DSM-IV) criteria score were increasing significantly in both moderate and highly exposed male and female groups during consecutive follow-up visits.
- Percentage of the people reporting numbness, extreme tiredness and itching increased in highly and moderately exposed male and female groups during the consecutive follow up visits.
- The percentage of women reported lump or thickening around the breast increased in highly and moderately exposed female group during the consecutive follow up visits. But malignancy could not be established by Mammography.

- Though no significant difference was found in terms of clinical parameters on cardiological observations but significant changes in frequency of snoring and increased levels of Cholesterol, LDL and Triglyceride and decreased levels of HDL in exposed groups needs to be followed for longer duration to draw a meaningful conclusion.
- It was observed and recommended by the DSMB and Experts Committee that the clinical and laboratory parameters of cardiovascular, neurological and oncological disciplines showed decreasing or increasing changes but they are within the normal range. The members of the board viewed that the present observations are not sufficient to draw any conclusion at this stage. Therefore, to draw any meaningful conclusion from these observations it is necessary that this study should be continued for longer duration.
- The percentage of apoptosis in lymphocyte and levels of malondialdehyde were increasing in male and female subjects of exposed groups.
- The levels of superoxide dismutase (SOD) were decreasing both in male and female subjects of exposed groups.
- The decreasing trend in total leukocytes and monocytes counts and increasing trend in lymphocytes counts were noticed both in male and female subjects of exposed groups.

above observations The indicate that biological changes are well evident in both male and female subjects of exposed groups in comparison to control group. But to find out whether these biological changes will result into health hazard / disorder the desired cohort has to be completed and needs to be followed for long duration. Statistically significant and clinically relevant conclusion can only be drawn with adequate sample size and with long term follow-up of the enrolled subjects for their clinical and laboratory investigations.

INSTITUTIONAL STRENGTHENING AND CAPACITY BUILDING

National Animal Resource Facility (NARF) for Biomedical Research

The agreement was signed between ICMR and CPWD for civil construction of the NARF-BR. As per the agreement, 33% cost of the civil construction has been transferred to CPWD. CPWD has appointed the consultant and after the finalization of all the drawings the mandatory approvals from various Departments of State Govt. have been obtained. CPWD has appointed the contractor to undertake the project. the boundary wall has been constructed around the land.

Multidisciplinary Research Units- MRU in North eastern states- with ICMR support

Four Multidisciplinary Research Units- MRUs in North-East States i.e. Assam Medical College, Dibrugarh Assam, Agartala Medical College, Tripura, Hospital & Medical Education, Govt. of Mizoram, Aizwal and Healthcare Laboratory & Research Centre Naga Hospital Authority, Kohima, Nagaland are working in full potential with all lab equipments and staff in place.

Advanced lab facilities equipped with Auto analyzer, trinocular microscope, fluorescent microscope imaging system & motorized stage, table top refrigerated centrifuge, microfuge (refrigerated) centrifuge are in use for regular hospital services for the region, Internship trainings, Multicenter Task Force studies, B. Sc, M. Sc students. Research work (hospital and population bsed studies) is undertaken at all four functional centers. At Agartala Medical College, Tripura-two studies, Mizoram, Aizwaltwo studies, Dibrugarh Assam-twenty studies, Nagaland- nine studies are ongoing. Research methodology training workshops were held at these MRUs apart from scientific conferences and seminars. Nineteen Ph.D students were using MRU facilities, among them at Agartala, Tripura one Ph.D student, at Dibrugarh thirteen Ph.D students, at Nagaland five Ph.D students are using these MRUs. All the sites including fifth upcoming at Arunachal Pradesh- Itanagar are further planning to undertake research in non-communicable diseases and locally prevalent problems. Eight research publications are reported 3 from Nagaland, 5 from Dibrugarh facility.

NUTRITION

The ICMR continues to be instrumental in developing public health activities with many significant contributions in the country in the field of nutrition. It has been made possible by undertaking the laboratory and hospital based research with community based participation. The salient features of various research activities undertaken during 2017-2018 are given below.

INTRAMURAL RESEARCH

NATIONAL INSTITUTE OF NUTRITION, HYDERABAD

CLINICAL RESEARCH

- Work on the indigenous development of the potassium counter facility for accurate measurement of body cell mass in children and adults has been initiated.
- Profiling of the built environment in the 29 study villages has been completed and an intervention to increase the fruit and vegetable consumption in the study areas has been initiated.
- Developed indigenous technology for fortification of rice with iron, folic acid and vitamin B12 with very good retention and stability of the added micronutrients during washing and cooking. Completed the RCT on fortified rice in the mid day meal in school children to assess the impact of anemia status. Data preparation and analysis is underway.

- The study has generated validated estimates of required duration of sun exposure for adequate cutaneous synthesis of vitamin D in different part of India.
- Completed recruitment of 200 pregnant women from 100 villages in Yadadri district, Telangana State for this prospective study with 6 follow ups.
- Information on state specific supplementary foods and cost of food stuffs from the respective eleven state governments and secondary data on home foods from NNMB 2011-12 database has been obtained. The data preparation is underway.

BIOCHEMISTRY

- Technology Development and Efficacy testing of extruded rice fortified with iron, folic acid and Vitamin B12. Funding: Industry.
- CRP-Crop Biofortification. Funding: ICAR.
- UNICEF-Comprehensive National Nutrition Survey. Funding: MoHFW.
- Role of advanced glycation end products (AGE) in diabetic nephropathy: Effect of dietary antiglycating agents. Funding: *DHR*.
- Micronutrients status and its influence on molecular mechanisms in diabetic nephropathy: A nutrigeomics study. Funding: *SERB*.
- Prevalence of deficiency of vitamin-B12 & folic acid and hyperhomocysteinemia among

urban geriatric population: A population-based cross-sectional study. Funding: *DBT*.

- Impact of vitamin-B12 deficiency and diabetes on retina: Molecular studies. Funding: *ICMR*.
- Proteasome inhibitory potential of cinnamon and its active components in prostate cancer: In vitro and in vivo studies. Funding: DBT.
- Molecular mechanism(s) involved in vitamin D deficiency induced muscle atrophy. Funding: Intramural.

LIPID CHEMISTRY

- Effect of fortification of edible vegetable oils with sesame/rice bran oil or with sesame lignans on the thermo oxidative stability of repeatedly heated oils.
- Currently studies are in progress to investigate the thermal stability of commonly consumed vegetable oils.

MOLECULAR BIOLOGY

In the adipose tissue of 180 day old WNIN-ob rats, about 173 miRNAs were found to be upor down regulated significantly as compared to their lean counter parts. About 57 miRNAs were found to be significantly upregulated and 116 miRNAs were found to significantly downregulated in liver. We also chased the expression patterns over time in liver from 60 days to 180 days in WNIN-ob rats and found that out of one 172 miRNAs that are significantly modulated, about 31 miRNAs were found to be significantly upregulated and 141 miRNAs were found to be down regulated. Some of these miRNAs were reported play some roles in the development of obesity and diabetes. However, a number of novel miRNAs were identified with no prior knowledge about their involvement in the development of obesity and insulin resistance. In addition, expression of adipokines like MCP-1 and RANTES found to be decreased in obese rats at 120 and 180 days time points.

- 1. In mice, DHA and EPA supplementation in High Fat Diet could significantly suppress ER stress markers like CHOP in adipose tissue but DHA did not have significant effect on CHOP in liver. Similarly, we found that High fat diet supplemented with DHA and EPA could significantly suppress the expression of another ER stress marker Grp78 in adipose tissue. In addition, expression of a proinflammatory marker RANTES was also found to be reduced in the adipose tissue in High Fat diet supplemented with DHA and EPA.
- ZnT1 and MT expression was found to be decreased in zinc deficient conditions in THP-1 cells. For other functionally contrasting cell lines like HepG2, RD cells or SaOS-2 cells we found expression kinetics of ZnT1 was almost similar to that of THP-1 at different TPEN concentrations for different time points of treatments.
- Optimal maternal long chain fatty acid nutrition is critical for brain and retina development of the neonate. This project investigated the roles of long chain fatty acids on early development of life by measuring parameters of feto-placental growth & development. Initial data reported for the first time that DHA may be equally important for early placental development activities as compared to its requirement at term for neonate development. Trans fatty acids (TFA), those are mostly derived from industrially produced vegetable fats, negatively affect the uptake of key long chain fatty acids in the first trimester trophoblast in vitro.
- Placenta of women with gestational diabetes mellitus showed several changes that may be associated with impaired functioning, leading to poor perinatal outcome. Effect of incremental glucose (25mM) on invasion properties of first trimester trophoblastic cell was examined by measuring placental angiogenesis in vitro. This work reported for the first time that glucose (25 mM) alters tube

formation of the first trimester trophoblast cells and stimulates the expression of matrix metalloproteinase-9.

• Deficiency of essential fatty acids (EFA) such as linoleic acid (n-6 PUFA) and alphalinolenic acid (n-3 PUFA) in pregnant women are prevalent in India. This led to a question whether such deficiencies during conception has any effects on the reproductive function and fetus outcome with particular to epigenetic changes. The objective of the project is to characterize placental and fetus phenotype during omega-3 fatty acid deficiency in mice.

BIOSTATISTICS

- Calculation of Nutrients of oral diet data, both individual as well as weighment, from previous completed NNMB surveys using new IFCT tables. NNMB Rural 2012 survey completed.
- Databases were developed by checking all the previous NNMB data sets (error free) to be uploaded to WEB for public use.
- B12 diet data for Nutrients computation of the community in different states.

FOOD TOXICOLOGY

- Prevalence of fluorosis in the community of selected districts of India and development of an appropriate intervention model for prevention and control of fluorosis (Extra mural ICMR Taskforce Project).
- *Staphylococci* contamination and the risk associated with production of toxin in milk products.
- Isolation of *Salmonella* infecting bacteriophages to control *Salmonella* contamination in food 16 FD 05.
- The biochemical and molecular mechanism of insulin signaling in fluoride induced insulin resistance in rats.
- Assessment of mycotoxin contamination in processed foods containing maize & groundnut. (#15FD03).

Achievements:

- High aflatoxin contamination in RTE groundnut snacks detected.
- Presence of discoloured kernels in RTE groundnut snacks with high aflatoxin levels present considerable public health concern.
- The study has given a lead to assess different kinds of RTE groundnut products consumed in the Indian context.
- Brochures on creating awareness on aflatoxin contamination in groundnut under preparation.
- Investigation of mycotoxin contamination in herbal and medicinal plants and products to formulate prevention & control strategies. (#15FD04)

Achievements:

- High aflatoxin levels detected in herbal plant mixtures up to 50ppb.
- Results indicate need for aflatoxin exposure assessments from herbal plant products as they are frequently consumed.
- Dietary intake of aflatoxins from spices and risk assessment (#14-FD04).
 - High aflatoxin contamination detected in several RTE spice mixtures.
 - Co-occurrence of aflatoxin with ochratoxins detected in these mixes.
 - Results indicate need for exposure assessment in the population and investigate association with chronic diseases such as renal or liver diseases.

PUBLIC HEALTH IMPORTANCE

Clinical Research

• Developed the indigenous technology for fortification of rice with iron, folic acid and

vitamin B12 that has the potential to address anemia that is widespread in India. The RCT trial will provide efficacy of the intervention and proof of the concept.

- The study on sun exposure and vitamin D has developed guidelines for optimal duration and time of sun exposure for adequate cutaneous synthesis of vitamin D in different part of India. This information can help education interventions for reducing the prevalence of vitamin D deficiency in the country.
- Provided technical guidance to reformulate the food model for supplementary nutrition program for 6-36 month old ICDS children for the state of Madhya Pradesh in collaboration with Clinton Health Action Initiative, India. The State is implementing the same since June 2018. We intend to undertake an Impact evaluation study.

Biochemistry

- An indigenous technology for extruded fortified rice has been developed in collaboration with the industry.
- Two biofortified maize genotypes providing 50% RDA of vitamin A/200 g have been identified in collaboration with IARI, New Delhi.
- Studies on micronutrients status of adult population indicated a high prevalence of multiple sub-clinical vitamin deficiencies, dietary inadequacies along with increased homocysteine among apparently healthy adults which are possible risk factors for disease burden. The overall prevalence of deficiency of vitamin-B2 was strikingly high (50%) followed by vitamins: B6 (46%), B12 (37%), folate (32%), D (29%), B1 (11%) and A (6%). Hyperhomocysteinemia (HHcys) was widely prevalent (52%) in the study subjects.
- Dietary micronutrient inadequacy was about 28% in the urban adult population and illiteracy and lower employment status were the major determinants of inadequate micronutrient intakes in this population.

- Cinnamon extract and its bioactive compounds decreased proteasome activity and led to cell death in human prostate cancer cells.
- Vitamin D deficiency altered expression of genes in skeletal muscle in a rat model.

Lipid Chemistry

• High prevalence (56.3%) of vitamin D deficiency among the urban elderly population in the south Indian city of Hyderabad was observed. High BMI, metabolic syndrome and hypertension were significantly associated with vitamin D deficiency. Hence, it is essential to take appropriate intervention measures to overcome vitamin D deficiency associated complications in elderly population.

Molecular Biology

• Supplementation of High Fat diet with long chain omega 3 fatty acids can ameliorate ER stress, thereby can reduce inflammation and risk for development of insulin resistance can be reduced.

Maternal nutrition those could be the basis for a large epidemiological study to investigate the impacts of early fatty acid nutrition on the outcome of the feto-placental growth & development. Initial data reported for the first time that DHA may be equally important for early placental development activities as compared to its requirement at term development. This data further elaborate that TFA intake could further down regulates the uptake of growth promoting fatty acids such as ARA and EPA. Our data extend to the notion that trans fatty acids, those are mostly derived from industrially produced vegetable fats, negatively affect the uptake of growth promoting arachidonic acid (ARA) and eicosapentenoic acid (EPA) in the first trimester trophoblast in vitro.

Food Toxicology

• The ameliorative potential of tamarind fruit extract (TFE) in fluoride ion (F) toxicity by enhancing the urinary excretion of F

is identified first time by the department. Subsequently the department is carrying various animal and human experiments on beneficial effect of tamarind. In the present publication we have identified the tamarind fruit extract's capacity to enhance the carbonic anhydrase activity which plays an important role in acid base balance at the tubular level and ameliorates fluoride toxicity.

EXTRAMURAL RESEARCH

NEW TASK FORCE STUDIES

Two Task Force studies have been initiated in March, 2018 and one recommended by experts and will be initiated in April, 2018.

- Task Force entitled "Prevalence of vitamin A deficiency disorders among children aged 1-5 years in selected districts of India" has been initiated recently at 7 locations of the country (Assam, Odisha, Telangana, Bihar, Madhya Pradesh, Rajasthan and Uttar Pradesh) with the objective to assess the prevalence of clinical sign of vitamin A deficiency (Bitot's Spots) in children 1-5 years of age. Approximately, 36000 children per district will be covered under the study.
- Study entitled "Development of District Level Model to address undernutrition and Hidden Hunger: An Intersectoral Approach": This study is an initiative taken by ICMR under the Chairmanship of Prof. M.S. Swaminathan, Founder Chairman and Chief Mentor, M S Swaminathan Research Foundation, Chennai and Hon'ble member of Rajya Sabha to address the problem of under-nutrition with special reference to underweight, wasting, stunting as well as anaemia by integration of agriculture and nutrition involving various stakeholders. The Expert Committee had its 1st meeting on 3rd July 2017 at ICMR Hqs., New Delhi wherein it was decided that a District level workshop may be organized in three selected districts, i.e. Kanpur Dehat (Uttar Pradesh), Koraput (Odisha) and Palghar (Maharashtra) involving all stakeholders to develop intervention strategy to address problem of undernutrition

and hidden hunger. As a follow up, the 1st District Level Consultation Workshop was held at Palghar on 25th September 2017 wherein it was decided that a rapid survey of the district on key parameters. Subsequently, a study has been initiated with main objectives to determine factors contributing to nutrition status of vulnerable group of population; to assess the convergence process and challenges at District level; and to develop a District Level Intervention Model following intersectoral approach.



Fig. 1: Expert Committee meeting on integration of agriculture and nutrition under the Chairmanship of Prof. M.S. Swaminathan, Founder Chairman and Chief Mentor, M S Swaminathan Research Foundation, Chennai and Hon'ble member of Rajya Sabha held on 3rd July 2017 at ICMR Hqs., New Delhi.

A multi-centre task force study has been recommended by Experts at 16 locations (Delhi, Bangalore, Bhopal, Kanpur, Srinagar, Nagpur, Ludhiana, Jaipur. Trivandrum, Rishikesh, Ahmedabad, Bhubaneswar, Jorhat, Dibrugarh, Agartala, Shillong) in the country with an aim to assess the consumption pattern of food and food products/items high in fat, salt and sugar, from organized and unorganized sectors. Under the study, consumption pattern on both preceding day and preceding week will be collected using pre-tested questionnaire. Besides, commonly consumed food samples will be collected from each site for analysis of fat, salt and sugar content. Blood samples will also be collected from a sub-sample. A total of approx. 80,000 households (approx. 4 Lakhs population) will be covered under the study.

ONGOING TASK FORCE STUDIES

Improving health and nutritional status of vulnerable segment of population by implementing multi-component health and **nutrition education intervention as a sustainable model of intervention** which is currently ongoing in 41 districts of 20 States (including all 8 northeast states). The endline survey is currently ongoing at most of the sites. Data cleaning and entry is also being done simultaneously.

Assessment of Iodine status among pregnant women in selected districts of India being carried out at 10 locations in the country with an objective to carry out cross sectional study to assess the urinary iodine level among pregnant and non-pregnant women at six centres; and to carry out longitudinal study to assess the serum/plasma micronutrient level, thyroid profile and urinary iodine level of pregnant women during all the three trimesters as well as up to one year after the delivery at four of the total ten participating centers.

Prevalence of fluorosis in the community of selected districts of India and development of an appropriate intervention model for prevention and control of fluorosis currently ongoing at 7 locations in the country (covering one district each in Orissa, Madhya Pradesh, Telangana, Chandigarh, Bihar, Rajasthan and Assam) w.e.f. March, 2017.

Another intervention Task Force study entitled 'Effectiveness of diet and lifestyle intervention through IEC tools with Angan Wadi Centres as the centre of knowledge dissemination for hypertension risk reduction' was initiated with the objective to assess the role of diet and lifestyle for hypertension risk reduction. The study was initiated at five sites during Phase I, i.e. Shimla (Himachal Pradesh), Puducherry (Pondicherry), Kangra (Tanda), Dhar (Indore, M.P) and Junagarh (Gujarat). The study was later expanded to five more sites among tribal population under Phase II; i.e. Adilabad (Andhra Pradesh), Udaipur (Rajasthan), Kalahandi (Orissa), Ranchi (Jharkhand) and Dibrugarh (Assam). Under Phase II, the baseline and intervention phase has been completed and repeat survey is ongoing. During the baseline a total of 18059 subjects (6195 households) in the age group of 18-59 years were covered. Blood pressure and anthropometric measurements were recorded for 16,086 subjects and 11,562 blood samples were

collected for lipid profile and glucose estimation. The overall prevalence of pre-hypertension and hypertension was reported as 37% and 20% respectively and the prevalence of diabetes was reported as 7.8% and pre-diabetes was 22.9%.

ADHOC PROJECTS

Supporting individual researchers working in various Institutions/ universities of the country through financial grant for carrying out research studies in the form of adhoc projects is one of the major activities of the Division. Currently twenty two adhoc projects are ongoing on issues related to nutrition like 'Effect of diet counseling on gut flora, inflammatory markers and oxidative stress in diarrhea predominant irritable bowel syndrome patients from North India'; 'Study on the hypocaloric balanced diet compared with conventional healthy diet on clinical and metabolic parameters of women with polycystic ovarian syndrome; Targeted Nutrition Communication for promoting Consumption of Micronutrient Rich Foods among Rural Households by Developing Dietary Diversity Scores etc.

FELLOWSHIPS

Forty three fellowship research studies addressing diverse issues on nutritional status of population, maternal and child health, food fortification, role of various micronutrients etc are being supported by the Division.

CENTRE OF EXCELLENCE

The Division is currently supporting one Centre of Excellence, i.e. Centre of Excellence for Fluorosis Research and Mitigation of the Diseases in Rajasthan under Prof. (Dr.) A.K. Susheela, Executive Director, Fluorosis Foundation of India, New Delhi. The aim of the centre is to set up Infrastructure for diagnosis of Fluorosis in Teaching Hospitals; to update knowledge of Doctors through Continuing Medical Education (CMEs) in Teaching Hospitals; to provide hand-on training to Dieticians for Diet Editing and Diet counseling etc. So far, Five sensitization workshops on fluorosis were held at 5 medical colleges in Rajasthan where more

than 100 HODs and Senior Professors participated. Two CMEs were also held in RNT Medical College, Udaipur. Feedback was also retrieved through Preand Post- training Questionnaire.

CENTRE FOR PROMOTION OF NUTRITION RESEARCHAND TRAINING WITH SPECIAL FOCUS ON NORTH-EAST, TRIBAL AND INACCESSIBLE POPULATION

The laboratory at the centre under Division of Nutrition was established in 2007. During the year

2017-18, a total of approx. 31,000 serum/ plasma/ urine/ salt samples were analyzed for over 1.5 Lakhs determinants. The laboratory is accredited by National Accreditation Board for Testing and Calibration Laboratories (NABL) for Clinical Biochemistry parameters. Samples collected under Task Force studies are being analyzed for nutritional parameters in the laboratory. Besides, collaboration from other medical colleges/ universities/ hospitals etc.

ENVIRONMENTAL & OCCUPATIONAL HEALTH

Research in priority areas of occupational and environmental health relevant to national needs for various working groups is actively undertaken by the National Institute of Occupational Health, Ahmedabad and the National Institute for Research in Environmental Health, Bhopal . Major highlights of various programmes undertaken by the ICMR in the areas of occupational and environmental health during the year 2017-2018 are given below.

INTRAMURAL RESEARCH

NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH, AHMEDABAD

Evaluation of CC16 as reliable biomarker for early detection of silicosis in occupational set up: Pilot study

Silicosis is usually diagnosed when a person does have occupational history along with specific shadows in chest x-ray as per International Labor Organization (ILO) criteria. Most often the diagnosis is made at late/terminal stages, when it is irreversible and no effective treatment could be offered; however, it is 100% preventable if detected early. Therefore, an effective biomarker for early detection of silicosis is of high public health importance and need of the day. Hence, the pilot study was planned to find out the suitability of Club cell protein (CC16) as an early biomarker for predicting the progress towards developing various stages of silicosis; from initiation to full blown silicosis (x-ray confirmed), which perhaps, the first of its kind in South-East Asian region, so far as the biomarker of silicosis/dust-related lung morbidity is concerned. This data showed the inverse relation of serum CC16 with the progression of the disease; highest in the healthy subjects, followed by some silica dust exposed workers and lowest in the full blown silicosis in this case-control study. Further, tobacco smoking along with silica exposure aggravates the disease burden more as observed in the target population. Hence, determination of serum CC16 value of the subjects along with occupational history of silica dust exposure could be used as an effective biomarker for early detection of silicosis, which isindicator of Club cell damage or modulation of lung epithelium permeability in dust (silica)-related respiratory morbidities.

Effect of Indoor Air Pollution on Women and Children in India- INDO-US project

Indoor air pollution (IAP) is a significant cause of morbidity and mortality. Fuels used for daily cooking are important pollution sources in the indoor environment. The study was carried out for evaluating indoor air pollution exposure and respiratory health effect in primary cooks and their children ≤ 10 yrs residing in slum areas and using kerosene and LPG as primary cooking fuel. Finding of study revealed that during the cooking hours the concentration of all the pollutants increases. Medical examination revealed that maximum families using kerosene as cooking fuel were found anaemic, suffering from tuberculosis, asthma, chronic bronchitis, recurrent cough and cold. Result

of spirometry test shows that, out of 571 primary cooks, 31 had abnormal PFT. Restrictive type abnormality was found in 26 primary cooks, while the obstructive type abnormality was found in 5 primary cooks, majority of subjects beingkerosene users.



Fig. 1: Exposure due to use of Kerosene.

Health Risks Assessment among Granite/ Stone Quarry Workers with special reference to pulmonary fibrosis through Molecular and Radiological Approaches

The occupational environment at the stone crushing sites poses a potential health hazard to the workers, since inhalation of particles rich in free silica for long periods of time may cause silicosis. The demographic status of study subjects (n = 62)indicates that the workers were engaged in different kinds of work activities in stone quarry unit. The mean age of the workers was 32.3 years with range of 18-52 years. The personal habits of workers like tobacco chewing, smoking, alcohol intake and tea/ coffee were recorded in the study subjects. Only 60% of workers reported of personal PPE usage. About 16% have experienced chronic recurrent cough, shortness in breath (3%), chest tightness (2%) and chronic diseases (2%). Abnormal range of blood parameters such as WBC count, RBC count, platelet count, and red blood cell indices (MCV, MCH & MCHC) were recorded among workers. DNA damage parameters such as tail length, % DNA in tail and olive tail movement (OTM) were studied among exposed subjects. Micronucleated cell (MN) assay parameter evaluated in this study was comparatively higher than control group.

A study of ophthalmic morbidity among traffic police personnel and its association with occupational determinants

As traffic police are one of the vulnerable groups for air pollution and heat related hazards, this cross sectional study has been undertaken to identify ophthalmic risk and associated health hazards among traffic police personal. This Study observed that out of enrolled 200 subjects, most prevalent ophthalmic complaints were burning sensation (54.1 %) and redness in eyes (37.1%) along with higher prevalence of eye cataract and dry eyes.

Occupational Health Assessment of Workers Involved in Bitumen Processing and Road Paving in India

This study intended to evaluate pollutants in workplace of road paving and its health effects on this group of workers in and around Bangalore. A total of 75 subjects (48 exposed and 27 controls) participated in this study. Backache was most common, along with headache, tiredness and chest tightness, and breathing difficulties were reported among workers. The levels of VOC, H₂S and CO detected were in the range of 0.02-2.37ppm, 0.01-0.23ppm and 0.02-1.72ppm. Biomonitoring study showed increased level of of Red Cell Distribution Width (RDW) %, liver function test (SGPT, SGOT, SGOT/SGPT ratio and total bilirubin), telomerase activity, oxidative stress and GM-CSF. Genotoxicity assessment revealed higher frequency of DNA damage with increased tail length and micronucleated cell (MN) among road paving associated job workers compared to control subjects.



Fig. 2: Road paving in India.

Assessment of occupational environmental health risks and challenges of migratory brick kiln workers in Gujarat

The study on the occupational and environmental health risks along with challenges faced by migratory brick kilns workers was carried out in 10 brick kiln industries situated in and around Adalaj and Uvarsad villages of Gandhinagar district, Gujarat. Migratory brick kiln workers (273) were enrolled in the study. The average age of workers was 29. 8±10.0 years with majority of them being uneducated (52.0%). Most of the brick kiln workers were migratory and belonged to Uttar Pradesh (39.9%) and Chhattisgarh (47.6%) state. The body mass index (BMI) of these workers indicated that 54.6% workers had lower BMI <18.0 i.e. underweight; which clearly indicates poor nutritional status. The duration of work showed that majority 83.9% of workers worked continuously for 8 to 12 hrs per day and 53.9% of workers complained about suffering with body ache. The results of biochemical parameters revealed that among subjects who had >5 years of association with brick kiln work showed altered level for CRP (17.9%), DBIL (12.3%), GLUC (39.6%), PHOS (12.3%), SGOT (25.5%), TG (16.0%) and UA (16.0%).



Fig. 3: Brick kilns health rinks.

A study to evaluate metabolic syndrome (MetS) among industrial workers

This study assessed the metabolic syndrome (MetS) in 137 (female=44 & male=93) industrial workers by using the definition of the International Diabetes Federation (IDF), Revised- National Cholesterol Education Program (R-NCEP-ATP) and NCEP -ATP. As per the definition of IDF, it was noted that 38.6% of female and 17.2% male workers had MetS. The prevalence of MetS in female workers (P=0.010) was found significantly higher as compared to male workers. The revised NCEP-ATP definition noted that the 27.3% of females and 32.3% of male workers had MetS. The prevalence of MetS in male workers was higher as compared to female workers.

Urban air quality assessment using remote sensing and GIS

This research study aims to detect and quantify the rural-urban transformation, assessment of urban air quality through synergistic use of remote sensing, GIS and mathematical models, with ground level measurement of gaseous pollutants and assessment of human health impacts during the recent period. During first year Air monitoring was conducted at 48 locations (Industrial, commercial and residential areas) of Ahmedabad district, Gujarat. The average level of respairable dust, NO2, NH3, O3, PAHs, VOCs, CO2, CO were found higher at commercial areas followed by industrial and residential whereas, the average level of SO2 was found higher at industrial area. Secondary health data were collected from Asarwa civil hospital, Sola civil hospital, LG hospital, VS hospital, ESIC hospital and SCL hospital. It was observed that during the period of October 2017 to December 2017 the level of air pollution as well as hospital admission of patients were increases.

Occupational health risk among veterinarians of Gujarat

This study conducted among veterinary professions in Gujarat state (n=208) were majority of male (96.2%) and only 3.8% women. Most of them (46.6%) were Government appointed veterinarian followed by 33.7% veterinarians from co-operative dairy societies involved in large animal practice mostly (63.1%) along with mixed animals practice (27%). Seventy-nine percent of the respondents experienced automobile injury >5 times. About 38% and 58% of the respondents reported animal related injury during the last two years and in their

career respectively. Among veterinary professions automobile (79%), needle prick (71%) were prominent causes for injuries were observed. It was also revealed from this study that although the most (85%) of the veterinarians of the total interviewed were suffering with stress at different level were still satisfied with their current job (78.5%). Despite of being high inherent risk of zoonotic diseases, majority of veterinarians (45.2%) of Gujrat State even did not have received common prophylactic vaccination such as rabies and tetanus and only 39.5% of the respondents has carried out their routine medical check-up. One third of the respondents showed an urgent need of inclusion of occupational hazards and safety training in Continue Veterinary Education programme (CVE) which may play an important role in preventing physical, psychological and biological hazards among veterinarians.

Pattern of poisoning reported at NIOH

A retrospective study of trend of poisoning in Ahmedabad for last 3 years was conducted. A total of 1373 cases of human poisoning was investigated. The incidence of poisoning was high in men compared to females (male to female ratio 1.89:1). More than 90% of poisoning cases were of suicidal in nature. The incidence of poisoning was higher among house wives (21.2%), labourers (11.2%), agricultural workers (11%) and industrial workers (7.7%). Agricultural insecticides were used as poisoning in 26.2% cases. House hold chemicals like insecticides, rodenticides, phenyl, bleaching powder and mosquito repellents constituted 12.31% of the poisoning cases. Investigation of cholinesterase activity in blood revealed that organophosphorus/carbamate poisons accounts for more than 40% of poisoning cases.

Protective Effects of Flavonoids against Cadmium and Arsenic Induced Reproductive Impairments in Experimental Model

We propose to test some of the flavonoids against Cadmium (Cd) and Arsenic (As) as these are found in various food materials and may be beneficial to human population at therapeutic doses in counteracting the effects of the As and Cd. The selected flavonoids/natural compounds i.e. Biochanin A, Phloretin, Epigallocatechin-3gallate (EGCG) may be able to prevent the toxicity of Cd as well as As because these flavonoids may able to combat the oxidative stress as well as protecting tissues injury by the prevention of toxicity at cellular and molecular level induced by these metals. The experiment is underway to test the protective effects of these natural compounds in counteracting the deleterious effects of As and Cd in *Swiss albino* mice.

Screening and brief intervention to reduce occupational harm from tobacco, alcohol and cannabis among coal mine workers in West Bengal

Alcohol and tobacco are major substance use problems among coal mine workers. Approximately 78% subjects have hazardous tobacco consumption and almost 36% have hazardous alcohol consumption. This population is expected to benefit most from early intervention, which can be instituted at the primary care level. Almost 41% subjects possibly have alcohol dependence problems, which suggest significant medical, social and economic impact. Referral as well as community based pharmacotherapy needs to be instituted for population with dependence problems.

NATIONAL INSTITUTE FOR RESEARCH IN ENVIRONMENTAL HEALTH, BHOPAL

Population based long term epidemiological studies on health effects of Bhopal toxic gas exposure

This long term epidemiological study has been continuing since 1985 (1985-1994 by ICMR under BGDRC; 1996-2010 under Centre for Rehabilitation Studies, Government of M.P; 2011 onwards under NIREH) wherein the available persons belonging to the originally assembled cohort of toxic gas exposed and unexposed persons in 1985, are being surveyed for morbidities and mortalities following the original protocol. The survey frequency was changed from twice a year to once in a year w.e.f 1/01/2017 and the 54th round was completed during the year (Jan-Dec). In this survey 23,379 individuals from exposed areas *viz*. severely exposed (7,813), moderately exposed (8,304) and mildly exposed (7,262) area; and 6310 individuals from unexposed control areas were followed up. Any morbidity recorded was 15.6% in severely exposed, 9.04% in moderately exposed, 15.7% in mildly exposed areas as compared to 10.8% morbidity in the control areas. Overall mortality of 5.3/1000 population in the exposed and 6.7/1000 population in control areas was recorded.

A total of 1,292 deaths (males 62.2%, females 37.8%) captured in the cohort between 2012-2016 were analyzed. Overall crude death rate (CDR) ranged from 4.71 (2016) to 12.72 (2013) recording wide variation among areas of different exposure levels. Standardized mortality ratio (SMR) ranged from 25.2 (2016) to 91.3 (2013). The gender wise distribution of SMR was comparable in most of the cases. The SMR of the exposed populations (Severe, Moderate and Mild areas) was comparable with that of non exposed populations (control area) in all years expect in 2013 where there was a wide difference in exposed (74.8 to 103.0) and non exposed areas (54.2). The most prevalent cause of death was vascular diseases 52.4%. Majority of the victims of vascular diseases died with acute myocardial infarction (80.8%) followed by cerebral haemorrhage (11.9%). Overall, the exposed cohort didn't differ much from the unexposed population in terms of death rates (CDR and SMR). The distribution of top 10 causes of death are in line with the national data and is similar among all exposure categories.

A cross-sectional study on current Health status of gas affected individuals of Bhopal: Phase I-Data triangulation to understand health status of gas exposed survivors of Bhopal

This study is documenting the pattern of morbidities with particular reference to the intensity of exposure, disease chronicity among available gas exposed survivors in Bhopal through data mining, triangulation and linking of the available major data bases. Three databases related to the health of gas exposed survivors (i) randomly selected 38,527 IPD records (belonging to 17,321 gas exposed survivors) obtained from BMHRC (2010-2015) (ii) Gas Rahat hospitals data base (Jan 2015-May 2017) and (iii) NIREH database of Long term epidemiological study (2011-2016) were linked after bringing as much uniformity as possible in the 3 data bases. From Gas Rahat hospitals database, 2,997 subjects and from NIREH's database, 584 subjects could be linked to BMHRC data base and after data cleaning three data bases were merged to form a single master list and disease profile of 17,321 gas exposed survivors was prepared. The highest no. of morbidities belonged to the cardiovascular system (22.4%) followed by ophthalmic morbidity (16.9%). Among cardiovascular system related morbidities almost half (50%) of the subjects had chronic ischemic heart diseases. Nearly 85% individuals (14,700 of the 17,321 subjects whose disease profiling was prepared) were found to be suffering from a single chronic morbidity while multi morbidity (2 or >2 chronic morbid conditions) accounted for 15% cases.

Development of a mito-epigenetic carcinogenic risk assessment model for environmental chemical exposures: A pilot study

This study is attempting to develop and validate а mito-epigenetic model of carcinogenic risk assessment for environmental chemical exposures in subjects exposed to highly reactive environmental pro-oxidants. Blood samples from 15 subjects exposed to broad chemical class of prooxidants at in utero stage and from equal number of age and gender matched healthy controls were collected. Mean levels of circulating cell free DNA was recorded to be significantly higher (p < 0.01)in the exposed subjects (46.50 \pm 3.16 ng/ul) as compared to age and gender-matched healthy control individuals (11.58 \pm 1.80 ng/ul). Quantum of miRNA in exposed group as compared to controls did not show appreciable changes. However, mean circulating nucleosomes was significantly ($p \le 0.05$) elevated in exposed subjects $[0.89 \pm 0.24 \text{ AU}]$ with

respect to controls $[0.20 \pm 0.03 \text{ AU}]$. Results so far indicate that prenatal exposure of environmental pro-oxidants not only impairs the mitochondrialnuclear cross talk but also modulates the fetal epigenome through aberrant regulations of DNA methylation and histone modifications. Further studies are on to understand the specific epigenetic modification patterns involved in the mitoepigenomic axis evoked upon environmental prooxidant exposure.

Aberrant circulating epigenomic signatures: Development and validation of minimal-invasive biomarkers for trans-generational monitoring of air pollution associated cancers

This collaborative study with IIT-Khadagpur is characterizing the epigenomic signatures in population, exposed to varying quantum of particulate matters (PM) residing in high-risk, mid-risk and low-risk air-pollution zones of India. Using a pan-India approach, cities were categorized as low-risk, mid-risk and high-risk based on the air quality index (AQI) \leq 60, 60-120 and \geq 120, respectively. The selected high-risk cities were Delhi and Gwalior; mid-risk cities were Bhopal and Jaipur; and low-risk cities were Sagar and Mandla.

Data obtained so far revealed that the levels of circulating DNA (p≤0.0001), circulating nucleosomes (p≤0.01), circulating miRNA and circulating mtDNA (p≤0.0001) in population living in high-risk cities were comparative higher. Mean levels of circulating nucleosome in mother & son in high-risk, mid-risk & low-risk cities were 3.177±0.270, 2.313±0.227; 2.914±0.318, 2.127±0.521; and $1.025\pm0.384, 0.696\pm0.264$ respectively (p≤0.01). The maximum mt DNA copy numbers were observed in the mother & son from high-risk zones i.e. 1319.10±107.41, 1179.94±125.77, while mtDNA copy numbers in mother & son from mid-risk and low-risk cities were 204.95±40.04, 139.50±12.64 and 18.49±3.57, 14.02±1.45 respectively. Comparatively, higher levels of 5-methyl Cytosine (5-mC) were observed in the high-risk group as compared to the lowrisk group. Measurement of oxidative DNA damage marker 8-OH-dG (ng/mL) revealed higher formation of modified nucleotide base among highrisk group as compared to the low risk ($p \le 0.0001$). The study is under progress.

Development of quantum dots based nanobiosensors for detection of circulating cell free miRNAs in environmental associated lung carcinogenesis

This Indo Russian collaborative project is attempting to identify a non-invasive biomarker capable of detecting the presence of lung malignancy or to predict tumor aggressiveness. The presence of circulating miRNA in the body fluids has emerged as a potential biomarker for the development and implementation of clinically relevant minimallyinvasive technology for risk assessment, early detection and monitoring therapeutic responses in lung cancers.

The levels of miRNA in lung cancer samples were assessed through conventional and one step PCR method. Analysis and profiling of a set of 21 ccf-miRNA (U6, Let-7a, Let-7b-5p, Let-7d, Let-7e, miR-202, miR-98, miR-221, miR-17, miR-200c, miR-29a, miR-128-2, miR-34a, miR-155, miR-24, miR-27, miR-28-5p, miR-150, miR-142-5p, miR-16-5p, miR-451a) were carried out using conventional PCR method that exhibited significant changes in the expression of some miRNAs under observation. miR-98, miR-200c, and miR-29a were found to be down-regulated. On the other hand miR-202 and 221 were significantly up-regulated. Through the real-time qPCR method, the expression profiles of several miRNAs showed noteworthy changes such as down regulation of miR-98, miR-24, miR-34, miR-128, miR-155, miR-16 and miR-29 with 0.33, 0.28, 0.48, 0.058, 0.22, 0.49 and 0.02 fold change respectively. B[a]P treatment of the lymphocytes resulted in substantial alteration in the expression profiles of Let-7e, miR-98, and miR-202. Upregulation of expression miR-16, miR-27 and miR155 down-regulated expression was observed. ANT treated lymphocytes exhibited increased expression profiling of miR-98, miR-16, miR27, miR-29, and miR-155. Lymphocytes treated with different concentration of PM (0.1, 2.5, 10) demonstrated a significant increase in the expression of miR-7d along with miR-16, miR-27, and miR-155. A reduction in the expression profile of miR-29 was also observed.

Initial results suggested a significant alteration in the expression of several miRNAs in the lung cancer patients such as Let-7e, miR-202, miR-98, miR-16, miR27, miR-29, and miR-155, that belong to the tumor suppressor miRNAs and are involved in the regulation of EMT signalling pathways. This altered expression suggested a direct relationship with the regulation of apoptotic pathway, cell proliferation, migration and invasion. The study is under progress.

EXTRAMURAL RESEARCH

INDO US MEMORANDUM OF UNDERSTANDING ON ENVIRONMENT AND OCCUPATIONAL HEALTH

In Environment and Occupational Health, the Indo US Joint Statement was renewed and signed in June 2015 as Indo US Memorandum of Understanding on Environment and Occupational Health. The JWG meetings were held annually alternatively in India and USA. Under the collaborative research on Indoor Air Pollution and Health, the four cohort studies viz: adult women, adult COPD patients, childhood asthma and mother-child cohorts were initiated to generate data on exposures from indoor air pollution and their health effects. The four cohort studies were recommended technically and were reviewed again keeping in view of the revised objectives. 2nd Meeting of Joint Working Group was held on 13th April 2017 at CDC, Atlanta followed by scientific meeting on "Air Pollution and Bio-monitoring". It was suggested that capacity building and work force development needs to be strengthened under Indo US Collaboration. Training programmes in collaboration with NIEHS and CDC to be explored further. Efforts needs be made for training in exposure assessments, laboratory methods and emergency response preparedness, epidemiology and risk communication for scientists and technical staff involved in research activities.

Under the High-Powered Committee on Global Climate Change and Health; the research activities

under two ongoing task force projects viz: "vector borne diseases" and "eye health" were completed. Under the project on "Evidence based assessment of biophysical determinants of malaria in the northeastern states of India and development of framework for adaptation measures for malaria control under climate change scenarios," the findings had elicited that climatic conditions are changing and the impact of such changes are also evident in terms of positivity of field collected mosquitoes in cooler months as well recording of malaria cases in hitherto malaria -free areas of Almora in Uttarakhand. The two proposals for phase II are initiated in March 2017 viz: "Epidemiological Study of Foci of Visceral Leishmaniasis in Himachal Pradesh" and "Vulnerability Assessment and Adaptation Measure towards Potential Impact of Climate Change on Malaria in Hot Spots of India".

EFFECTS OF AIR POLLUTION ON ACUTE SYMPTOMS IN DELHI

ICMR has initiated a task force project titled "Effect of outdoor air pollution on acute respiratory symptom in Delhi : A multicite study" with effect from June 2017 at 5 centre, AIIMS-Pulmonary medicine department, **AIIMS-Paediatrics** department, Vallabhbhai Patel Chest Institute, Kalawati Saran Children's Hospital and National Institute of Tuberculosis and Respiratory Diseases for a period of 1year and 6 months. Objectives of the study are to study the association of acute respiratory symptoms with changes in outdoor air quality and weather variables. Emergency visits data are being collected in Paediatrics and adult population and there will be correlation with ambient air pollution data from DPCB. Study is an ongoing study and result are expected to be available from 2019.

A Multicentric study to assess the Health effects of pesticides on general population

ICMR has initiated this study on the health effects of pesticides. Data available from the Agricultural Commissioner, Ministry of Agriculture, Govt of India, provided a detailed account of pesticide

consumption by the different states of the country and accordingly, five highest pesticide consuming states had been identified, as UP, Punjab, Haryana, West Bengal, and Maharashtra and considered for inclusion in the multi-centric study with following objectives: To assess the health status of the population in areas with high and low pesticide usage (5 selected areas) and to estimate the levels of pesticide residues in blood and urine. These states were identified based on the pesticide consumption patterns wherein the states with high pesticide consumption were selected. Medical colleges are the implementing agencies.

Within each state one district with the highest consumption and one district with lowest pesticide

consumption will be covered. 50% of the villages under the identified PHC will be surveyed and all the people in the village will be administered the questionnaire. For pesticide levels 2% of the sample will be selected in an age stratified manner and biological samples will be collected. The pesticide exposure assessment will be made through history (occupation, living or working near high risk area, dietary history, history of pesticide poisoning etc), and wherever possible though biological sampling. These will be analysed in NIOH, Ahmedabad and IITR, Lucknow for the identification and estimation of the commonly used pesticides in the relevant district.
NON COMMUNICABLE DISEASES

n the area of non-communicable diseases, ICMR's National Institute of Cytology and Preventive Oncology, Noida continues to carry out research studies for prevention and early detection of cancer. The National Centre for Disease Informatics and Research, Bangalore focuses on the National Cancer Registry Programme and related activities like software module for cancer registration, patterns of cancer patient care and survival studies. Major highlights of various programmes undertaken by ICMR in the area of non-communicable diseases during the year 2017-18 are given below.

INTRAMURAL RESEARCH

NATIONAL INSTITUTE OF CANCER PREVENTION AND RESEARCH, NOIDA

Empowering health care providers to update knowledge and skills in the area of Cancer prevention through ECHO

An online training program on oral, breast and cervical screening, along with tobacco cessation was organized from September 2017 to January 2018. A total of 58 participants were trained and received a completion certificate in this course. The participants included gynecologists, radiation oncologists, dentists, public health specialists, medical social workers and lab technicians.

Implementation of population based cancer screening in North East region of India

NICPR has implemented operational framework guidelines for cancer screening in 2 districts in

the state of Assam viz; Cachar district and Tata tea garden Dibrugarh. This is the first pilot project in the country implementing the cancer screening guidelines released by the MoHFW.

Development of DNA vaccine constructs against India specific HPV-16 variant: enhancement of Immunogenicity of L1 constructs and characterization of T-cell epitope based E6/E7 constructs

Persistent infection with high risk Human Papillomavirus (HR-HPV) is an established factor for the development of cervical cancer, especially HPV-16 followed by HPV 18. In our previous study, (Indo-German Task force project - ICMR, Ref. No. IG/7/07) we identified major variations in L1 and E6 /E7 in HPV-16 and their impact on immunogenicity.

Currently work is being done to enhance the efficacy of the DNA based vaccine constructs using genetic or non- genetic adjuvants in animal model. We will also focus on T-cell based epitopes for the development and enhancement of therapeutic efficacy of the DNA vaccine construct for ultimate development of an indigenous cost-effective second generation HPV vaccine.

Pharmacokinetic evaluation of plant-based anticancer molecules

In order to translate the traditional knowledge for discovering drugs it is important that the pharmacokinetic potential of anti-cancerous molecules is measured. So with a view of exploring the absorption, distribution, metabolism, excretion and toxicity (ADMET) profile, plant-based anticancer compounds were analyzed to identify molecules having properties favorable for drug ability.

The results revealed that out of ~5000 phytomolecules, 63% were orally absorbable, 52% distributable, 45% could be metabolized/ excreted and 30% non-toxic. Overall, 28% of the molecular dataset was found to have suitable pharmacokinetic properties. Further, to make these evaluations and their measured values available for aiding in drug discovery, an interactive database (ADMETCan) has been created, which provides access to predicted ADMET of these anticancer phytomolecules. The results of this study are expected to minimize failure rate of these compounds and pave way for identifying and designing novel natural products as anticancer agents.

PUBLIC HEALTH IMPORTANCE

• Facilitation of Roll out of population based screening program for prevalent cancers by Govt of India.

The cancer screening of three common cancers viz oral, breast and cervix is being rolled out in 158 districts of the country in 2018 and NICPR has been designated as one of the training hubs for training the master trainers of ASHAs, ANMs, staff nurses and Medical Officers. Training for staff nurses (2 batches-36 nurses in each batch) was organized at NICPR and hands-on training in cervical cancer screening was provided along with the theory, didactics and video presentations in May 2017.



Fig. 1: Training of master trainers in cancer screening at ICMR-NICPR, Noida.

 WHO-FCTC Smokeless Tobacco Knowledge Hub at NICPR organized an Inter-country expert group meeting on smokeless tobacco control and prevention in Delhi, Aug 2017. Based on the expert group consultation and recommendations of the meeting a 'Report on Global Smokeless Tobacco Control Policies and their Implementation' was compiled and released to assess the progress of various Parties to the Convention on smokeless tobacco control and to assist/guide them in implementing these measures.



Fig. 2: Inter-country meeting on smokeless tobacco policy, Aug 2017, New Delhi.



GLOBAL SMOKELESS TOBACCO CONTROL POLICIES AND THEIR IMPLEMENTATION

Fig. 3: Release of 'Report on Global Smokeless Tobacco Control Policies and their Implementation', Apr 2018, ICMR-NICPR, Noida.

 National Tobacco Testing Laboratory established at NICPR. This is a state-of the art laboratory intended to provide scientific inputs for implementation of directives of WHO Framework Convention on Tobacco Control (FCTC) in the South-East Asia Region; contribute to technology validation and assist Government of India in development and monitoring of strategies for harm reduction of tobacco products. A National Level Induction cum Training program for scientific and non-scientific staff of all three NTTLs was organized at NICPR; 29th Jan -1st Feb 2018. Formal inauguration of the NTTL was done by Honorable Minister of State, Ministry of Health & Family Welfare on 31st May 2018.

Lab has started functioning and analysis of constituents of SLT products has been initiated by analytical methods using latest equipment and technology.

• Setting up of Population based Cancer Registry at NICPR to cover Distt. Gautam Budh Nagar, U.P. to generate reliable data on the magnitude and patterns of cancer and to undertake epidemiological studies based on results of registry data.

NATIONAL CENTRE FOR DISEASE INFORMATICS AND RESEARCH, BENGALURU

Population Based Cancer Registries (PBCR)

This is the regular and long term activity of NCDIR under its National Cancer Registry Program (NCRP) which provides information on the incidence rates, burden and trends of cancer in the population. There are 33 PBCRs under NCRP with addition of two PBCRs in 2017-18 at National Institute of Cancer Prevention and Research, Noida and Kamala Nehru Memorial Hospital, Allahabad.



Fig. 4: Network of Population and Hospital Based Cancer Registries.

Some ongoing PBCRs are extending their area of coverage (Kamrup, Dibrugarh, Barshi and Kollam) and a new PBCR in Sher I Kashmi Institute of Medical Sciences (SKIMS), Srinagar is being initiated in 2018-19 covering 10 districts.

Hospital Based Cancer Registries (HBCR)

This is the long term ongoing activity of the NCDIR. The HBCRs are concerned with recording patient identifying information, diagnostic details, clinical stage and treatment for all the proved malignant cases that are registered/diagnosed in a particular hospital. Data collection is done by standardized common core form for all the registries. 26 new HBCRDM centres have been registered under the network of NCDIR-NCRP during 2017-18.

Under the 12th Five Year plan, the Regional Cancer Centres Scheme was renamed as Tertiary Cancer Care Centres/State Cancer Institutes (TCCC/SCI) and Ministry has identified 70 hospitals across the country to be funded. NCRP aims to establish HBCRs in these hospitals as and when they get the Scheme approved.

The present status of HBCRs under NCRP under various projects is as follows:

| Sl. No. | Registries | No. of Centres |
|---------|---|----------------|
| 1 | HBCRs funded by ICMR (including HBCRDM and HBCR in Sources of Registration) | 60 |
| 2 | HBCRs (RCC/TCCC/SCI) funded by MoHFW | 21 |
| 3 | HBCRs without any financial assistance | 38 |
| 4 | HBCRs under Karnataka Cancer Notification | 92 |
| | Total | 211 |

Series of workshops/meeting were held to train the investigators and the staff working at the above registries.

The data collection is being continued under the project of Patterns of Care and Survival Studies.

Development of an Atlas of Cancer in Haryana State

The overall aim of the study since 2015 is to get to know the similarities and differences in patterns of cancer across this state of the country in a relatively cost-effective way, using recent advances in computer and information technology transmission. Knowing patterns of cancer would provide important leads in undertaking aetiological research, in targeting cancer control measures and in examining clinical outcomes.

127 centres have been registered as on date and 96 centres are transmitting data. Information on a total of 39567 confirmed malignancy cases has been transmitted from centres with 992 cases (Dec 2015), 19457 cancer cases for the year 2016, 17226 cases for 2017 and 1982 cases for 2018 as on 31, March 2018.

Population Based Cancer Survival Studies

The project has been initiated with the aim of generating reliable data on population based cancer survival in cancers of the breast, cervix and head and neck cancers; and to know wherever feasible survival based on clinical stage/extent of disease across the Population Based Cancer Registries (PBCRs). Core proforma has been designed and sent to the centres. 12 PBCRs have started collecting follow-up data.

Cancer Samiksha

It is a data visualization portal was developed by NCDIR team launched by Dr Soumya Swaminathan, former Secretary Department of Health Research & Director General, ICMR. The portal shows the point of presence of 101 Hospital Based Cancer Registries (HBCRs) and 33 Population Based Cancer Registries (PBCRs) in the map of India, cancer statistics, allows online analysis, provides dashboard, generates tables and charts for further analysis. A feedback window seeking opinions and suggestions from the users was provided for improvement. It can be accessed from www.ncdirindia.org\cancersamiksha.



Fig. 5: Cancer Samiksha.

Development of Population Based Stroke registry(PBSR) in different regions of India

Population Based Stroke Registries have been established in the country. The main objective of the PBSR are to generate reliable data on the magnitude and incidence of stroke. The project has been initiated in 5 PBSR centres in one geographical area from the south, north, east, west and north east regions of India. The PBSRs started and their areas with population are:

- 1. Institute of Medical Sciences, Banaras Hindu University, Varanasi.
- 2. Tirunelveli Medical College, Tirunelveli, Tamil Nadu.
- 3. SCB Medical College and Hospital, Cuttack, Odisha.
- 4. Silchar Medical College, Cachar, Assam.
- 5. Govt. Medical College & Associate Group of Hospitals, Kota.

Online software has been developed for the purpose of capturing data on incident first ever stroke cases of respective Population based stroke registries. Core proforma has been finalized and the workshops were held August 2017 and March 2018 to train the investigators and the staff for collection, coding and transmission of data. The centres are transmitting data.

Implementation of NCDIR electronic Mortality software (NCDIR e-MOR) in hospitals of the National Cancer Registry Programme (NCRP) network in North East India

NCDIR electronic mortality (NCDIR e-Mor) software has been developed by the NCDIR team. The software captures information on all causes of deaths as per National list of the Office of Registrar General of India. The project aims to strengthen Medical Certification of Cause of Death(MCCD) reporting in hospitals through training, quality checks to avoid mode of dying and guide doctors in recording the underlying cause of death and report deaths.

In the first year of implementation, the following hospitals in the North East are involved.

- 1. Cachar Cancer Hospital and Research Centre, Meherpur, Silchar(Assam).
- 2. Dr. B. Borooah Cancer Institute, Guwahati (Assam).
- 3. Silchar Medical College, Ghungur, Silchar (Assam).
- 4. Bakin Pertin General Hospital, Pasighat (Arunachal Pradesh).
- 5. Tomo Riba Institute of Health and Medical Sciences, Naharlagun (Arunachal Pradesh).
- 6. Naga Hospital Authority, Kohima (Nagaland).
- 7. Regional Institute of Medical Sciences, Imphal (Manipur).
- 8. Civil Hospital, Aizawl (Mizoram).
- 9. STNM Hospital, Gangtok, (Sikkim).

National NCD Monitoring Survey- 2017-18

The ICMR-National Centre for Disease Informatics and Research (NCDIR) has implemented the survey at the behest of the Ministry of Health and Family Welfare, Govt of India to monitor the progress made at the national level towards achieving the national NCD targets by 2025. It has been undertaken in partnership and collaboration with AIIMS Delhi, National Institute of Medical Statistics (NIMS) New Delhi, National Institute of Epidemiology (NIE) Chennai, AIIMS Bhopal, AIIMS Jodhpur, AIIMS Bhubaneshwar, National Centre for Disease Control New Delhi, Assam Medical College Dibrugarh, BJ Government Medical College Pune, National Institute of Nutrition Hyderabad, AMCHSS Sree Chitra Trinamool Institute of Medical Sciences, Kerala.

The survey has been completed. Data is being processed for analysis and subsequently the report will be prepared.

National Burden of Noncommunicable Diseases and associated risk factors - Cancer working group

The project aims to estimate burden of cancer and its associated risk factors in India. The report would be prepared by end of 2018.

BIOETHICS

Finalization and release of ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017

The revised ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants and ICMR National Ethical Guidelines for Biomedical Research Involving Children have been released on 12th October, 2017 at ICMR Hqs. by Shri Jagat Prakash Nadda, Hon'ble Union Minister, Ministry of Health and Family Welfare and Smt. Anupriya Patel, Hon'ble Union Minister of State, Ministry of Health and Family Welfare, in the presence of various other dignitaries Dr. Soumya Swaminathan, DG ICMR & Secretary DHR, Dr. P N Tandon, Former Chairperson, Central Ethics Committee on Human Research (CECHR) and Dr. Henk Bekedam, WHO-WR.

The Guidelines have become effective from 12th October, 2017 and all research related to biomedical and health in India should follow them.



Fig. 6: Release of National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017 at ICMR Headquarters, New Delhi on 12th October, 2017.

ICMR Dissemination programs of the 'National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017

Dissemination programs were organised in collaboration with medical colleges at AIIMS-New Delhi, PGIMER Chandigarh, Sri Ramachandra Medical College Chennai and AIIMS Bhubaneswar. Another set of 4 dissemination programs were conducted in collaboration with Clinical Development Services Agency (CDSA) at AMCMET Medical College Ahmedabad, Andhra Medical College Visakhapatnam, Amrita Institute of Medical Sciences Kochi and Gauhati Medical College Guwahati. Across the country the details were shared with more than 6000 stakeholders including students, researchers and ethics committee members.

Release of the Report on End of Life Care

A report on "Definition of terms used in limitation of treatment and providing palliative care at end of life" were released at NCDIR, Bengaluru on 12th March 2018 and provided clarity on the terminology used in End of Life Care.



Fig. 7: Report on End of Life.

EXTRAMURAL RESEARCH

ONCOLOGY

National Cancer Registry Programme

The Coordinating Unit of National Cancer Registry Programme (NCRP) which is now new permanent institute of ICMR-National Centre for Disease Informatics and Research has been functioning at Bangalore for almost more than three decades. The NCRP itself started in 1982 with three Population Based Cancer Registries (PBCRs) and three Hospital Based Cancer Registries (HBCRs). The NCRP developed a unique concept of an Atlas of Cancer in India covering several regions in the country by use of internet for data collection for the year 2001-2002 thus mapping the patterns of cancer region-wise. As of now, there are 29 PBCRs under the network of NCDIR-NCRP which are contributing data to the center on a regular basis. The PBCRs of Hyderabad, Naharlagun, Pasighat and Patiala have recently commenced data collection. There were 9 HBCRs under the network of NCDIR-NCRP which have now expanded to 29 HBCRs after inclusion of RCCs in the registry network. The data collected from above registries is published periodically in form of consolidated reports. Besides being a source of authentic information for the national programme, the reports have been cited by researchers /clinicians/Public Health Bodies/administrators on several occasions.

Review of Cancer Management Guidelines

Cancers are an important disease entity in India. While survival after treatment in certain sites of cancer is good, the response in many other common sites (like lung, oesophagus, stomach, etc.) is extremely poor. This is especially true about India, where despite availability of leads from western world, survival is lower. In view of the above, a task force on management of cancers was constituted. Twenty-three sub-committees were constituted initially to review the management of cancers of various cancer sites. The consensus document for management of buccal mucosa cancer, colorectal, stomach, gall bladder, breast, soft tissue sarcoma, pediatric lymphoma and solid tumours, oesophagus, multiple myeloma, and tongue cancers are printed and available at ICMR website (www.icmr.nic.in). The documents on Uterus, Myelodysplastic syndrome, Acute Myeloid Leukemia, Pancreas, Neuroendocrine Tumours and Hepatocellular Carcinoma are at different stages of preparation. The summary of consensus documents is also published in journal.

Cancer Monograph

The Division has compiled cancer research activities undertaken in the form of centrally commissioned projects, important research out puts in adhoc research schemes and major research programmes undertaken by the ICMR institutes engaged in the cancer research. The document has been compiled and as per recommendations of Expert Group meeting; the document has been revised. The document is sent for final printing.

Immunophenotyping of Hematolymphoid Neoplasms

In view of the increasing use of flow-cytometer in diagnosis of haematolymphoid malignancies, and need for standardization on procedure, a task force on the subject was initiated. The expert group reviewed the proposal and suggested development of standard operating procedures, which would help in initiation of a study on assessing the role of various antibody panels for diagnosis and follow up of such patients. The Standard Operating Procedures (SOPs) for flow cytometer in diagnosis of haematolymphoid malignancies are printed and available on Council website (www.icmr.nic.in).

Molecular Basis of Genesis of Breast Cancer

The project entitled "Comparative Study of Genetic, Clinical and Epidemiological Factors of Breast Cancer in Rural and Urban Area of India," was aimed to understand prevalence of breast cancer among rural and urban populations, reasons of variation, if any; analyze the genetic susceptibility by single nucleotide polymorphism (SNP) in familial and sporadic breast cancer. The identified centers are rural and urban areas with centers at ICPO, Noida; NIOP, Delhi; AIIMS, Delhi; RCC, Thiruvananthapuram and RMRC, Dibrugarh. The project at Dibrugarh has completed its duration and final report has been submitted by Principal Investigator. The proposal entitled, "Comparative Study of Genetic, Clinical and Epidemiological Factors of Breast Cancer in Rural and Urban Area of India," was initiated. The operational details at AIIMS, Delhi, ICPO, Noida, NIOP, Delhi and RCC, Thiruvananthapuram are finalized. In meetings of Expert Group; the Group suggested restricting study to genetic component for remaining centres and the same is being formulated.

Comparative study of Genetic, Clinical and Epidemiological risk factors of breast cancer in Indian population

Breast cancer is the most common female malignancy worldwide with approximately 1,000,000 new cases every year, representing over 20% of all female malignancies. Globally, incidence rates vary over tenfold, with low rates being observed in Asian populations and highest rates being observed in North American and Western European populations. These strong geographic differences are likely to be due to lifestyle, hormonal, reproductive and nutritional habits, although the relative contribution of each of these factors and their role are unclear. This is mainly because breast cancer has been extensively studied in high-risk populations, but little studied in low or moderate-risk populations, and direct comparisons are therefore not possible. Based on all available cancer incidence data from National Cancer Registry Programme 2012-14, the lowest breast cancer incidence rates are found among women from the rural region in India. Among urban Indian women, breast cancer incidence rates are approximately 100% higher than in rural women. These figures indicate that the transition from a rural to an urban society within India is associated with large increase in breast cancer risk. The cause of this strong urban: rural difference is not known, although it is likely to be due to one or more lifestyle

factors which differ strongly between rural and urban women. Identification of these factors will be important for the prevention and control of breast cancer among Indian women, as well as providing important etiological information, which may be relevant for prevention of breast cancer in Indian population. The multi-centric study involving Institute of Cytology and Preventive Oncology, Noida; National Institute of Pathology, Delhi, All India Institute of Medical Sciences, Delhi and Regional Cancer Centre, Thiruvananthapuram is initiated with objectives to (i) determine lifestyle, clinical, hormonal and other factors associated with breast cancer and (ii) identify the mutational landscape of breast cancer (exome & transcriptome with validation). Each centre has been given task to undertake the research as per available infrastructure and expertise. The project is initiated in March 2017. The Standard Operating Procedures have been drafted for laboratory methods and questionnaire for data collection are finalized.

Screening and Early Detection of Cervical, Breast and Oral cancer in Cachar, Assam: a pilot project

The first phase of the study includes the training of the master trainers on screening and early diagnosis of common cancers by NICPR, Noida. In the second phase, the front-line workers trained by master trainers would implement the screening program in the community. As per the guidelines of the NCD Control program of the Ministry of Health, GOI (NPCDCS) screening for oral cancer is being performed on all men and women of 30-60 years of age who are habitual users of tobacco/ alcohol. Cervical and breast cancer screening is being provided to the women between 30-65 years of age. ASHAs undertake door to door survey to counsel and motivate eligible men and women to undergo screening using the IEC material. The National Institute of Cancer Prevention and Research, Noida has developed the proforma for collecting data from field. A mobile application has been developed based on this proforma, which can be used for data collection online as well as offline. Currently, the application is available in English,

Hindi and Bangla languages for convenience of data collection by frontline health workers. During screening, the App captures data regarding reproductive health, personal medical history and other relevant information. Following the screening of the study participant, the diagnosis is filled by the frontline health worker and will be referred to the higher referral centre, if required. A web portal has also been developed for obtaining the information of the health care providers who collect/manage/ rectify data from study participants.

Strengthening State Non-Communicable Disease Programme for Early Detection of Breast Cancer Involving Strategic Education and Awareness among the Women: A Joint Programme of State Government and ICMR-Desert Medicine Research Centre, Jodhpur

It is aimed to strengthen state breast cancer screening programme and develop a referral system for diagnosis and treatment of suspected cases at state medical colleges/ district hospitals. The proposal is aimed to create awareness amongst women aged 30+ in the state about the disease and practice of breast self-examination, train para- medical staff to create awareness and locate the suspects and develop referral system for diagnosis and treatment of suspected cases. Capacity building of health care and improving awareness and knowledge of community about symptoms of breast cancer would be undertaken in one district only. A feasibility study would be undertaken for screening of three common cancers (oral, breast and cervix) in one PHC area of Jalore district of Rajasthan. Screening of women for early detection of cervical and oral cancer may be carried out besides screening of breast on the lines of National Programme. Men may also be screened in PHC population for oral cancer.

Indian Childhood Collaborative Leukaemia (ICiCLe) Group Multicentric Study for Children with Acute Lymphoblastic Leukaemia (ALL)

The study is aimed to improve the outcome of children with ALL in India and develop a model for other countries with limited health resources. The core ICiCLe group have developed multi-centric collaborative clinical study, using standardized molecular tools to establish a common national protocol for children with ALL in India. The ICiCLe study is focused on using risk stratification to accurately identify patients who require the least therapy and delivering a curative approach for this population. The main strategy of the trial is to use modern cytogenetic and MRD tools to provide risk stratified therapy. The aim is to identify low risk children with ALL and offer them lower intensity therapy to decrease toxicity, costs and improve outcomes. Pilot phase has been completed.

Concurrent evaluation of Human Papilloma Virus (HPV) vaccine program and vaccine acceptance among adolescent girls in Punjab, 2017

It is aimed to review the HPV vaccination program in terms of various inputs (material and human resources etc.), implementation processes and coverage in four program districts in Punjab. It is also aimed to estimate the acceptance of 2nd dose of HPV vaccine, awareness about HPV vaccine and concerns (if any) among adolescent girls, vaccinated with 1st dose of HPV vaccine in a health facility based program in the two program districts (Bhatinda and Mansa) and school based program in another two districts in Punjab and also to estimate the acceptance of HPV vaccine, awareness regarding HPV vaccine and concerns (if any) among parents of non-vaccinated adolescent girls in the study districts. Punjab is the first state in India to initiate the HPV vaccination in the program mode for 6th standard girls studying in the government schools in Bhatinda and Mansa districts. Program would be gradually scaled up to all girls in 6th standard in both government and private schools across the state.

Task Force on Gall Bladder Cancer

Three proposals viz: Genomics of Gall Bladder Cancer; Pattern of Care and Survival Studies (POCSS) on Gall Bladder Cancer in Indian Hospital Based Cancer Registries, NCDIR, Bangalore and Incidental Gall Bladder Cancer and Other Pre-malignant Gall Bladder Condition in India Towards Early Detection of Gall Bladder Cancer, are recommended for initiation.

Cancers in North East Region

The North-East region of country is quite different from mainland in terms of lifestyle. The consumption of alcohol and tobacco is very high and different modes of consumption are practiced. As per ICMR's Cancer Registry data, Mizoram is reported to have highest incidence of cancers of all sites in males and Arunachal Pradesh for all cancer sites in females. Risk factors are different in this part of country owing to different food habits. Based on recommendations of expert group meetings; two proposals are being reviewed for initiation: (i) "Comprehensive study on upper Gastrointestinal cancers (esophageal & stomach) and nasopharyngeal cancer in Northeast India" by RMRC Dibrugarh with the aim to study clinical, dietary and genetic risk factors in oesophagus, stomach and nasopharyngeal cancers and (ii) Comprehensive microbiome characterization in esophageal, stomach and nasopharyngeal cancers of North Eastern India by Cachar Cancer Hospital and Research Centre, Silchar, Assam with aim of undertaking comprehensive microbiome profiling in these cancers and their correlation with clinical findings.

INDO-FOREIGN COLLABORATION

• Indo-University of Minnesota Collaboration on Cancer Research

ICMR has signed a Memorandum of Understanding with the University of Minnesota, USA, to undertake collaborative research in the field of biomedical sciences. The areas for collaborative research included tobacco cessation; training in management of lung cancer; guidelines for supportive care in cancer and terminally ill patients; tissue procurement facility; toxins in smokeless tobacco in India; biomarkers for lung cancer; stem cell transplant; screening for breast cancer; mesothelioma; HLA typing in hematopoietic

malignancies; and surgical approaches in management of breast cancer. These areas were agreed to by the Joint Steering Committee for possible collaboration. The following project is completed:

HLA haplotypes frequency analysis within India: pre-requisite for bone marrow donor registry and cord blood bank planning.

Using HLA haplotype frequencies derived from the data accumulated in this project population genetic models were built that predict the likelihood of identifying a suitable adult donor or CBU for Indian patients in 14 regional groups. The match rates vary by regional groups largely due to the genetic diversity within each group and the genetic distance or HLA sharing between regional groups. Overall the results show that at the current registry size in India (~25,000 donors) 64% of patients can find a 9/10 or better match if they search both India and the US-NMDP registry but only 30% have a match within India. Doubling the registry size from 25,000 to 50,000 and again from 50,000 to 100,000 appears to have a linear increase in match rate.

• Indo-European Union Collaboration on Cancer

Following a collaborative workshop on cancer and neurodegenerative diseases; the Indian Council of Medical Research (ICMR), Department of Health Research (DHR) of the Ministry of Health and Family Welfare, New Delhi and the European Commission's Directorate General for Research and Innovation (DG RTD), Brussels have mutually agreed to enhance opportunities for coordinated activities in health research between European and Indian teams. The following two proposals are ongoing during year under report:

i. Role of HPV infection and other co-factors in aetiology of Head and Neck Cancers in India & Europe: The project aims to determine the role of Human Papillomavirus infection (HPV) and other risk factors in the development of head and neck cancer (HNC) in India. The proposal is focused on the elucidation of the role of HPV types and other environmental risk factors in India and the impact of HPV vaccination in oral cavity. The study is aimed to understand the role of HNC aetiology in geographical regions with different incidence rates. It is also aimed to identify the clinically most useful HPV markers and new biomarkers for different types of HNC, which can be used for screening and/ or therapy strategies. Due to strong link with HPV-AHEAD, the Indian findings would be complimented with data obtained in Europe. So far, 100 tumor blocks have been processed for HPV testing, including HPV DNA detection and p16^{INK4a} over expression. The combined positivity for HPV DNA and p16 is considered as a marker of HPV positivity. The tumors were classified into HPV16 DNApositive/ p16-overexpressing (referred to as HPV-related), HPV16 DNA positive/ p16negative, and HPV16 DNA-negative tumors. This algorithm was initially developed by comparing different methods for HPV detection among 48 oral and oropharyngeal cancers, and it is assumed to be relevant for laryngeal cancers. The most common type identified was HPV16, accounting for 86% of the total HPV DNA positivity (n=68). Thirty three of these cases were also positive for over expression of the surrogate marker p16 (37.5%). When restricting to HPV16, the combined positivity for HPV16 DNA and p16 over expression was noted in 27 cases (31%). These preliminary data indicate a much higher proportion of HPV related oropharyngeal cancer in this southern Indian population.

ii. Role of HPV in Head and Neck cancer in Rural and Urban India: The project is aimed to (i) conduct a large-scale epidemiological study in Mumbai and Barshi so as to provide an unbiased estimate of the proportion of HPVrelated head and neck cancer (overall and in the different organs) in rural and urban India, and the interaction between HPV infection and other risk factors of the disease, in particular to betel chewing. It is also aimed to investigate

the natural history and the prognosis of head and neck cancer with respect to HPV infection status and presence of other risk factors after stratification for known prognostic markers and treatment. There is an association between tobacco smoking and sub-sites of head and neck cancers. The risk is highest for oropharynx cancers followed by hypopharynx, larynx and oral cavity cancers. The risk varies according to the type of tobacco chewed. Chewing gutka has highest risk for oral cavity cancers. There is also association between chewing only areca nut and betel quid (without tobacco) with oral cavity and oropharynx cancers. There is observed linear trend between duration of chewing (in years) and risk of sub-sites of head and neck cancer with risk being highest for oral cavity cancers. Alcohol drinking is observed to increase the risk for primary sub-sites of head and neck cancer. The risk is highest for oropharynx cancers. Drinking various types of alcoholic beverages has also shown to increase the risk of subsites of head and neck cancer. Beer drinking has shown highest risk for oral cavity cancers. Drinking country spirit has shown increased risk for oropharynx cancers. With increase in duration and number of alcohol drinks there is linear increase in risk for sub-sites of head and neck cancer. There is significant statistical interaction between alcohol drinking and tobacco smoking. The risk is highest for highest quartiles of drinking and smoking for head and neck cancers. Increase in level of education has shown to decrease the risk of all sub-sites of head and neck cancer. The overall Human papilloma virus (HPV) prevalence in head and neck cancer sub-sites is 29.2% with HPV16 being most prevalent. The prevalence is more in hypopharynx cancer followed by oropharynx and then oral cavity cancers. There is significant statistical interaction between tobacco smoking and HPV prevalence.

• Memorandum of Understanding (MoU) on Cooperation in Cancer Research, Prevention, Control and Management The MoU was signed between ICMR/DBT/ NCI-AIIMS and NCI-US in June 2015 with the aim to establish general framework of intended collaboration for promoting and conducting high quality research to strengthen evidence base necessary for cancer prevention. The activities of mutual interest under this MoU are initiated viz: ICMR-NCI Workshop on Presentation Skills at ICMR Headquarters; in which scientists from ICMR Headquarters, NIMR Delhi, NIOP Delhi and ICPO, Noida participated and were trained by international coach for skill development (from NCI). The Workshop for Scientific Communication Skills was undertaken at NICPR, Noida in which ICMR scientists participated. Brain Storming meet with US-NCI and other national stakeholders on national stakeholders on implementation of national cancer screening and early detection that resulted in finalization of "operational guidelines for national screening of common cancers (oral, breast and cervix); national screening has been implemented by Ministry of Health and Family Welfare, New Delhi. The collaborative workshops on different cancer sites are being undertaken to address researchable issues. During period; the collaborative workshops on Gynecological Cancer and Gall Bladder Cancer were undertaken with technical support of ICMR.

DIABETES

ICMR Advanced Centre for Genomics in Type 2 Diabetes Mellitus

The centre completed its tenure in 2011 but training activities in newer laboratory techniques are still ongoing by centre. As per request of Centre, approval was granted to retain the name of ICMR (after completion of sanctioned duration); the ICMR guidelines of which were drafted in consultation with Expert Committee.

Changing treatment profile in Monogenic forms of Diabetes such as Neonatal Diabetes & Maturity-Onset Diabetes of the Young (MODY) by Translational Genomics Research

The study was initiated based on leads obtained in research projects under Centre for Advance

Research. The project is aimed at screening of genetic abnormalities involved in the etiology of neonatal diabetes, monogenic syndromes and hyperinsulinemia and the 13 subtypes of Maturity Onset Diabetes in the Young (MODY) patients. The project is based on replicating the findings of information generated on the subject through previous studies. The monogenic diabetes patients including neonatal diabetes mellitus (NDM), Congenital Hyperinsulinism (CHI) and Maturity Onset Diabetes in the Young (MODY) referred to Department of Molecular Genetics, MDRF for genetic screening and analysis were screened. The NDM patients harboring mutations in KCNJ11 and ABCC8 genes have been successfully transferred from insulin to sulfonylurea tablets and now these infants are under good glycemic control. Patients with congenital hyperinsulinism (CHI) were also screened for detection of mutations in KCNJ11 ABCC8 and INS genes. The KCNJ11 gene mutations and ABCC8 gene mutations in 3 patients were identified. Of these, 2 CHI patients have been completely weaned off drugs and 4 have undergone partial pancreatectomy and are now showing normal glycemia. The highlight of the work is that a novel mutation MODY 12- KCNJ11 mutation (Arg347Ser) has been described for the first time, showing co-segregation with diabetes in a threegeneration pedigree. After genetic testing, the dose of insulin has been reduced from 24 units per day to 14 units per day. Yet another important outcome is one of the patients with ABCC8 mutation has been shifted from Insulin to SU drug and is maintaining good glycemic control. The treatment strategy has been changed in 12 patients. Genetic testing and analyses has proved to be of great value in translational medicine and precision diabetes. The family pedigree would be constructed including healthy children. Adding birth order would add value to the pedigree chart. Efforts would be made to get multiplex families of NDM and MODY subjects.

Registry of People with Diabetes in India with Young Age at Onset

The project was aimed to (i) understand the magnitude of problem; (ii) disease pattern or

types including the geographic variation and (iii) incidence and prevalence rate of complications. The Technical Coordinating Unit at All India Institute of Medical Sciences, Delhi has compiled the combined report of all the eight collaborating centres (collected data from approximately 300 centres). The important leads have come out of the work undertaken under the project. The mean age at diagnosis for T1DM was 12.9 ± 6.5 years, while that for T2DM in youth was 21.6 ± 3.7 years. Nearly half the patients with T1DM registered within 6 months of the onset of symptoms of disease. The most common mode of presentation among patients with T1DM was a combination of osmotic symptoms and weight loss (28.8%). Onethird of youth onset T2DM patients were identified incidentally during routine medical examination. 15.4 % of patients (11.1% of T1DM patients; 26.4% of T2DM patients) had at least one chronic complication of diabetes at registration. 14.1 % of the YDR patients had at least one co-morbid condition such as hypothyroidism, dyslipidaemia, hypertension, tuberculosis; sepsis etc. 56.1% of the registered patients had at least one episode of hospitalization due to acute medical condition related to diabetes. Future follow-up of the cohort is planned. Under this collaborative project; it is proposed to estimate incidence of youth onset diabetes for the years 2006-2011 in Delhi and Chennai. The denominators will be estimated for the years 2006-2010 using growth rate method (from the 2000 and 2011 census data). To achieve the secondary objective of the project; the Guidelines for Management of Type 1 Diabetes are being formulated by making use of leads obtained from this registry data.

Phenotyping North East Indian Young Type 2 Diabetes (PHENOEINDY-2)

There is a substantial prevalence of Type 2 DM in young patients from North East India as reported by "Registry of Youth Onset Diabetes in India (YDR)". The NE people are short and thin and the life expectancy of Assam is 58.9 years, which is lower than the national average of 63.5 years. Whereas changing the socioeconomic conditions

and lifestyle factors predisposes to Type 2 DM. The project is hypothesized on the DOHaD (Developmental Origins of Health and Disease) theory which suggests that intergenerational and early life deprivation, combined with rapid socio-economic development predisposes to a range of NCDs including diabetes, hypertension and coronary artery disease. So far data on anthropometry, body fat composition, pancreatic β -cell function, whole body insulin resistance, and co-existence with cardiovascular risk factors, diet history, ethnic and social migratory history of young Type 2 DM patients coming to Assam Medical College has been collected. It is also planned to bank blood, urine and DNA samples of patients for future research purpose.

Fetal Growth, Neonatal Size and Its Relation to Composition and Insulin Resistance upto 8 years of Age-a Feasibility Study (PHENOEINDY-P)

The project is aimed to study the association between fetal growth, birth weight and body composition with glucose tolerance, insulin resistance and neuro-cognitive function in childhood. The selected subjects for the study are children delivered at AMCH, Dibrugarh between the years 2008 and 2011, who will be of 6-10 years of age at present. Delivery records of mothers and babies residing in an area within 200 km radius of Dibrugarh town are screened for the study. A comprehensive data file is prepared with information containing identifiers such as name, age, family head, address, contact numbers, delivery details etc. The subjects are approached by telephone, individual visits and ASHAs of different areas. The selected subjects undergo a detailed history including: dietary habits, physical activities, standard of living; anthropometry, fasting blood sugar after standard diet and overnight fasting, blood sugar after glucose challenge, insulin, HOMA-IR, lipid profile, parental fasting blood sugar, haemogram, glucose, lipids, creatinine and liver profile is taken. Sample of urine, plasma and blood (for DNA) is stored at -80°C from all subjects.

ICMR-Indian National Diabetes Study (ICMR-INDIAB)-North East

The study is aimed to estimate prevalence of pre- diabetes and diabetes among rural and urban population in north eastern region of the country. A sample size of 32,000 individuals covering the North-East regions representing eight states in India namely Sikkim, Assam, Meghalaya, Tripura, Mizoram, Manipur, Nagaland and Arunachal Pradesh have been completed. All the states in North East have completed their survey. In summary, the overall weighted prevalence of diabetes varies from 5%-8.6%. The overall weighted prevalence of pre-diabetes varies from 4-12%. It was observed that the prevalence of diabetes was higher in urban compared to rural areas. The prevalence of hypertension was higher in urban compared to rural areas, whereas, dyslipidemia was similar in urban and rural areas of all the six states. During 2017-2018; the two states (Nagaland and Sikkim) completed survey.

ICMR-India National Diabetes Study (ICMR-INDIAB)-Rest of India

Following study undertaken in 4 states during phase I; the five states [Andhra Pradesh, Bihar, Gujarat, Karnataka and Punjab] of India undertook the survey during phase II. The weighted prevalence of diabetes (both known and newly diagnosed) in five states which completed survey varied from 4-10%. The prevalence of pre-diabetes varies from 8-11%. The prevalence of hypertension, dyslipidemia and metabolic syndrome were higher in urban compared to rural areas in all five states, except Gujarat. During year under report; four states viz: Delhi, Madhya Pradesh, Rajasthan and UP completed the field survey.



Fig. 8: Prevalence of Diabetes and Prediabetes in 15 states of country (2017).

Impact of Yoga on Chronic Care

As per directives of PM office the ICMR constituted Expert Group on the subject; the following three proposals were initiated:

 (i) A multicentre open label parallel arm RCT evaluating whether yoga can prevent worsening of glycemic control in patients with type 2 diabetes mellitus on maximum doses of oral anti-hyperglycemic drugs.

It is aimed to achieve the primary objective (time to event: 1-HbA1c > 8.5% at 4 months; HbA1c > 8.0% at 8 months; HbA1c > 7.5 % at 12 months and increase of HbA1c by 1% as compared to baseline at any point of evaluation) with secondary objectives to evaluate the effect of voga on (i) metabolic parameters: weight and waist circumference at 4,8,12 months; (ii) psychological parameters: depression at 4 and 12 months; (iii) PAID score at 4 and 12 months; (iv) Pittsburg sleep quality index (PSQI) at 4 and 12 months, etc. Three small batches with total of 10 patients were randomized over these four months at Delhi site, so that follow up data at 4 months can be observed and challenges can be observed in initial small number of patients. It was suggested that efforts should be made for supervised yoga for participants so that the effects of yoga can be properly documented. The supervision is required at least once in month; evaluation by instructors and assessment of yoga compliance is required. The possibility of using mobile software is being explored basically to check the duration of the yoga practice.

 (ii) To study the effect of structured long term yoga intervention on biomarkers of stress, oxidative stress and inflammation in subjects with prediabetes.

The proposal is aimed to determine whether structured long-term yoga can improve stress, oxidative stress and inflammatory biomarkers in non -diabetic subjects with IFG/IGT. The proposal is an off shoot of project "A multicentric, randomized, controlled trial of yoga and fenugreek in prevention of type 2 diabetes mellitus – The Indian Prevention of Diabetes Study (IPDS)," being funded by Research Society of Study of Diabetes in India which is aimed to determine whether up to 3 years of intervention with yoga and fenugreek can change the composite outcome of type 2DM in nondiabetic people with IGT/IFG. The main objective of this study is to investigate whether there is an effective and safe modality for the prevention of type 2 DM which is also cost effective and can be implemented easily on a large scale so as to reduce the burden of the emerging epidemic of type 2 DM. The pre-diabetic subjects from Indian Prevention of Diabetes Study (IPDS) are enrolled for present study funded by ICMR. These pre-diabetic subjects receive 40 minutes of structured yoga in addition to lifestyle advice in one group and in the other group subjects receive lifestyle advice alone for 3 years. The markers of stress (cortisol, DHEAS and prolactin), inflammatory biomarkers (hsCRP and IL-6), oxidative stress biomarkers (malondialdehyde (MDA), anti-oxidants, markers for DNA damage and others (adiponectin, leptin and 25-OH-Vit D) would be estimated. Baseline biomarkers were estimated at the time of randomization to yoga or lifestyle alone group and these would be repeated at 12 and 24 months at the time of the annual visit. The changes in different biomarkers before and after yoga at various time points of the study would be analyzed and correlated with the glycemic status of the study subjects. There appears to be a trend towards decline in systolic and diastolic blood pressure in yoga group. There is a fall in fasting and post -prandial plasma glucose in both groups but in yoga group it appears to be greater than that in the placebo group. Samples of baseline and follow up i.e. six month, one year and two years of subjects from all the three groups have been stored for various biomarker estimations.

(iii) Impact of yoga on stress, metabolic parameters and cognition of Indian adolescents.

The project is aimed to assess the effectiveness of an intensive 25 session yoga intervention (twice a week for 2 months, followed by weekly once session for next 2 months and finally a refresher session) in adolescents studying in grades VIII – X (~ aged 13-15 years) in north (Delhi) and south (Chennai) India in a school based setting on: (i) stress levels using a stress scale and salivary cortisol levels; (ii) metabolic parameters such as body weight, waist circumference, pulse rate, body fat and blood pressure; (iii) adoption of healthy lifestyle behaviors focusing on improving dietary habits, physical activity levels and attention span and concentration using a cognitive psychometric test called the Letter Cancellation Test (LCT). The outcomes proposed are: decreased salivary cortisol and/or improved scores on the stress scale; improved body weight, body fat%, waist circumference and/or blood pressure; increased step count assessed through pedometers and increased leisure time physical activity (PA) in the study participants and improvement in letter cancellation tests (LCT) scores. One grade from VIII to X, including all its sections and comprising of a total of 60-130 students (average 70-80), are randomly selected from each school to participate. The adolescent yoga questionnaire was developed and was pre tested in 25 adolescents aged 13-15 years in English and Tamil (boys - 13 and Girls -12).

Diabetes Cohort Study

Diabetes Cohort Study is a five-year longitudinal study that would help understand the factors involved in the development of Type 2 Diabetes Mellitus & its complications and provides opportunities for interventions at different levels and collateral studies. Its primary objectives are to study the risk factors for development of Diabetes, Pre-diabetes and Complications (micro & macro) among Asian Indian adults. It is also aimed to compare screening rates and prevalence of pre-diabetes, diabetes, and diabetic complications across a cohort of urban and rural subjects who have been identified as NGT, IGT/IFG or NDDM based on OGTT. The incidence rates and predictors for pre-diabetes, diabetes, and diabetic complications including predictors of earlier development and more rapid progression of glucose intolerance would be evaluated. The Diabetes Risk Score would also be validated in independent settings. Besides defining the relative

risk of different conventional risk factors of diabetes and prediabetes, this study is expected to ascertain the role of emerging risk factors for diabetes such as environmental pollution, stress, osmolarity, inflammation. It would also, throw important insights at various points in the spectrum of glucose tolerance that would help, define & crystallize action at various points that might help prevent prediabetes, diabetes, diabetic complications or diabetes related deaths & disability.

Guidelines for Management of Type 2 Diabetes

The Workshop was organized at MDRF, Chennai in February 2018 and the working groups were constituted to debate on the content mentioned in chapters listed in draft document. The document was uploaded on ICMR website for inviting comments from peer group and has been finalized.

Guidelines for Management of Type 1 Diabetes

The ICMR in collaboration with AIIMS and IIPH is in process of formulating guidelines for management of type 1 diabetes and also using leads obtained from ICMR's Young Diabetes Registry.

Three Indo US collaborative projects are ongoing.

(i) Harmonization of existing registries of diabetes in youth: a U.S.-India Collaborative Research Partnership: The study is aimed primarily to harmonize ICMR's Young Diabetes Registry (YDR) and USA's SEARCH registry data and to compare phenotypic, clinical and demographic characteristics by type of diabetes between YDR and SEARCH; thereby comparing the burden of diabetes in youth by age, sex, race/ ethnicity and type of diabetes between India and the US. To harmonize the data of two registries; data dictionary and frequency table for YDR-Phase-1 variables was developed. The first set of YDR and SEARCH variables were mapped for data harmonization and the YDR data was converted to SQL format. The OMOP data platform was set up at the AIIMS institute server. It is planned to compare and discuss similarities and differences in diabetes characteristics and diabetes type data collected by SEARCH and YDR. Further to compare burden of diabetes in youth by age, sex, race/ ethnicity and type of diabetes between India and US; denominators of population for Delhi and Chennai for years 2006-2011 were estimated.

- (ii) Genetics of Type 2 Diabetes- a multi-centric population specific study. It is aimed to evaluate genetic determinants of T2D using pedigreebased data sets from distinct endogamous ethnic groups (EGGs) representing the North and South Indian states. Thus, the diabetic pro-bands in each FDRC study constitute a population-based case series of T2D. All 1st, 2^{nd,} and 3rd degree relatives (T2Ds and non-2TDs), aged from 18 or above, are invited to participate in each FDRC study. The information on shared and non-shared environmental factors including physical activity, medical history, smoking, alcohol consumption, socioeconomic status, dietary intake (24-hr recall method) and psychological/ behavioral attributes were collected using the standardized questionnaires.
- (iii) Association of persistent organic pollutants with incident diabetes among urban Indian adults: The project is aimed to standardize and cross validate gas chromatographymass spectrometry (GC-MS) methods for measuring the identified Persistent Organic Pollutants (POPs). To accomplish the same, the investigator from JNU, was trained at Emory University, Atlanta at the time of project initiation. The training was conducted on research protocol to be followed for the JNU laboratory investigators. The staff was trained at JNU to conduct sample preparation and analysis. Towards end of second year, extraction of 80 unknown plasma samples selected for cross validation has been completed and cross validated at Emory University.

Indo German Collaboration

Identification of **me**tabolic biomarkers for **r**isk stratification in obese **a**dolescent population in India – **IMERSAI:**

This project is initiated under Indo German Collaboration in response to call for proposals made by Division of International Health. The metabolic biomarkers of pre-diabetes and type 2 diabetes have been so far analyzed in Europid populations. As the prevalence of type 2 diabetes is rising in Asia and especially in India, it is intended to validate and replicate diabetes biomarkers in Indian adolescent population. The major challenge of the metabolomics analyses in India is the less information on sample quality and metabolites coverage. The mass spectrometry analyses are conducted by German collaborator to evaluate the individual and inter-individual variability, collection and storage parameters, and number of metabolites within the quantification range. Transfer of technology for metabolomics analysis is envisaged from German collaborators.

NEUROSCIENCES

Centre for Advanced Research for Innovation in Mental Health and Neuroscience: Manpower Development and Translation Research at NIMHANS, Bangalore, Karnataka (2014-2019)

(a) Post doctoral fellowship in Neurocritical Care

Neurocritical care requires a Neurointensivist and a Neurocritical care unit for improving outcomes in patients. However, in India this has not been formalized and grown into a sub specialty and neurological patients are often taken care by physicians other than Neurologist. Hence there is a need for a training program in neurocritical care to render care to these groups of patients with acute neurological disorders. This Centre at NIMHANS has trained 11 PDF's in Neurocritical care in last 4 years.

(b) Development of Neuroscience Educational Material for popularizing Neuroscience under Human Brain Bank

A 'Histological Atlas of the Common Infection of CNS', along with set of histological slides depicting the pathological features and CD containing the text & photographs in the Atlas has been prepared. Teaching boxes of CNS neuroinfections were supplied to 13 Medical Institutions along with Atlas and has been used for EURO-CNS teaching course of European Confederation of Neuropathological Societies, in CME for 200 postgraduates for CNS infections at Dhaka. To create interest in neurosciences, the Neuropathology Brain Museum has installed interactive 48" display alongside touch magix with ARENA software to give a detailed description of the pathological mounted specimens, educational videos and few brain games in the museum. Interactive digital displays, quiz and jigsaw puzzles to "play and learn" for children with brain games to learn neuroscience being developed. This initiative of learning of neuroscience by school children has been extensively covered by Doordarshan, BBC Hindi Indian express, India Today etc.

(c) Translation research in ALS-Development of biomarkers for diagnosis, monitoring disease progression and evaluation of toxicity

CHIT-1 level was increased by eighteen fold in ALS-CSF (cerebrospinal fluid) compared to Normal CSF and twenty-three fold when compared to Non ALS-CSF. CSF from patients with lesser disease duration (<6 months) had significantly higher CHIT-1 levels compared to CSF from patients with more than 6 months of disease duration. The test had positive predictive value of 99.12% and the negative predictive value of 52.38%. This molecule appears to have the potential of developing a biomarker for ALS diagnosis and monitoring disease progression.

(d) ELISA test for Creutzfeldt Jakob Disease (CJD)

This test has been developed and in 103/106 samples, the results correlate with clinical tests.

External quality assurance will be done at Mayo Clinic, VSA. A joint ICMR-NIMHANS reference centre for CJD, a rare disease, is planned once the test is validated.

Development and validation of a comprehensive clinical and neuropsychological test battery for use in the Indian context for patients with Vascular Cognitive Impairment

Dementia is a growing problem with serious socioeconomic consequences in India. Limited research evidence is available due to lack of high quality Indian population specific diagnostic tools for use in diverse populations that characterize India. A multidisciplinary research group developed a novel harmonised, valid and reliable diagnostic tool, the ICMR Neuro Cognitive Tool box, in six different Indian languages to diagnose neuro cognitive impairment and dementia across diverse geographic, demographic and sociolinguistic communities in clinical and research settings in India. A five minute screening tool has also been developed for clinical use. The Tool has the capacity to diagnose dementia in illiterate population and in six Indian languages. Validation of this tool was done in one thousand five hundred and seven subjects from five centers across the country (Delhi, Hyderabad, Bangalore, Kolkata and Trivandrum) and data analysis is being carried out. The ICMR Neuro Cognitive Tool Box will be made available free of cost for use both within the country and by other developing countries.

Population Based Rural Stroke Registry at Ludhiana

The project covers 70 villages of Pakhowal and all 94 villages of Sidhwan Bet blocks and utilizes ASHA workers. Project has a toll free number 1800-270-8585 for stroke related enquires and notification of stroke cases by general public and ASHAs. The incidence of stroke in 2016-17 was 149 (95% CI 130-168); among males was 151 per lakh and 175.3 per lakh in females. Among the first ever stroke in rural population, imaging by CT/MRI was done in only 52% of cases. Ischemic stroke was seen in 32% of cases and hemorrhagic in 6% of cases. The

number of stroke deaths identified through verbal autopsy in project area was 19.4% and 25.5% among males and females, respectively. Risk factor analysis of stroke cases showed high frequency of hypertension (66.86%). Desi Ghee consumption and diabetes mellitus in first ever stroke cases. Of the 199 stroke cases in 2016-17, 173 cases were reported by the ASHA workers. These were examined by the Neurologist for confirmation of stroke along with examination of the MRI/ CT scan films or reports available. These were analyzed to assess the sensitivity of the methodology. The sensitivity of stroke identification by ASHA was 86.43% and a positive predictive value (PPV) was 86.13%. This high score implies that trained ASHA can be used for stroke identification.

Study of Feasibility in Establishing a Stroke Surveillance and Management System through Community involvement and Technology Use in Rural Tirunelveli (MRHRU Field Practice Area)

The primary objective of this study is to assess the feasibility of establishing a stroke surveillance and management system in rural Tirunelveli through community involvement and technology use for estimating the burden, types, risk factors, clinical presentations, diagnosis, management methods, help seeking patterns and timelines in terms of public and private health system responses and outcomes of stroke in rural Tirunelveli under the MRHRU field Practice area. The study has been initiated.

Establishment of the Indian Stroke Clinical Trial Network (INSTRuCT)

Stroke incidence in India ranges from 135 to 145 per 100,000 population. ICMR's recent Ludhiana population based Stroke Registry observed that 25% of the patients are below 49 years of age. Though India has good epidemiological data on stroke, the country lags behind in conducting large scale clinical trials and multicenter research in stroke. A vast majority of stroke trials have been carried out in Caucasian population e.g. acute thrombolysis trials, imaging related studies and

secondary prevention trials. The findings of these trials may not be applicable to Indian population. In order to answer simple research questions in stroke treatment, genetics and prevention a large sample of patients is required which can be undertaken through a well structured Stroke Clinical Trial Network in India. A total of 26 stroke centres across the country have been included in INSTRuCT and efforts are being made to expand this so that all geographical areas are equally represented.

Following trials are being conducted under INSTRucT network

NATIONAL TRIALS

Secondary Prevention By Structured Semi-Interactive Stroke Prevention Package in INDIA (SPRINT INDIA) Trial

The study is a multicenter, randomized, paralleldesign, adaptive and blinded end-point clinical trial of sub-acute stroke patients. The objective of this trial is to assess the role of a structured semiinteractive stroke prevention package to reduce the risk of recurrent strokes, acute coronary syndrome and death in patients with sub-acute stroke after one month. The participants will be block randomized into two groups in a 1:1 ratio, the intervention arm will receive a Structured Semi-Interactive Stroke. A Stroke prevention workbook according to the Federal Plain Language Guidelines and National Culturally and Linguistically Appropriate Services (CLAS) Standards has been developed. Personalized text messages providing reminders for medications, motivation to adopt healthy habits, and health information to improve dietary habits, increase physical activity, encouraging smoking and alcohol intake cessation to be sent via SMS and videos have been developed in nine different languages for the intervention arm patients/ caregiver.

Ayurvedic Treatment in the Rehabilitation of Ischemic Stroke patients in India: A Randomized controlled trial (RESTORE)

Approximately 50% of patients have persistent motor disability following stroke.

Ayurveda has certain beneficial effects in the rehabilitation of stroke patients. Since their efficacy in human stroke subjects is unproven, it is planned to study their safety and efficacy in improving the motor functions of stroke patients in a randomized trial. One hundred and forty (n=140) consecutive haemo-dynamically stable adult patients with first ischemic stroke, 1 -3 months from stroke onset will be randomized into two treatment groups to receive either Ayurvedic treatment alone, or Physiotherapy alone. Outcome will be assessed using Fugl Meyer assessment for physical performance, Rankin Scale, and Barthel index for functional disability and quality of life using SF -36. Routine hematological investigations, liver function tests and renal function test will be conducted at baseline and different time intervals .The study has been initiated in AIMS, Kochi, Kerala. SCTIMST, Thiruvananthapuram, Kerala and CMC, Ludhiana, Punjab are developing links with Ayurvedic facility/establishing Ayurveda facility within the hospital premises.

INTERNATIONAL TRIALS

The INSTRUCT platform provides support to academic international trials of importance to the country thereby hoping to leverage benefits of these trials to the country

• Enhanced Control of Hypertension and Thrombolysis Stroke study (ENCHANTED) Funded by NHRMC, Australia

ENCHANTED is an independent, investigator initiated, international collaborative, quasifactorial randomised controlled trial involving a package of 2 linked comparative treatment arms. The rtPA dose arm of the study concluded with a publication of the results in May 2016. The BP intensity arm of the study is ongoing. The Trial was initiated in India in September 2017. This arm of study has 2 questions: (i) Does intensive blood pressure (BP) lowering (130-140 mmHg systolic target) improve outcomes compared to the current guideline recommended level of BP control? (ii) Does the addition of intensive BP lowering to thrombolysis with rtPA reduce the risk of any ICH? The Trial was initiated in India in September 2017. Thirty five patients have been recruited till 30th April 2018.

• Early Remote Ischemic Conditioning in Stroke (ERICS) trial funded India Alliance The Wellcome Trust/DBT. Phase 2a trial

Despite best medical management, high-risk transient ischaemic attack (TIA) and acute ischaemic stroke are associated with early neurological deterioration (END), recurrent strokes and death, highest in the first week and persists for 12 weeks. Remote ischaemic conditioning (RIC) involves brief-cyclic ischaemia and reperfusion of a distant organ (upper arm muscles) to protect at-risk (cerebral tissue) organ tissue by increasing ischaemia tolerance. Its role in high-risk ischemic stroke patients remains unknown. Study aims to assess feasibility and safety of early RIC in high-risk ischaemic stroke patients (Phase IIa).; to assess efficacy of early RIC in highrisk ischaemic stroke patients (Phase IIb) and to assess predictors of favourable RIC therapy in high-risk ischaemic stroke patients.

NATIONAL STROKE RESEARCH NETWORK

The objective of this Network is to carry out multicentric stroke studies to improve quality and outcome of stroke care in the country and; to establish capacity for collaborative stroke research for basic, clinical and translational stroke research, including genetics, proteomics, metabolomics. A project 'Fever, hyperglycaemia, swallowing and hypertension management in acute stroke: A cluster randomized controlled trial (Indian Quality Improvement in Stroke Care study)' has been supported. The objective is to evaluate the impact of a multidisciplinary team-building intervention designed specifically to improve evidencebased management of fever, hyperglycaemia, hypertension and swallowing in patients following acute stroke and; to establish a blood biobank of

phenotypic ally well characterised stroke patients for conducting genetics and proteonomics study. Six government medical colleges/ institutions along with 6 district hospitals are participating in this study. Training modules are being prepared.

CARDIOVASCULAR DISEASES

A Web Based National Network of Management for Acute Coronary Events (MACE) Registry

The Management of Acute Coronary Events (MACE) Registry has now enrolled 13,150 patients since its inception. It is the first registry from India that is documenting long-term outcomes (6 months) after Acute Coronary Syndromes in India. This study is being conducted from 31 centers across India. The study is ongoing and an interim analysis of 6,462 patients is presently being conducted. Nearly 45% of patients were hypertensive and 35.9% were diabetic. ST elevation myocardial infarction (STEMI) was present in 54.1% and Unstable Angina or non ST elevation myocardial infarction (NSTEMI) was the presenting diagnosis in the remaining patients. Percutaneous coronary intervention was performed in 46.7% of patients with STEMI and fibrinolysis in 22.3% of the patients with STEMI. Of the STEMI patients 5.1% died during hospitalization, 7.8% at 28 days with a total mortality of 10.7% at 6 months. In patients with NSTEMI, total mortality was 2% during index hospitalization, 3.6% and 6.1% at 28 days and 6 months, respectively. Overall mortality in patients undergoing PCI was half that of patients who underwent fibrinolysis for STEMI (2.5% vs. 5.4%, respectively). Echocardiogram was done in 80% of patients with an EF less than 40% in 18% of patients during index admission. There was a mild progressive improvement in EF with 17.2% and 16.9% having an EF <40% at 28 days and 6 months, respectively. However, total mortality was higher amongst patients with an EF < 40%.

Assessment for accreditation and comparative analysis of health profile in selected accredited schools of Chandigarh

The "Health Promoting School" (HPS) is a holistic and comprehensive approach to integrate health promotion within the community. A pilot activity for accreditation of 'Health promoting schools' was undertaken in 17 schools in Chandigarh. Up scaling and carrying this further, ICMR initiated current project in 2016. The rationale for this study is that comprehensive implementation of HPS would contribute to differences in certain health behaviours and health profile of school children. In phase I of the project, all schools of Chandigarh have been assessed and accredited. A manual for Accreditation including Swachh Vidhalaya guidelines was developed. Baseline assessment by certified assessors in 112 of Government schools and 74 private schools showed similar pattern of accreditation level in government and private schools with 82% below bronze, 13% bronze and 5% silver level in Govt. Schools as compared to 81% below bronze, 12% bronze, 5% silver and one gold levels in private schools, respectively (p > 0.5). Only 40% of the Government schools had toilet ratio of one unit for every 40 students (Swatch Vidayalaya Guidelines) as compared to 78% in the private schools. Availability of adequate water was 53% of private schools as compared to 28 % of Government schools. Government schools were better in monitoring canteens/meals in the schools and implementation of MHRD's Shaala Siddhi program but were behind private schools as far as access to clean drinking water, clean toilets and adequate lighting and nutrition education in school was concerned. Playgrounds were available in more of government schools. In phase II, an assessment of health profile of students belonging to higher accreditation schools is being compared to students from lower accreditation schools.

Delhi Emergency Life Heart- Attack Initiative: Mission Delhi

ST elevated myocardial infarction (STEMI) is a serious form of heart attack and requires early reperfusion to reduce mortalities. To avoid delays in STEMI care arising due to patient not being able to reach emergency care in time, this project has been initiated with an aim to develop, test and implement a 24-hour emergency response system for a pre-hospital thrombolysis service, using bolus-dose of thrombolytic agent for the treatment of acute myocardial infarction in a geographically defined area of Delhi. The project plans to use Nurses on motor cycle as 'First Responders'. On receiving a call from patient with chest pain, a nurse team on motor cycle will be dispatched. This team will make assessment for Acute Coronary Syndrome (ACS) and monitor vital signs. ECG recording will be transmitted to AIIMS cardiology consultant. Thrombolytic therapy will be initiated on advice of Consultant and patient will be shifted to AIIMS in an ambulance for further management.



Fig. 9: Mission Delhi.

During the first phase of the project, a control room center ~ 1000 sq. ft area has been built on 2^{nd} floor of old O.T, AIIMS, New Delhi. A 24 hr dedicated helpline number has been also issued with support from MTNL. UK specialist ambulance services (UKSAS), London who are experts in provision of specialist medical transport are acting as Advisors for developing the call center and IT facilities. The UKSAS has also trained Nurses in ACLS (*Advanced Cardiac Life Support*).

India Hypertension Management Initiative (IHMI)

High blood pressure is a leading cause of CVD in India-and of the millions of adults with hypertension - just 1 in 7 have their disease under control. The India Hypertension Management Initiative (IHMI) is a collaborative project of ICMR, MoHFW, State Governments, WHO and Vital Strategies. The primary goal of this project is to reduce morbidity and mortality due to CVDs, the leading cause of death in India, by improving the control of high blood pressure in adults. IHMI aims to strengthen the CVD component of the National Programme for Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS). It is targeted to facilitate progress towards 25 percent reduction in high blood pressure and reduce disability and premature death from NCDs by Strengthening hypertension management and monitoring at the primary health care level. Enabling a continuum of care and Aligning with government's commitment universal care. ICMR will undertake to implementation to understand the bottlenecks in managing hypertension at primary care level and drug dispensing at subcentre level by ANM and provide solutions to these bottlenecks.

Five districts from Punjab (Bathinda, Gurdaspur, Hoshiarpur, Mansa, Pathankot), three districts from Madhya Pradesh (Bhopal, Chhindwara, Ratlam), four districts from Kerala (Kannoor, Thiruvananthapuram, Thrissur, Wayanad), nine from Telangana (Karimnagar, Jagtiyal, Rajanna, Pedapally, Jayashankar, Warangal, Warangal, Jangaon, Mahboobabad) and four districts in Maharashtra (Bhandara, Satara, Sindhudurg, Wardha) have been a selected for Phase I of the study. The project has been rolled in Punjab in January 2018 and in Madhya Pradesh and Kerala in April 2018. Treatment algorithms have been built up at State level through workshop of key stakeholders. Training modules, reporting formats and registers have been finalized and printed. Efforts have been made to sync the treatment algorithms and training modules with the National Program. These modules have been used for trainings of consultants and care providers in the States. Key challenges include non availability of drugs and involvement of private sector. For example, Telmisartan required inclusion in the Punjab State's Essential Drug List (EDL). This resulted in substitution of the drugs in the treatment protocol. State was appraised of this so that drug is made available.

National Heart Failure (HF) Registry of ICMR

ICMR's Trivandrum Heart Failure Registry (THFR) enrolled 1205 (834 men, 69%) consecutive admissions from 13 urban and five rural hospitals in Trivandrum with a primary diagnosis of HF. Indian patients are younger by 10 years and Mean (standard deviation) age was 61.2 (13.7) years. The most common HF aetiology was ischemic heart disease (IHD) (72%). Heart failure with preserved ejection fraction (\geq 45%) constituted 26% of the population. The median hospital stay was 6 days (interquartile range = 4-9 days) with an in-hospital mortality rate of 8.5% (95% confidence interval 6.9-10.0). The 90-day all-cause mortality rate was 2.43 deaths per 1000 person-days (95% confidence interval 2.11-2.78). Guideline-based medical treatment was given to 19% and 25% of patients with LVSD during hospital admission and at discharge, respectively. Older age, lower education, poor ejection fraction, higher serum creatinine, New York Heart Association functional class IV, and suboptimal medical treatment were associated with higher risk of 90-day mortality. The registry identified key areas for improving hospital-based HF medical care in Trivandrum. A National Heart Failure registry program has been initiated with 9 nodal heart failure registries set up in Government hospitals. Each nodal centre has 5-6 sub- centres under them (Total of around 45 centres). The registry network is planned to be expanded into a Comprehensive National Heart Failure Program aimed at improving quality of care, initiating clinical trials of importance to the country.

NATIONAL BURDEN OF NON COMMUNICABLE DISEASES

Under the aegis of the Ministry of Health and Family Welfare, Government of India, the India State-level Disease Burden was launched in October 2015, is a collaboration between the Indian Council of Medical Research (ICMR), Public Health Foundation of India (PHFI), Institute of Health Metrics and Evaluation (IHME), University of Washington. The work spanning over the past two years has involved about two hundred senior academics and decision makers from over 100 institutions across India. Data from all available sources over the past 25 years have been compiled and analyzed using the Global Burden of Disease study to produce robust state level estimates of disease burden and risk factors in India. This includes estimates for all diseases leading to health loss in each state of India from 1990 to 2016, along with estimates of risk factors driving this burden. In order to present the key trends of the state-level disease findings and risk factors over the past 25 years, and to engage central and state-level policy makers in India on the implications of the variations in these trends across the states on how the health system should develop to tackle these disease burden and control of the risk factors, the findings of the report "India: Health of the Nation's States-The India State-Level Disease Burden Initiative" and a publication in the Lancet with title "Nations within a nation: variations in epidemiological transition across the states of India, 1990-2016 in the Global Burden of Disease Study" was disseminated in November 2017.

OTORHINOLARYNGOLOGY

Congenital deafness in dhadkai village of doda district of Jammu & Kashmir

This study is a research cum intervention project which aims at estimation of burden of hearing impairment in Dadhkai village of Doda district of J & K, determination of its possible genetic basis and at the same intervene to help the community . The initial phase has helped the affected people in terms of getting due attention for medical and rehabilitation support, & subsequent analysis of genetic basis will help in developing and implementing counselling to prevent transmission of relevant genes so that the future generations could be saved.

The epidemiological work in Dhadkai (a sensitive military area and a difficult terrain to reach) has already been completed in form of baseline survey for entire village. A sound proof room unit has been established at community health centre, Gundoh which had served as base center for all activities. PI has identified 80 hearing impaired out of a total population of 2522. Pedigree chart of entire village has been constructed and family groups with relatively higher number of hearing impaired have been identified. They have provided hearing aids (80) to hearing impaired and have sent 600 blood samples to JNCSAR for identification of genetic defects. The status of homozygous mutations OTOFp.R708X (c.2122C>T), SLC26A4 p.Y556X (c.1668T>A) and CLDN14 p.V85D (c.254T>A) among the hearing-impaired members is very high. From these hearing-impaired members 37 individuals show OTOFp.R708X, 16 members showed SLC26A4 p.Y556X, 4 members showed CLDN14 p.V85D variation. In addition, 1 member had both OTOF p.R708X and SLC26A4 p.Y556X changes. Nine hearing-impaired individuals do not show any of the three above mentioned mutations and are being examined at the whole exome level. Carrier status of the unaffected members from the population which are positive for the above mutations has been investigated and valuable conclusive data has emerged.

ICMR National Task Force Project - prevalence and etiology of hearing impairment

This project was initiated in 2015 with the objective to estimate the prevalence of hearing impairment in six representative regions of India viz., South region (Bangalore),West region (Bhavnagar),East region (Bhubneswar),Central region (Raipur), North region (Shimla), North East region (Shillong) & to describe the etiology of hearing impairment in cases detected with hearing impairment. The study was sanctioned Sample Size: From each regional center.The study involves a total sample size of 84,000 which includes 14000 individuals (rural 7000 and urban 7000) per centre. The study includes systematic random sampling [probability proportional to size, PPS]. It includes

both rural and urban areas [70 rural clusters and 30 urban clusters] based on Census 2011. The unit of study includes household with Inclusion criteria being all family members of household with age 6 months and above and thereby Exclusion criteria being (i) children less than 6 months. The study is using conventional WHO methodology for hearing screening. The study preliminary trends of data is revealing etiology wise distribution of hearing impairment as following.



Fig. 10: The study has collected data from approximately 55000 population uptil now.

DISABILITY & REHABILITATION

National Disability & Rehabilitation Research Centre (NDRRC)

ICMR has in-principle agreed to establish "National Disability & Rehabilitation Research Centre (NDRRC)" under ICMR, consisting of National Disability & Rehabilitation Research System (NDRRS) and National Disability & Rehabilitation Research Network (NDRRN).

GERIATRICS

The Division under ICMR-FORTE collaboration in the area of Geriatrics has initiated five projects jointly agreed for support on home based care of elders.

MUSCULOSKELETAL DISORDERS

PeptidebaseddiagnosisofosteoarticulartuberculosisusingimmunodominantB-cellepitopesofsecretoryRDantigensofMycobacteriumtuberculosis

The project aimed at developing highly sensitive Immuno-PCR for diagnosis of osteoarticular tuberculosis using the multi-epitope cocktail of

the immunodominant peptides of RD proteins using bioinformatics identification of secretory RD proteins of *Mycobacterium tuberculosis* known to be absent in BCG and environmental mycobacteria. The study has identified the proteins and peptides having potential for diagnosing Osteo-articular TB, and is in the process of validating it in new patients.

Comparative evaluation of genetic and cytokines profile in age matched Indian subjects with and without knee Osteoarthritis

This project has been sanctioned for initiation with the aim to study the baseline genetic association by exome sequencing of Indian patients with and without knee osteoarthritis followed by validating the candidate gene list in bigger by RT PCR and also to validate the related cytokines which will be correlated to first phase candidate genes.

Overuse injuries among school-going children in Manipur

This project has been initiated with the objective to identify and compare the type of overuse injuries among school-going children (7-15 years) in valley and hill districts of Manipur and to identify the factors that contributes to the overused injuries.

KIDNEY DISEASE

Chronic kidney Disease

Chronic kidney disease (CKD) is a major public health issue worldwide and an important contributor to the overall non-communicable disease burden. It is associated with major serious consequences including increased risk of mortality, end-stage renal disease, accelerated cardiovascular disease (CVD), mineral and bone disease, adverse metabolic and nutritional consequences, infections, reduced cognitive function and increased risk of acute kidney injury. Mortality from CVD is estimated to be 8- to 10fold higher in CKD subjects compared to non-CKD subjects. Diabetes and chronic glomerulonephritis are the two commonest aetiologies of CKD in India. This study was initiated across seven sites- Delhi, Mumbai, Jaipur, Hyderabad, Bhubneshwar, Kolkatta, Guwahati.

Registry for Assessing the Determinants of Dialysis Outcomes in India

The study has been sanctioned for initiation to prospectively follow a cohort of kidney failure patients starting dialysis for a duration of one year inorder to evaluate medical, social, economic and environmental determinants of access and quality of care and health outcomes in patients starting dialysis therapy in India. The aim of this registry will be to establish a pragmatic approach that utilizes existing routine data collection mechanisms, where it is possible. This information will be useful for patients, clinicians, hospitals, funding agencies and governments to identify populations in greatest need and how existing social and economic resources can be capitalized upon in meeting challenges of ensuring equitable access to dialysis care in India.

Grand Challenge Scheme on CKDu in Srikakulam

The STOP CKDu study is aimed at addressing all aspects of the problem – estimate the disease burden using rigorous scientific methodology and sociological tools, undertake an environment mapping and additional investigations as needed. The study also aims to establish the etiology, economic consequences of chronic kidney disease of uncertain etiology (CKDu) and develop evidence guided interventions for general improvement of health conditions in the high CKDu incidence areas of Andhra Pradesh. The implementation of the study is monitored through a Scientific Technical Advisory Group (TAG) constituted by ICMR and the Government of Andhra Pradesh, on a quarterly basis.

Gene Environment Interaction In Congenital Uropathies

Genetic basis underlying congenital uropathies follows Mendelian inheritance. Host and environment factors are implicated in the pathogenesis of aberrant renal development. It is proposed to validate the 'two-hit' hypothesis for renal damage in congenital uropathies as a sequelae of gene-gene interaction between i) pathogenesis of aberrant renal development & ii) ACE I/D induced renal parenchymal injury., besides studying the effect of Nitric Oxide on renal function recovery as a baseline study for a future role of 'iNOS gene transfer studies' for renal recovery.

Centre For Advanced Research (CAR) In Paediatric Uropathies & CKD

Patients with urologic abnormalities, especially children, in whom tubulointerstitial involvement

from urological abnormalities is a major cause of progressive renal damage. early detection of renal dysfunction at its inception is also of immense relevance It is therefore proposed to initiate a Centre of Excellence aiming at studying pathways for finding out pathophysiology and pathogenesis of various uropathies and kidney diseases among children at its inception. This centre has been initiated in December 2017.

BASIC MEDICAL SCIENCES

During the year, the intramural research in the field of basic medical sciences was carried out by the National Institute of Pathology (NIP), New Delhi, the National Institute of Immunohaematology (NIIH), Mumbai, National Institute of Traditional Medicine, Belagavi (NITM) and also at several other centres. The extramural research was undertaken in several areas viz. haematology, biochemistry, pharmacology, human genetics, nano medicines, stem cell research and biomedical ethics.

INTRAMURAL RESEARCH

NATIONAL INSTITUTE OF PATHOLOGY, NEW DELHI

TUMOR BIOLOGY

Comparative study of Genetic, Clinical and Epidemiological factors of Breast Cancer in Indian population (ICMR Task Force project)

The genomic basis of breast cancer in Indian women is being evaluated in a multicentric task force project. The work done so far includes collection of samples, both tumour and adjacent parenchyma from mastectomy and lumpectomy specimens Cases were classified according to molecular classification after immunohistochemistry for ER, PR and Her2neu and FISH where Her2neu by IHC was 2+. RNA was extracted from the sample and after passing QC were used for library preparation and run using the Ion proton for transcriptome profiling. More number of samples will be collected and transcriptome profiling and analysis will be done.

Molecular profiling of invasive urothelial carcinoma

The tissue samples of bladder tumour and adjacent normal appearing tissue as well as urine are being collected from the urology ward. The tissue samples are being used for RNA extraction and transcriptome profiling. PKCe gene profiling by RT-PCR was performed and the difference in fold change was found to be 12 fold upregulated. The expression of both PKCe and PKC ζ was localized in membrane and cytoplasmic region. More samples are being processed.

Determination of causes of death in under-five children in India by MITS technique

CHAMPS (Child Health and Mortality Prevention Surveillance) network aims to develop a long-term network of sites that collect primary data aimed at understanding and tracking the preventable causes of childhood deaths globally.

It is proposed to carry out a Pilot study first in one hospital in Safdarjung Hospital, New Delhi to assess feasibility and acceptability of MITS in a tertiary care setting in India. The pilot project will have ICMR as the coordinating centre for CHAMPS Network site and NIOP being the CHAMPS nodal laboratory in Delhi to provide pathology-based mortality surveillance in India.

Homology based models were generated for proteins MCM2, MCM3, MCM5, MCM7 and MCM10,

molecular docking was done to identify inhibitors (IBS library) against each protein. Some of the top inhibitory molecules based on their binding energy (<-8K.cal/mol) were selected for simulation (*in silico*) and *in vitro* analysis of inhibitory role of the molecules identified. The inhibitory molecules identified in vitro may serve as potential molecules for therapy of breast cancer.

Genome wide analysis of genetic alterations and gene expression profile in hormone sensitive and hormone refractory prostate cancer

The study aims to identify potential molecular signature that can distinguish histologically similar prostate cancer with differing clinical behavior. Additionally, this may provide valuable information about the pathways that may be associated with progression of prostate cancers. In less-aggressive form of prostate cancer, genetic alterations as regions of gains, were observed in Chr1q, 2p, 7p, 7q, 10q, 14q, 16p, 19q while region of loss was observed in Chr17. More aggressive form of prostate cancer showed regions of gains in Chr2, 4p, 22q, yq, yq and regions of loss in Chr 6, 10q, 15q, 16q, 17p.

TOP2B showed up-regulation in less aggressive form of prostate cancer, which renders double strand breaks leading to genomic re-arrangements. More-aggressive form of prostate cancer, however, showed up-regulation of UBC, HACE1, TRIP12, UBE3A, ITCH which encodes for ubiquitin mediated proteosomal/lysosomal degradation.

Identification of circulatory markers for early diagnosis of gallbladder carcinoma (GBC)

Proteomic analysis of extracellular vesicle (EV) in early and advanced stages of GBC was isolated from blood plasma of healthy individuals. The identified proteins belong to signal transduction, metabolism, transport and cell growth and maintenance. Transporter activity, GTPase activator activity and receptor activity are among the top molecular functions. Clinical samples required for discovery phase study have been collected.

ADULT STEM CELL BIOLOGY

Identification of growth stimulating proteins expressed by feeder cells following a novel growth arrest protocol

Growth arrested fibroblast feeders are indispensable in supporting the growth of epidermal keratinocytes and embryonic stem cells. However, the actual growth promoting proteins in such feeders are broadly unknown. It was therefore, proposed to evaluate the growth promoting action of proteins extracted from the efficiently growth arrested Swiss 3T3 cells followed by identification of proteins of interest by proteomics.

Initially, the whole protein extract from a lab-grown clone of 3T3 cells was tested on human epidermal keratinocytes and compared with the standard feeder-dependant Rheinwald-Green method and feeder less culture system using Bovine Pituitary Extract (BPE). The overall keratinocytes cell growth in feeder group with 21×10^3 feeder per cm^2 (F21K) is higher than in the P15K 15 x 10³ feeder per cm²) or BPE groups (Figure 2), where in feeder dependent culture groups with 15 x 10^3 (F15K) and 21 x 10^3 feeder per cm² (F21K) showed clonal growth of keratinocytes surrounded by disintegrating feeder cells. Similar strategies are initiated with proteins extracted from a labgrown subtype of Swiss 3T3 cells which has been validated for the production of cultured epithelial autografts.

This is the first ever study so far in which the fibroblast cell proteins promoted the growth of human epidermal keratinocytes in feeder-free and serum-free culture conditions as much as in the presence of serum and feeders.

Technology to grow non-xenogeneic CEA using human dermal fibroblasts as feeders

This project is aimed at substituting the standard murine Swiss 3T3 feeder cells with human

neonatal, adult or embryonic dermal fibroblasts in keratinocyte in order to construct Cultured Epithelial Autografts (CEA).



Fig. 1: Human epidermal keratinocyte cell cultures in the presence of various combinations of feeder proteins from 15 x 10³ (P15K) and 21 x 10³ (P21K) feeder per cm² and Bovine Pituitary Extract (BPE) in feeder less culture system and in the presence of 15 x 10³ (F15K) and 21 x 10³ (F21K) feeder per cm² in Rheinwald-Green method.

Grant for construction of cGMP for facilitating Clinical trial with the cultured epidermis has been obtained from ICMR.

INFECTIOUS DISEASES

LEISHMANIASIS

Mechanism of resistance towards paromomycin in *Leishmania donovani*

Paromomycin (PMM) is an effective drug against for visceral leishmaniasis, but at the risk of resistance selection. Gene encoding acetyltransferase like protein (ATLP), implicated in PMM resistance in bacteria, exhibited >2 fold up-regulated expression in three PMM resistant Leishmania donovani (Ld) parasites. In silico analysis predicted 3D modeled structure of *LdATLP* consisting of 4 α -helices and 5 β -sheets. Major residues present at active site constituted glutamic acid and aspartic acid. Indolicidine, a broad spectrum inhibitor of bacterial aminoglycoside modifying enzymes, showed 3 times better binding ability to LdATLP as compared to PMM by comparative docking study under same environment. Further, in presence of indolicidine, PMM-R parasites exhibited reversion of phenotype into sensitive parasites indicating role of LdATLP in PMM resistance.



Fig. 2: A. Predicted 3D model of LdATLP shows four helices and five β -strands amino acids, B. Structural rendering of Docked complex of *LdATLP* and PMM and C. *LdATLP* and Indolicidin in the active site of *LdATLP*.

Studies on mechanism of resistance towards artemisinin in *Leishmania donovani*

Artemisinin, isolated from *Artemisia annua*, is a potent antimalarial compound that has demonstrated effectiveness in experimental models of leishmaniasis. Global mRNA expression profiling of WT and AS-R parasites revealed approx. 2.26% genes with modulated expression. Detailed analysis of transcriptome data were carried out using various bioinformatic tools revealed following adaptation in AS-R parasites,(a) resistant parasites enter quiescence state b) showed reduced autophagy c) dependency on amino acids for energy generation and d) increased stress tolerance.

Development of multiplex loop mediated isothermal amplification assay (m-LAMP) for differential diagnosis of PKDL and Leprosy.

This study is aimed to develop a molecular assay for differential diagnosis of Leprosy and PKDL that are co-endemic diseases with similar clinical presentation. We designed a set of six LAMP primers targeting repetitive and specific *RLEP* gene sequence uniquely present in *M. leprae* to develop LAMP assay. Leprosy LAMP assay was positive in 33/36 (91%) tissue samples and 22/30 (73.3%) Slit skin smear samples. The assay was 100% specific for *M. leprae*. Further work has been initiated for the development of a multiplex LAMP (m-LAMP) assay for differential detection of *L. donovani* and *M. leprae*.

Phenotypic and genotypic characterization of polymyxin resistant Gram-negative bacteria isolated from patients with blood stream infections

Polymyxin resistance is mediated by increased expression of efflux pumps, capsule formation and alterations in LPS of bacterial outer membrane. Screening of colistin resistant (MIC $\geq 2 \ \mu g/ml$) isolates, identified Klebsiella pneumoniae and Acinetobacter baumannii. K. pneumoniae isolates were characterized in detail; these isolates exhibited multidrug resistant and extensively drug resistant phenotype, with colistin MICs ranging from 8 µg/ ml to $\geq 128 \ \mu g/ml$. Multiple mutations and base deletions were observed in chromosomally located phoO, pmrA, pmrB and pmrC genes. Inactivation of regulatory gene mgrB by the insertion of IS1 family transposase and IS5/IS1182 family transposase elements was observed in three isolates. All isolates were negative for plasmid mediated resistance due to mcr-genes, however, a few of the multidrug resistant Klebsiella isolates harboured blaNDM-1 and blaOXA-48 genes.

CHLAMYDIASIS

Modification of the extracellular matrix during ectopic implantation makes diagnosis of ectopic pregnancy (EP) difficult. To understand the chlamydial disease pathogenesis and identification of markers/ predictors for an early intervention during Chlamydia trachomatis infection, a study was conducted to investigate whether the presence of chlamydial heat shock protein (chsp) 60 can be used together with matrix metalloproteinases (MMPs) as marker of EP for an early diagnosis/ management of an unruptured tubal pregnancy in C. trachomatis-positive women. The expression analysis of selected MMP genes by qRT-PCR in the tubal tissue of women undergoing salpingectomy (SALP) during laparotomy for ruptured/ unruptured tubal EP (Group I) and agematched women undergoing mini-laparotomy for tubal ligation (controls) showed that the mRNA expression of MMP-2/ MMP-14 was increased among the infected Group I patients in comparison

to the controls. Expression of MMP-2/ MMP-14 was also high in *C. trachomatis*-positive women undergoing SALP for EP *versus* uninfected women with EP undergoing SALP. Further studies are underway to study the expression of MMPs/ TIMPs in relation to chsp60 for ascertaining their role in the pathogenesis of tubal EP in infected women.

TUBERCULOSIS

Role of virulence factor in antimicrobial defence through autophagy

The virulence mechanism of mycobacteria is very complex. RipA a virulence factor is a cell associated and secretary protein of *M.tb*. The institute's data demonstrated that RipA represses autophagy which is TLR4 dependent (Fig. 3) and it also increases the ratio of P62/SQSTM1/Beclin1which is a hallmark of autophagy inhibition.



Fig. 3: RipA treatment represses autophagy in RAW 264.7 macrophage cells through the activation of innate immune receptor TLR4 and reduces the formation LC3IIB puncta.

Multifunctional Signature Protein (SP2) of *M. tuberculosis* acts as Transcriptional

The hypothetical signature protein (SP2) displayed DNA methyltransferase activity, could scavenge iron, binds DNA, and protect DNA from oxidative stress by preventing generation of free radicals. These functions along with computational and structural clues suggest a transcriptional modulation activity. Recombinant *M. smegmatis* expressing SP2 showed several phenotypic changes indicating its role in trans. RNA-Seq analyses indicated SP2 to functioning as global transcriptional regulator inducing expression of genes related to oxidative stress, drug resistance and many transcription regulators (Fig 5).



Fig. 4: A representative heatmap showing the top 25 Up and Down-regulated genes. Blue and green represents up regulation while yellow and red represents down-regulation.

PUBLIC HEALTH IMPORTANCE

Affordable, rapid, point of care diagnostic systems for tuberculosis

With focus on major public health intervention, this research is focussed on early diagnosis as well as low cost POC diagnostics platforms. Genomic DNA from sputum is isolated by liquefying with an in house CLR® reagent which is devoid of any PCR inhibitory components.

Since diagnostics of TB has a critical disadvantage of being infectious, it is important to develop a rapid point of care device. In an IMPRINT funded project "Immunomagnetic cell capture device $(imc^2)^{\text{@}}$ " in collaboration with IITD is developed. Assays based on the principle of liquefying the sputum in a closed container using CLR and capturing the *M.tb* bacilli using magnetic nanoparticle and detecting them using a fluorescent detector with turnaround time of one hour is being developed. This device is currently being validated at NIP and Jamia Hamdard.



Capture bottle for sample Magnet collection

Magnetic capture in imc²

Fig. 5: Schematic depiction of magnetic capture of *M.tb* bacilli for rapid detection by imc^2 .

Study group (NIP, IITD, Jamia Hamdard) have developed a unique fluorescence microscopy technology, SeeTB®: compact Total Internal Reflection Fluorescence illumination device". The SeeTB® converts a simple bright-field binocular microscope to fluorescence microscope without any hassle of tedious illumination mechanism, optical filters, and additional lens installation. This 3D-printed module is highly compact (~approx size of calculator), robust, cost-effective and allows rapid (lesser than 2 mins) TB diagnosis without additional infrastructure and training.



Fig. 6: Assembly of See-TB \mathbb{R} with a binocular microscope for fluorescent detection of M.tb bacilli.

AWARDS AND HONOURS

- Dr. Lakshman K Yerneni was awarded National Innovation Award under NRDC for his invention entitled "Low Cost Production of Autologous Cultured Skin for Grafting in Life Threatening Burns".
- Dr. Ruchi Singh was awarded Major General Saheb Singh Sokhey Award by ICMR.
- Dr. Nasreen Z. Ehtesham was elected as a Court member of Kashmir central University

NATIONAL INSTITUTE OF IMMUNOHAEMATOLOGY, MUMBAI

ICMR-NIIH has undertaken projects including 33 intramural, 37 extramural and 4 projects under tribal health research forum. Some of the important projects along with their salient achievements are as follows:

Establishing the advanced centre for diagnosis and management of primary immunodeficiency disorders (PID)

This project was sanctioned in Feb 2017 and study has established the state of art facilities for

evaluation of suspected cases of PIDs including enumeration and functional analysis of different components of immune system as well as use of molecular techniques for confirmation of diagnosis. In the last year, the study evaluated total 1027 suspected cases of PID; of these in 100 cases were diagnosed for specific PIDs, of these 22 have been molecularly confirmed. Total 55 patients with strong clinical suspicion of PID which remain undiagnosed by targeted clinical exome analysis were performed by NGS and confirmed diagnosis was established in 21 patients. Study also identified some of the very rare immune deficiencies like LRBA deficiency, PI3KCD deficiency, BENTA syndrome, MHC-II deficiencies, etc with the help of targeted NGS. This year 5 families were offered with prenatal diagnosis (1 LAD-I, 1 CGD, 1 SCID, 2 HLH family). Apart from this, institute initiated 5 research projects on the different PIDs which include HLH- a disorder of immune dysregulation, ALPS, INF-y-IL-12 loop defects causing MSMD and LAD-I.

Harnessing induced pluripotent stem cells (iPSCs) technology for understanding the pathophysiology and management of human Primary Immunodeficiency Disorders

In this current duration of project, erythroblast like cells generation from PBMCs was standardized. Then these cells were reprogrammed using Cytotune-iPS Sendai-kit containing Oct4, Sox2, Klf4, cMyc. After maintaining cells for 20-25 days small to large colonies of iPSC were observed. These iPSC colonies were characterized using Alkaline Phosphatase Assay and by immune cytochemistry staining of Oct4, Sox2. Observed data showed successful generation of iPSC from PBMCs of normal sample. Other characterization of these iPSCs will be done by Karyotyping, checking gene expression of Oct4, Sox2, Klf4 and by checking embryoid body formation.

Interim Satellite Centre on Hemoglobinopathies at Chandrapur, Maharashtra

This centre has been established since 2015 in the TB Hospital premises near GMC Chandrapur as the prevalence of haemoglobinopathies is very high in central India. Comprehensive diagnosis facilities including HPLC and molecular diagnosis have been established at the center and it is currently running programmes like population screening, antenatal screening, newborn screening and antenatal diagnosis. A total of 446 SCD, 21 Sickle/β thalassemia and 34 β-Thalassemia major have been enrolled for comprehensive evaluation, management and follow up. A dedicated sickle cell clinic also has been established at GMC for regular follow-up of these patients. Under antenatal screening programme, a total of 8500 pregnant women were of which 300 women were found to be sickle cell trait and 8 were sickle cell anemia (SS) while 16 were β -thalassemia trait. The spouses of these women were also tested for carrier/ disease status. Newborn screening programme has identified 85 sickle cell heterozygous and 3 sickle cell homozygous babies. Multiple research projects including understanding role of microparticles, ubiquitin-proteosome system and oxidative stress in pathophysiology of sickle cell anemia have been undertaken in identified cohort of patients.

Molecular characterization of undiagnosed cases of congenital hemolytic anemia using a multigene next generation sequencing panel

Institute provides tertiary referral services for patients with unexplained hemolytic anemia. Under this DBT funded project 50 cases of severe transfusion dependent anemia were done by targeted next generation sequencing and discovered many rare genetic defects such as Adenylate kinase deficiency, Novel SEC23B gene mutation causing CDA type II first time in Indian populations. Several novel mutations were detected in pyruvate kinase gene, NADH cytochrome be reductase gene, 12 cases of R347H mutation in glucose phosphate Isomerase gene and 3 novel mutations in pyrimidine 5' nucleotidase gene. First time prenatal diagnosis is successfully offered to glucose phosphate Isomerase deficient and NADHcytochrome b5 reductase deficient patients.

Red cell membrane pathology in Hereditary Spherocytosis (HS) in India

Under this DBT funded project molecularly characterized hereditary spherocytosis cases were

seen for the first time in Indian patients and detected several novel mutations in red cell membrane protein such alpha Spectrin, beta Spectrin, ankyrin and band 3 proteins.

India Japan collaborative research aspiring for prevention and diagnosis of erythrocyte associated disease

This project was sanctioned by Indo-Japan cooperative science programme funded by DST-JSPS. Under this project, team explored the role of ubiquitin proteasome system in the pathogenesis of sickle cell anemia and response to hydroxyurea therapy. This has provided a novel insight into the role of ubiquitin-proteasome system pathophysiology of SCD and its clinical heterogeneity and has shown that it may be a suitable therapeutic target for the better management of the patients.

Indo Japan collaborative Project: Collaborative effort to study pathophysiology and molecular characterization of congenital anemia in India

This collaborative study was undertaken to establish NGS facilities for diagnosis of unexplained hemolytic anemia at NIIH. One scientist received training at Japan for the same. 20 Indian patients of unexplained rare hemolytic anemia were analyzed by NGS at Tohoku University, Sendai and study identified genetic mutations in 3 Indian CSA and DBA patients, 2 cases showed defect in Pyruvate kinase gene, 2 cases showed GPI, 2 cases showed mutation in PIEZO1 gene associated with hereditary xerocytosis/stomatocytosis.

Assessing the role of microRNAs in clinical severity of Thalassemia Patients, and its role in hydroxyurea mediated HbF induction

This DBT funded project has been undertaken to understand the role of microRNA in HbF induction mediated by Hydroxyurea (HU) and its correlation with clinical response. A total of 10 thalassemia intermedia patients who are taking hydroxyurea treatment regularly along with 10 healthy controls have been recruited in the study so far, showing upregulation of miRNA in responders to hydroxyurea treatment as compared to the nonresponders.

Study of RH gene variants in Indians

In this study genotyping of RhD variants in Indian population was done. The discovery of Novel molecular mechanism was predominantly responsible for weak D variant in Indian population. An Indian-specific genotyping assay has been designed. Patent filed in Europe on March 8, 2017 under number 17 305246.5

Understanding the molecular mechanism of oxidative stress and mitochondrial function in impaired Fanconi Anemia (FA) pathway

This study on large cohort of FA patients has revealed significant mitochondrial copy number variations and deregulation of mitophagy genes leading to ineffective clearance of impaired mitochondria suggestive of significant oxidative stress related damage to mitochondria and its role in pathogenesis of bone marrow failure associated in patients with FA.

Increasing the hemostatic potential of recombinant factor VIII by combining it with platelet-derived microparticles (PMPs)/ synthetic phospholipid vesicles containing phospatidylserine

This study has shown that PMPs can provide better and cost effective treatment in haemophilia patients than the recombinant FVIII alone which may significantly reduce the cost of the therapy.

Molecular pathology of AT deficiency in patients with arterial and venous thrombosis

This is the first study on large cohort of patients with thrombosis with AT deficiency. The major finding of this study is that deleterious mutations are seen in thrombotic patients with both normal and reduced activity, thus raising issues about the sensitivity of the currently available kits in the market. Thus we recommend that genetic screening for variants in AT gene should be performed in all thrombosis cases.

Study of RH gene variants in Indians (project funded by CEFIPRA)

In this study genotyping of RhD variants in Indian population was done. The discovery of Novel molecular mechanism was predominantly responsible for weak D variant in Indian population. An Indian-specific genotyping assay has been designed. Patent filed in Europe on March 8, 2017 under number 17 305246.

NATIONAL INSTITUTE OF TRADITIONAL MEDICINE, BELAGAVI

Studies on resolving identification issues and identification of elite clones in *Saraca asoca* (Roxb.) De Wilde from Western Ghats

Saraca asoca (Roxb.) De Wilde, commonly known as "Ashoka" is a highly traded Indian medicinal tree used in many health conditions. Increasing commercial demand and overexploitation has threatened wild populations and resulted in extensive adulteration/substitution in crude drug market. In the present study, a method employing highperformance chromatography liquid of phenolic compounds (gallic acid, catechin, and epicatechin) coupled to multivariate analysis followed by multivariate hierarchical cluster analysis and principal component analysis was established to discriminate the adulterants of S. asoca. Further, a study was undertaken to estimate the genetic and phytochemical diversity of S. asoca in Western Ghats and to identify markers for the differentiation of S.asoca from common adulterants / substituents. Samples from 106 S. asoca plants were collected from 11 populations/locations in the Western Ghats. DNA fingerprinting was carried out employing Inter Simple Sequence Repeat (ISSR) and Random Amplified Polymorphic DNA (RAPD) markers. A novel time and cost-effective methodology was developed and standardized to simultaneously extract and estimate these phytochemicals by HPLC method. Phylogenetic analysis with ISSR and ITS region coupled with HPLC analysis was found to be effective in differentiating S. asoca from common adulterants viz., Polyalthia longifolia, Shorea robusta, Mesua ferrea, Trema orientalis and Bauhinia variegata). It was also found to be useful in detection of adulteration in crude powdered drug samples.

Formulation of thermo-reversible gel of cranberry juice concentrate: Evaluation, biocompatibility studies and its antimicrobial activity against periodontal pathogens

The efficacy of thermo-reversible gel of cranberry juice concentrate (CJC) as local drug delivery for the treatment of periodontitis was investigated. CJC was tested for its antimicrobial activities against the panel of organisms responsible for periapical and periodontal infections. Influence of CJC on periodonto pathogen PG derived virulence factors (fimA and kgp) was studied using real time polymerase chain reaction (RT-PCR) technique wherein down regulation of selected genes demonstrated inhibitory effect against PG virulence factors. Thermoreversible gel of CJC was formulated by cold method using poloxamer 407 as thermosensitive polymer and carbopol 934 as mucoadhesive polymer the formulated thermoreversible gel of CJC could serve as a novel herbal alternative to currently available periodontal treatment modalities.

Preclinical evaluation of safety and efficacy of the decoction of the plant RMRC-BM IP_156 for anti-diabetic activity and characterization of active compound(s)

Herbals are paving way for development of valuable new medicines for humankind, especially for chronic and lifestyle conditions. Recently, World Health Organization Expert Committee on diabetes recommended that traditional medicinal herbs be further investigated for better management of diabetes. In the present study, one such identified traditional practice (decoction of leaves) for the management of diabetic mellitus was investigated.

Acute toxicity study carried out as per OECD guidelines revealed that the decoction is safe with median lethal dose (LD50) more than 5000 mg/kg body weight. The decoction did not decrease the fasting glucose level of the normoglycemic rats after 2 hours, indicating that decoction does not cause hypoglycemia in normal rats. In oral glucose tolerance test (OGTT) the decoction at 2X and 4X doses was found effective in reducing blood glucose level by 2 hours after treatment. Blood

glucose levels were increased in all groups due to oral glucose administration. Glucose levels were reduced when compare to diabetic control after 30 and 90 minutes at the doses of 34.2 (x/2) and 136.8 (2x) mg/kg. Overall, reduction of blood glucose at the highest dose of decoction i.e., 273.6 (4x) mg/kg is comparable with standard drug glibenclamide after 180 minutes.

Validation of *Kunapajala* and *Panchagavya* and their evaluation on cultivation aspects and phytoconstituents of *Ashwagandha* (*Withania somnifera* Dunal) and *Kalamegha* (*Andrographis paniculata* Nees.)

Vrikshayurveda deals with treatment of plants. Kunapa jala (KJ) and Panchagavya (PG) are two such prescriptions recommended in Vrikshayurveda for stimulating growth and development of plants. The present work has been carried out to evaluate the efficacy of these preparations on two of the important medicinal plants, viz. Ashwagandha (Withania somnifera Dunal) and Kalamegha (Andrographis paniculata Nees.). The results showed that in both the plants, the groups with KJ and PG treatment have better morphological features like height, number of leaves per plants and number of branches per plant, when compared to control and standard (NPK and Vermicompost treated groups). The test groups also exhibited better yield, both quantitywise and quality-wise. The study also resulted in development of HPLC methods for simultaneous detection and quantification of steroidal lactones viz. Withaferin A, Withanolide A and Withanolide B in Withania somnifera and diterpenoids viz. Andrographolide (A1), Neoandrographolide (A2) and 14-deoxy-11,12-didehydroandrographolide (A3) in Andrographis paniculata.

Micropropagation of *Curcuma pseudomontana* and *Iphigenia stellata*: Endangered Medicinal Plants from Western Ghats

Present study is an effort to conserve two endangered species, *viz. Curcuma pseudomontana* and *Iphigenia stellata*, which are having potential medicinal values and are extensively used in traditional medicine. These plants are also known for their active components such as curminoids and colchicine respectively. The mother plants of *Curcuma pseudomontana* were collected from the forests of Amboli-Maharashtra. The protocol was developed for micropropagation of the plants from its rhizome buds. The extraction of Curcumin from rhizomes of both in vitro and in vivo grown plants for their comparison.

Evaluation of Analgesic and Anti-Inflammatory Activities of *Plumbago zeylanica* **L. Root Paste in Osteoarthritis Patients**

This study is in association with Shri BMK Ayurveda Mahavidyalaya, Belagavi. The objective of the study is to assess the clinical efficacy of *Plumbago zeylanica* L. root paste topical application, which is a well documented traditional claim, in subjects of osteoarthritis (OA). So far, 55 subjects completed the study, of which 38 were classified in to mild OA group, 13 in to moderate group as per ACR guidelines, while 4 subjects were with moderate OA, but non-responsive to corticosteroids. The parameters for Pain, WOMAC, walking velocity, tenderness, crepitus, knee circumference and range of movements indicated marked improvement in the condition when the subjects were assessed on day 0, 8, 22 and day 37. The study is in progress.

Effect of *Sauropus androgynus* leaves extract on inflammatory response in zebrafish larvae by leukocyte migration assay

Inflammation is the defense response to an injurious stimulus. However, inflammation unresolved are associated with several chronic disease. Neutrophils are first cell which rapidly recruited to damaged site and has important role in maintenance of inflammatory response. Sauropus androgynus (Euphorbiaceae) commonly called as star gooseberry is traditionally used as antiinflammatory, wound healer, analgesic, slimming agent and antihypertensive. The present study aimed to evaluate the effect of Sauropus androgynus leaves extract on inflammatory response in zebrafish larvae by leukocyte migration assay. Preliminary phytochemical investigation of extract of leaves of Sauropus androgynus revealed the presence of alkaloids, amino acids, carbohydrates, saponin glycosides, terpenoids, resins and vitamin C. Inflammation was induced by injuring the tailfin of 4 dpf (days post fertilization) larvae and were exposed to aqueous extract of Sauropus androgynus leaves (25, 8.3 and 2.5 µg/ml) for 1 h then larvae were fixed and stained with 0.16% of Sudan Black, imaged for quantifying number of neutrophils recruited at site of injury. RLM at <0.5 is considered for anti-inflammatory activity. Sodium diclofenac (10µm, 3µM and 1µM) was used as positive control. Aqueous extract of Sauropus androgynus leaves inhibited migration of leukocyte towards injury site. At concentration 25µg/ml of relative leukocyte migration (RLM) value was 0.42 as compared to RLM value 0.15 for Sodium diclofenac at 10µM. Groups exposed to the aqueous extract of Sauropus androgynus leaves (25µg, 8.3 µg and 2.5µg/ml) showed significant (p<0.05) inhibition of leukocyte migration towards injury as compared to normal control group. At concentration 25µg/ml of aqueous extract of Sauropus androgynus leaves has showed 58% of anti-inflammatory activity, while Sodium diclofenac (10µM) has showed 85 % of anti-inflammatory activity. (Table 1). Aqueous extract of Sauropus androgynus leaves significantly (p<0.05) decreased the number of neutrophil migrated to the site of injury at all concentration is 0.42, 0.46, 0.67 at 25, 8.3 and 2.5 µg/ml respectively and it is comparable to that of Sodium diclofenac which has 0.15, 0.21, 0.29 at 10µm, 3µM and 1µM respectively. It is concluded by the observation of present study that aqueous extract of Sauropus androgynus leaves exhibits anti-inflammatory activity through modulation of leukocyte migration/recruitment at site of injury.

Table 1: % of Anti inflammatory activity



Effect of *Sauropus androgynus* leaves extract on metabolic rate and lipid accumulation in zebrafish larvae

Obesity is a chronic metabolic disorder which is a major risk factor for diabetes and cardiovascular disease. Obesity is a result of imbalance between calories intake and expenditure which leads to fat accumulation. Sauropus androgynus is claimed and is in folklore use for the treatment of obesity. Presence study is aimed to investigate the effect of Sauropus androgynus leaves extract on metabolic rate & lipid metabolism in zebrafish larvae. Zebrafish larvae of 72 hpf exposed to aqueous extract of Sauropus androgynus SAAE (25, 8.3 and 2.5 µg/ ml) for 1hr and quantified by following previously published/ standardized protocol for metabolic rate by reading absorption at 570nm measured at 10min interval for 1hr. zebrafish larvae 5dpf were exposed to SAAE (25, 8.3 and 2.5 µg/ml) for 24hr and larvae fixed, stained with 0.5% Oil O red and imaged for quantifying lipid accumulation. SAAE significantly increases metabolic rate decreases lipid accumulation in zebrafish larvae as compared to normal control. The observations of present study revealed that SAAE increases metabolic rate and decreases in lipid accumulation, supporting the possible anti-obesity effect.



Fig. 7: Representative Photographs of SAAE effect on lipid accumulation in zebrafish larvae. 48hr HFD fed larvae exposed to SAAE for 24hr at different concentration 25µg/ml (A), 8.3µg/ml (B) &2.5µg/ml (C).

Preclinical Toxicological Evaluation of *Sauropus androgynus* leaves extract in Zebrafish.

Sauropus androgynus is a shrubby plant belonging to Phyllanthaceae family. In India, the plant is widely used by various tribes as food and medicine as well as a curative of various diseases. However, there are some adverse event reported eliciting the safety concern. The SA leaves were subjected for extraction (decoction) with distilled water. OECD guidelines 236 were followed to determine MNLC and LC_{10} , LC_{50} of the extract which were further used for cardiotoxicity studies. For cardiotoxicity

studies, the 72hpf zebrafish larvae were exposed to aqueous extract (SAAE) (68.03, 25, 2.50 and 8.30 µg/ml) and heart rate and pericardial edema were assessed after 4 hrs and 24 hrs exposure respectively. For developmental toxicity study, zebrafish larvae were evaluated for viability and morphological anomalies using a score system and teratogenic index (LC₂₅/NOAEL) was determined after 120 hrs of exposure to concentration ranging from 25 to $1000 \mu g/ml$. The LC₁₀, LC₅₀ and MNLC were found to be 68.03 µg/ml, L255.71 µg/ml and 25µg/ml respectively. SAAE (25, 2.5 and 8.3 µg/ml) did not cause any change in heart rate. However, at high dose i.e., 68.03 μ g/ml caused significant (p<0.05) increase in the heart rate. The teratogenic index of the extract LC_{25} /NOAEL was found to be less than 10. Hence, it may be non-teratogenic at the tested dose. However, at high doses it may be teratogenic as LC_{50} /NOAEL values were estimated as 13.



Fig. 8: Microphotographs of morphological changes of 5-dpf zebrafish larvae after exposure of aqueous extract of *Sauropus androgynus* leaves for 120 hrs. (n=12 zebrafish larvae per treatment). A: Control, S1: SAAE (25 μ g/ml), S2: SAAE (50 μ g/ml), S3: SAAE (100 μ g/ml), S4: SAAE (200 μ g/ml), S5: SAAE (400 μ g/ml), S6: SAAE (600 μ g/ml), S7: SAAE (800 μ g/ml), S8: SAAE (1000 μ g/ml).

PUBLIC HEALTH IMPORTANCE

- Development of HPLC methods for simultaneous detection and quantification of steroidallactonesviz. WithaferinA, Withanolide A and Withanolide B in *Withania somnifera* and diterpenoids viz. Andrographolide (A1), Neoandrographolide (A2) and 14-deoxy-11,12-didehydroandrographolide (A3) in *Andrographis paniculata*.
- Taking two of the traditional practices (One each for management of Osteoarthritis

and Dengue) in to clinical evaluation in translational mode.

The reporting of an upsurge in cases of diphtheria in North Karnataka, particularly in Vijayapura District, with the report of the emergence of penicillin resistance for the first time in India. A policy brief for prevention of deaths and reduction of cases has been submitted through ICMR to the Govt of Karnataka on 15th Aug 2017.

EXTRAMURAL RESEARCH

The study on Integration of in silico and biossav techniques for the identification of novel inhibitors against mycobacterial L, D-Transpeptidases at Amrita Institute of Medical Sciences, Kochi, with the aim to identify novel inhibitors for microbial activity using computational techniques to repurpose an FDA approved drug, C-1 compound for anti-microbial therapy. It was demonstrated that the C-1 can also bind/inhibit bacterial L,Dtranspeptidase activity and therefore it can be used to inhibit nonclassical cell wall cross-linking. It was found that a combination of C-1 compound, beta-lactams, betalactamase inhibitors and other suitable antibiotics demonstrates superior in vitro anti-microbial activity.



Fig. 9: SEM images of M. marinum grown in the presence of Augmentin and C-1 . M. marinum grown without any drugs (A), with Augmentin (8 μ g/ml) (B), C-1 (500 μ g/ml) (C), Augmentin (8 μ g/ml) - C-1(500 μ g/ml) combination (D), C-1 added 24 hrs after Augmentin (8 μ g/ml) (E), Augmentin (8 μ g/ml) added 24 hrs after C-1 (500 μ g/ml) (F).

Till date, there is no effective vaccine or cure for HIV-1. Majority of the HIV-1 viruses infecting Indian patients belong to subtype C. A study on Generation of human Recombinant scFv phage library was carried out at Dept. of Biochemistry, AIIMS, Delhi with the aim to generate human recombinant scFv monoclonals. First time
successfully generated a human recombinant scFv phage library from nine HIV-1 subtype C chronically infected antiretroviral naïve children. From this library, the institute identified two binding-site HIV-1 anti-CD4 specific scFv monoclonals. Among these scFvs, the study found 2B10 as a cross-neutralizing CD4bs directed scFv monoclonal with reasonable breadth and potency, demonstrating neutralizing activity against tier 1, 2 and 3 viruses, including viruses of both adult pediatric origins. Such anti-HIV-1 human scFvs, are potential candidates for conferring passive protection. Moreover, combination of scFvs with antiretroviral drugs can be an effective strategy to suppress viremia at an early stage and thus block HIV-1 infection in children, mainly acquiring infection by vertical transmission.

The broadly neutralizing scFv monoclonals may be used in passive immunotherapy in combination with ART therapy. The human broadly neutralizing scFv monolconals may be of potential use for passive immunotherapy. This may provide important information on subtype C virus specific epitopes for designing an HIV-1 vaccine that can induce neutralizing antibodies.

Dyslexia also has complex, multifactorial genetic etiology like other neurodevelopmental disorders. The study held at National Brain Research Centre, Manesar was aimed at identifying genetic loci and validates risk loci for dyslexia risk/causality through next generation sequencing methods in selected individuals from a multigenerational family of Parsi ethnicity. In this study, co-segregation of two genomic locus encoding neural adhesion proteins like protocadherin gamma, protocadherin 1 and contactin 6, together with dyslexia was identified. Every affected individuals with dyslexia had at least one copy of risk haplotype from each locus. Thus, probably co-inheritance of these two loci together contributes to develop dyslexia characteristics because this kind of complex phenotype often develops with the cumulative effect of multiple genetic loci. Neural adhesion proteins play key role to establish neural connection in the brain. The results reinforce the hypothesis of aberrant neuronal connectivity in the pathophysiology of dyslexia. Additionally the striking conservation of the variations segregating with dyslexia indicates a potential role proto-cadherin gamma gene cluster towards the evolution of human specific cognitive skill specific to reading.

The project 'Development of nanotechnology based drug delivery system for lipid lowering drugs' at Manipal University, establishes that the model lipid lowering drug, rosuvastatin can be produced as nanoformulation using chitosan and hyaluronic acid to treat atherosclerosis more effectively. From the pharmacodynamic study, which was done in male Wistar rats by the tyloxapol-induced hypercholesterolemia method, it was observed that rosuvastatin nanoparticles were able to reduce the serum cholesterol as well as triglyceride levels much more than the standard treatment.

PHARMACOLOGY

A study on development of natural alternatives to synthetic Dipeptidyl peptidase IV inhibitors for Diabetes with Metabolic Syndrome at Dept of Pharmacology, MGM Medical College, Kamothe, Navi Mumbai with the following objectives: To develop an animal model of diabetes mellitus co-existing with metabolic syndrome using a combination of high fat diet and low dose streptozotocin; To study the cardiac effects of natural Dipeptidyl peptidase (DPP-4) Inhibitors (Berberine, Mangiferin) alone and in combination with metformin in diabetic rats with metabolic syndrome; To evaluate the metabolic effects of natural DPP-4 inhibitors alone and in combination with metformin in diabetic rats with metabolic syndrome. To elucidate the mechanisms of cardiometabolic effects of Mangiferin and Berberine alone and in combination with Metformin; To compare the cardio-metabolic efficacy of natural DPP-4 inhibitors Vs Metformin, Vildagliptin monotherapy and Metformin + Vildagliptin combination therapy and to evaluate the safety of the test drugs in the experimental model of diabetes with metabolic syndrome.



Fig. 10: Representative photographs demonstrating the histopathological changes of pancreatic tissue in diabetes coexisting with metabolic syndrome. **1A: Normal control (NC):** The NC group rats pancreas were characterized by an organized pattern and showed normal architecture of beta cell mass; **1B: High Fat Diabetic control (HF-DC):** The HF-DC group rat pancreas showed damaged islets of langerhans and the atrophy of beta cells and reduced beta cell mass. The arrow showed beta cell mass. Scale bar = 100 m.



Fig. 11: Representative photomicrographs of pancreatic tissue section stained for immunohistochemistry for insulin localization. 2A: Normal control (NC): Imunohistochemistry of NC group pancreas showed increased localization of Insulin 2B: High Fat Diabetic control (HF-DC): The HF-DC group showed decreased insulin localization and hence loss of beta cell functions. Arrow indicates immunohistochemical localization of insulin.

The results showed that the DPP-IV Inhibitory activity of Berberine and Mangiferin was comparable to synthetic marketed DPP-IV Inhibitors; Vildagliptin and Sitagliptin. The highlight of the study is that the cardiometabolic efficacy of Mangiferin and Metformin combination therapy was found to be comparable to Vildagliptin and Metformin combination therapy.

A study on regulatory effect of cinnamaldehyde in skeletal muscle atrophy was carried out at Department of Biochemistry, Kurukshetra University, Haryana. The following were two specific aims: I. Investigate the effect of CNA in TNF-a mediated skeletal muscle atrophy in cell line. Hypothesis 1: TNF-a, a proinflammatory cytokine, causes muscle atrophy and fiber-type switching by activating NF-kB transcription factor while CNA

with its opposite effect on NF-kB activation might inhibit skeletal muscle atrophy. II. Investigate the regulatory check of CNA in H2O2 induced skeletal muscle atrophy in cell line. Hypothesis 2: H2O2 generates reactive oxygen species in biological system which imbalance the oxidant and antioxidant system of the cell and causes muscle loss while CNA with its opposite effect on oxidant and antioxidant imbalance might inhibit skeletal muscle atrophy. This is the first study to determine comparative effect of CNA and its derivatives and simultaneously their effect on C2C12 myoblasts as myotubes under normal and stress condition. Being cinnamaldehyde as a parent compound, seven more derivatives were synthesized .All the compounds were initially tested for their antioxidant potency by different in vitro methods. 2BzCNA and 2MeCNA come to be two potential candidates with comparable anit-atrophic effects.

MEDICINAL PLANTS & TRADITIONAL MEDICINE

A study on assessing the anti-HIV properties of some novel mannose-binding lectins (mbls) from Indian subcontinent was conducted at Dept. of Immunopatholgy, PGIMER. Chandigarh with the aim to check the anti-HIV properties of some of the novel mannose-binding lectins (MBLs) isolated by many laboratories throughout the India. The study demonstrated that the HIV-1 Env has glycan patterns diverse in nature among different viruses. These heterogeneous glycans are responsible for the differential sensitivity of the viruses to lectins, which are being explored extensively for the development of anti-HIV microbicides. Further, not only the DC-SIGN-HIV interaction is regulated and determined, but also the inhibition of the DC-SIGN mediated HIV infection by lectins is determined by the relative glycan composition of the virus. These findings may have far reaching implications for the better design and selection of anti-HIV-1 lectins besides helping in understanding the relative glycan heterogeneity among different HIV-1 strains.

PUBLIC HEALTH IMPORTANCE

National Guidelines for Stem Cell Research - 2017

The field of stem cell is ever evolving with everyday developments leading to newer processes and products. In addition to such developments across the globe, ICMR received several representations, complaints and suggestions from different stakeholders. These factors led to the revision of the guidelines that were released on 11th October 2017 by MoHFW. 2017 document was an attempt to harmonize all the existing guidelines, acts and rules. The efforts resulted in comprehensive revised guidelines which are one stop guidance document for all the stakeholders defining status of stem cell treatments that are safe and have

proven efficacy, providing directions to scientists, clinicians and industry working in the field, on necessary regulatory requirements. And an effort to curb unethical practices rampant in the country.

ICMR jointly with CDSA (DBT) initiated dissemination of NGSCR-2017 through organising public consultations inviting all the stakeholders to educate them regarding the existing guidelines and regulatory framework. Five such meetings were held at Ahmadabad, Vishakhapatnam, Chennai, Kochi and Guwahati.

ICMR has also developed Frequently Asked Questions (FAQs) for stem cell research displayed on ICMR and NACSCRT websites, for the education and awareness of general public.

REGIONAL MEDICAL RESEARCH CENTRES

o deal with health problems of the regional and marginalised population, ICMR has established a total of 4 Regional Medical Research Centres at Port Blair (Andaman Nicobar), Bhubaneswar (Odisha), Jodhpur (Rajasthan), and Dibrugarh (Assam). The effort of these institutes is to focus on the regional health problems and find suitable solutions with the help from the respective state governments. The significant outcome of the research activities carried out by these centres during 2017-18 is mentioned below.

REGIONAL MEDICAL RESEARCH CENTRE, BHUBANESWAR

RMRC, Bhubaneswar was established in 1981 under the 6th five-year plan period to undertake research activities in both communicable and non-communicable diseases, human resource development programme and in establishing strong linkage with State Health Department in finding solutions to the regional health problem. The centre in the past three decades has worked effectively towards identifying regional health problems and contributed significantly in evaluation & implementation of government health programme & policies. During the period 2017-18, the centre has undertaken several projects and worked actively in the field of public health and biomedical research.

STRENGTHENING OF HEALTH RESEARCH CAPACITY

The centre as part of its mandate is actively involved in developing a sustainable health research

capacity of the region through various academic courses, training & internship programmes. In the year 2017-18, a total of 4 MD students carried out their thesis work, 39 M.Sc dissertation students and 8 Pre-PhD students undergone their course work and 12 PhD students are carrying out their studies. The centre was also actively involved as a nodal unit of ICMR for training of 16 Interns under ICMR-IIT Kharagpur-IIM Ahmedabad MedTech Internship programme, 2018. The centre as part of its capacity building programme has organised various workshop on Systematic Review & Meta-Analysis, Mixed Method Research, Research Methodology, Clinical data registry. Two workshops have been conducted during 24-26th November, 2017 and 11-13th January 2018 on Systematic Review & Meta-analysis. A workshop on Research protocol development was organised for MRUs' of various Medical colleges of Eastern and North eastern India. More than 150 participants across the country from various premier academic institutions, research organizations, medical colleges, international organizations participated in these workshops. The centre has also conducted various trainings on Laboratory diagnosis of infectious diseases for technicians to support the state government to develop a trained manpower for effective management and control of emerging infectious diseases. The scientific staff of the centre are also involved as resource person for training at various national and international level workshops.

EVIDENCE TO POLICY TRANSLATION

The centre has over the years undertaken several projects with E2P translation.

VIROLOGY RESEARCH AND DIAGNOSTIC LABORATORY

The centre has been upgraded to Regional Laboratory for Virology research and diagnostics and catering service to Chhattisgarh and Andhra Pradesh in addition to Odisha.

- The centre is rendering diagnostic services to the referral cases from various medical colleges, tertiary hospitals, and IDSP.
- The unit is also investigating the various outbreak of viral aetiology.
- Diagnostic facility was provided to more than 38,000 patients suspected of viral illness admitted to different secondary/ tertiary care hospitals of the state.
- The observations on clinical presentation and viral agent identification improved the clinical diagnosis by the physicians of the region through information sharing and publications.
- One of the major findings showed HSV I and II as commonest viral agent for AES which prompted use of antivirals in management of suspected AES cases reducing morbidity and mortality.
- Likewise among cases of febrile rash, identification of specific agents like Entero viruses (HFMD), Varicella, Parvo, Measles etc could provide proper direction to case management.
- Besides above typing of virus in acute/ chronic hepatitis, HPV in STI, viral agents (Rota major around 30%, others Adeno, Astro) contributing to diarrhea, severe respiratory infections in children and adults (including H1N1), unexplained anaemia and lymphadenopathy etc. were covered.
- Pandemic H1N1 2009, Dengue all serotypes (Genotype III of serotype 1 & 3, Genotype IV of serotype 2), Measles genotype D8, HEV genotype 1A, Chik genotype ECSA etc. were identified both from human and/or vectors.

- This lab is also providing technical support to medical colleges, public health labs in different districts of the state and outside state (Andhra Pradesh, Chhattisgarh). Quality control has also been initiated with these labs.
- Part of laboratory network for enhancing diagnostic capabilities for surveillance, outbreaks and epidemics investigations of high-risk group of viral pathogens causing viral hemorrhagic Fevers.

OUTBREAK INVESTIGATION

The centre supported both field and laboratory investigation for management of outbreak due to pandemic H1N1, ChikV, Dengue, JE, Chandipura, Measles, Rubella, Chicken Pox and Hepatitis A, E reported in the region by immediate diagnosis and recommendation for control, within minimum turnaround time. The reports were provided to respective authority within 6-24 hours in emergency/outbreak situations. During 2017-18 around 40 outbreaks were investigated for jaundice, chickenpox, AES/JE, Dengue and Measles.

TUBERCULOSIS

The centre is working actively towards the countries vision for a TB free India by 2025.

- The National Reference Laboratory of Tuberculosis and is catering services to 10 states of the country including 8 NE states. The NRL laboratory is in the final stage of NABL accreditation.
- RMRC, Bhubaneswar is also carrying out several land mark studies which includes Targeted Intervention to Expand and Strengthen TB Control in Tribal Populations under the Revised National Tuberculosis Control Programme, India (The TIE-TB Project).
- Effectiveness of Food supplementation on Treatment Outcomes and Nutritional status of Adults with Pulmonary Tuberculosis in Odisha.

NUTRITION AND NON-COMMUNICABLE DISEASES

- A longitudinal study is being undertaken to assess the serum/plasma micronutrient level, thyroid profile and urinary iodine level of pregnant women during first, second and third trimester as well as at the time of delivery, at 6 months and at one year after delivery and also to assess the newborns for birth weight and growth up to one year of age and to estimate the iodine content in edible salt samples collected from household of study volunteers.
- Prevalence of fluorosis in the community of Nayagarh districts of Odisha is also being studied to develop an appropriate intervention model for prevention and control of fluorosis in this district.
- Development of district level model to address under nutrition and hidden hunger.
- Carried out cluster randomized controlled trial on effectiveness of diet and lifestyle intervention through Information Education Communication (IEC) tools with Angan Wadi Centres (AWCs) as the centre of knowledge dissemination for hypertension (including hypercholesterolemia) and diabetes risk reduction.

ZOONOTIC DISEASES

• Anthrax: Knowledge Attitude Practice (KAP) analysis study on Anthrax was carried out in 4 most effected indigenous population dominated district of Odisha. The study involved household survey, FGDs, IDIs of the stakeholders. About 48% of respondents were unaware about mode of transmission of Anthrax. The study identified as butchering and deskinning of dead animal as a major cause of Anthrax spread. Awareness among the respondents, Interdepartmental coordination and a proper vaccination programme were identified as main roadblocks in control & management of Anthrax in these districts. • Scrub typhus: A study on epidemiology of *Scrub typhus* carried out by the centre identified a prevalence of 43.1% among suspected cases, with eschar, as the most prevalent pathognomonic sign.

VECTOR BORNE DISEASES

- Japanese Encephalitis: Post the AES/ JE outbreak investigated and confirmed by RMRC, Bhubaneswar in the tribal district of Malkangiri, the JE vaccine was administered in 12 districts of the state. Currently the centre is undertaking a study on Japanese Encephalitis Virus (JEV) Infection associated Acute Encephalitis in Malkangiri District: Pre & Post Vaccination Period.
- **Dengue:** A multi-centric study to estimate the age-specific sero-prevalence of dengue virus infection in India was also carried out in 4 districts of Odisha, in which more than 1000 individuals were enrolled in the study.
- Malaria
 - a) Prevalence of asymptomatic malaria infection below 5 years and mode of transmission in Kandhamal district of Odisha is being studied to determine the prevalence of asymptomatic Plasmodium infection below 5-year children in Kandhamal district of Odisha and the per man hour density and transmission potential of vectors of the study area. A total of six blocks of the district were surveyed and slides were collected from children below 5 years of age for Rapid diagnostic test.

Bionomics of malaria vectors and their sibling species, and establish their role in malaria transmission in Odisha, India

- b) The centre is also involved in vector mapping in high endemic districts of Odisha.
- c) Phase III evaluation of Deltamethrin 62.5 SC-PE long lasting indoor residual

spraying against *An. fluviatilis* and *An. culicifacies*, the vectors of malaria, is being carried out in Koraput and Kalahandi districts of Odisha

 d) Zika: The centre is a part of the ICMR's multi centric project on Vector surveillance for Zika/JEV in selected high risk areas in India.

MATERNAL & CHILD HEALTH

A task force study on feasibility of using two simple tools for improving documentation during childbirth in peripheral health facilities is being currently undertaken by the centre, which aims to improve the documentation on maternal case sheet and still birth case sheet by introduction of this simple and concise case sheets. Under this project, two innovative tools (maternity case sheet and still birth sheet) have been introduced in the labour rooms of five health facilities in the tribal district of Kalahandi, Odisha. Five facilities of Kalahandi district (1 DHH, 1 SDH and 3 CHCs) are the intervention sites; whereas five similar facilities of Kandhamal district (another tribal district of Odisha) are control district.

TECHNOLOGY ENABLED SOLUTIONS

- Dual Combo refrigerator for vaccine cold chain management in rural remote areas is being developed in collaboration of Dept. Of Biomedical Engineering, IIT, Kharapur.
- Development of partograph & auto interpretation using android based software application is being undertaken by the centre.

DIARRHOEAL DISEASE AND ANTIBIOTIC RESISTANCE

A study is being carried out to identify the environmental reservoirs of *V.cholerae* sero groups from environmental water sources of Kalahandi and Rayagada districts of Odisha. Laboratory surveillance system for Antimicrobial resistance (LSSAMR) unit of the centre has also been set up. Two studies on bacterial aetiology of childhood diarrhoea and prevalence of *Salmonella ent*erica serotype Typhi and Paratyphi among enteric fever cases were undertaken by the unit to collect the baseline data of antibiotic resistance among bacterial pathogens.

SUPPORTING PROGRAMME IMPLEMENTATION THROUGH RESEARCH

The centre is involved in various projects on evaluation of government programme and policies. Mid-day Meal programme evaluation is being carried out with support of Dept. of School & Mass Education, Govt. of India. The centre is also involved in health impact assessment of Pradhan Mantri Ujjwala Yojna (PMUY). The centre has been designated as apex laboratory for JE diagnosis by the state government and have been supporting the various programmes of NVBDCP, IDSP and implementation of RNTCP. The Health Technology Assessment of a neonatal hearing impairment device, SOHUM is being carried out prior to its introduction into RBSK. The centre has 2 field units in tribal dominated districts of Rayagada & Kalahandi, an outpatient facility which is attending patients and dispensing free drugs and a Model Rural Health Research unit in Tigiria and is currently developing a cohort population (including rural, urban & tribal) for various studies and intervention for improving the health condition.

ORGANISED DATA SYSTEMS AND PLATFORMS FOR RESEARCH

The library of the centre has been upgraded to National Information Centre for Public Health Research. The library of the centre acting as knowledge resource centre and catering service to various medical colleges, hospitals, academic and research institution. The centre has been undertaken various projects on documenting the health profile of Primitive Vulnerable tribal group of the state. The centre is also working on developing human resource for Public Health informatics. A rare disease registry is also being developed by the centre.







Field unit in Rayagada

Out-patient facility Model Rural Health Research unit, Tigiria

Fig. 1: Units Of RMRC.



Fig. 2: Outbreak investigations.



Interview of Anganwadi worker



IDI with DFO, Koraput



FGD In Sundargarh



FGD in a village in Rayagada

Wauld TD Jac. 2010

World TB day, 2018

Fig. 3: Field studies.



Rashtriya Ekta Diwas, October 2017





Awareness on handwash on Global Handwash day



International day for Yoga, 2018



World Mental Health Day, October 2017

Fig. 5: Awareness Programme.



MedTech Internship programme, 2018



Research Protocol development for MRUs



Workshop on Systematic review and metanalysis

Fig. 6: Strengthening of Health Research Capacity.



REGIONAL MEDICAL RESEARCH CENTRE, DIBRUGARH

ONCOLOGY

Study of risk factors of hepatocellular carcinoma (HCC) in Sikkim and Arunachal Pradesh

Alcohol consumption, especially 'sai-mod', higher consumption of red meat, processed meat, and processed fish were found to be significantly associated with increased HCC risk, whereas consumption of fresh fish, milk, fresh fruit were found to be protective in nature. Positive synergism index was observed between hepatitis B virus and alcohol consumption for risk of HCC. Homozygous variant of ADH was found significantly associated with HCC risk. Statistically significant upregulated gene expression was observed for IL10, EGR3, ING4, and CTLA4.

Study of the pattern of survival and quality of life of the oesophageal & stomach cancer patients in North Eastern Region of India

This study revealed that the median age at diagnosis of oesophageal and stomach cancer patients was 58 and 55 years respectively. The survival time of the oesophageal and stomach cancer patients was 12 months and 10 months respectively.

Germline mutation spectra of *BRCA1* and *BRCA2* genes in multi-ethnic breast cancer patients from N.E. region based on direct sequencing

Screening of germline mutations in BRCA1 tumour suppressor genes in 282 patients from Assam, Tripura, Mizoram and Nagaland was determined by High Resolution Melting (HRM) Analysis (**Figure-1**). Blood samples from Mizoram shows highest germline mutation within BRCA1 exons [Ex- 3, 5, 7, 10, 11.2, 11.5, 12, 18, 19 & 22] followed by Assam [Ex- 2, 6, 8, 9, 11.4, 21 & 23], Nagaland [Ex- 11.1, 11.3, 13, 14 & 16] and Tripura [Ex- 15, 17, 23 & 24].Cluster analysis revealed similarities in pattern of mutation in different BRCA1 exons in patients from Mizoram and Nagaland. Assam occupies the intermediate position while Tripura clustered separately as compared to other states [Assam, Mizoram & Nagaland].On the other hand, HRM data analysis of BRCA2 genes shows that Mizoram has maximum percent of mutated breast cancer samples (8.6 %) followed by samples from Tripura (6.2%) and Assam (5.8). Overall percentage of mutation in BRCA1 (N=282) is higher than that of BRCA2 (N=282) i.e. 11.8% and 7.1% respectively. To conclude confirmation of mutation found in BRCA 1 & 2 genes detected by HRM analysis method is being done by Sanger sequencing and is under progress. Further presence of mutation in BRCA 1 & 2 genes in few samples from all the four states will be done using NGS plate form.

Study on molecular epidemiology and risk factors of gastric cancers in Tripura and Nagaland

Betel nut chewing, local drinks consumption and tobacco chewing has been found to be significantly associated with increased risk of stomach cancer in Tripura and Nagaland. Polymorphisms in GSTM1 and TNF alpha gene have been found to be associated with increased risk of gastric cancer. Following tumor suppressor genes showed mutations: *APC*, *CDKN2A*, *TP53*, *CDH1*, *CTNNB1*, *FBXW7*. Following Proto-oncogenes showed mutations: *BRAF*, *ERBB2*, *HRAS*, *KRAS*, *NRAS*, *PIK3CA* and *PDGFRA*. Detection of mutation spectra in key tumor suppressor and proto-oncogenes have shown that there are population specific mutation patterns in gastric cancer cases from Tripura and Nagaland.

Newly initiated project

Screening & early detection of oral, breast & cervical cancers in Dibrugarh District (Assam): A demonstration project in TATA Tea gardens.

HAEMATOLOGY

Micro mapping of G6PD deficiency among the tribals of India and its importance for antimalarial therapy

So far, total of 1343 tribal individuals (Males: 338; Females: 1005), belonging to Deori, Mising,

Kachari tribes, were screened. It was found that 52 (3.87%) individuals had G-6-PD deficiency, 9 (0.67%) had intermediate G-6-PD levels and 1282 (95.46%) had normal G-6-PD levels. All the individuals with intermediate G-6-PD levels were females while among the G-6-PD deficient individuals, 31 were males and 21 were females.

Establishment of Prenatal Diagnosis of β-Thalassemia Syndromes and Sickle Cell Disorders in Madhya Pradesh, Assam and the Andaman and Nicobar Islands

So far, 461 pregnant women were screened. Sickle cell trait was found in 18 (3.9%), HbE disease in 21 (4.6%), and HbE trait in 104 (22.6%) women. β -thalassemia heterozygous was confirmed in 3 (0.65%) women, all having IVS 1 – 5 mutations, whereas 18 (3.9%) women had HPLC-based evidence of β -thalassemia heterozygous. One woman had hereditary persistence of foetal haemoglobin.

CARDIOVASCULAR DISEASES

Effectiveness of diet and lifestyle intervention through IEC tools with angan wadi centres as the centre of knowledge dissemination for hypertension (including hypercholesterolemia and diabetes) risk reduction - a cluster randomized controlled trial

So far, all the clusters have been resurveyed and the updated data was sent to the co-ordinating centre (CCDC), New Delhi.

Health system preparedness for interventions for diabetes, hypertension, chronic respiratory diseases and cardiovascular disease and deaths due to non- communicable diseases (NCD) among the tribal population in India

It was observed that non-communicable diseases accounted for more than half of the deaths in Meghalaya (67%) and Assam (66%) and for more than three fourth of the deaths (79%) in Nagaland.

MOSQUITO AND MOAQUITO BORNE DISEASES

Malaria Evolution in South Asia (South Asia-ICEMR)

The current study shows a significant reduction in malaria cases in the study area following intensive surveillance and treatment activities. The high load of asymptomatic cases also indicates the importance of active case surveillance to detect and control the hidden reservoirs of infection.

Novel malaria surveillance system along international borders to North- east India using mobile platforms (MoSQuIT)

Deployment in Tripura and Assam was carried out during the year. The President's Award in the category of ICT for Social development awarded to C-DAC, Pune for development of the MoSQuIT app in collaboration with ICMR by the Open Group in Bangalore.

A pilot study to understand the malaria situation among Jhum cultivators in the state of Tripura and impacts of vector control measures on malaria transmission

In this study, Jhum related and other risk factors for malaria specific to this eco-demographic area were found. The physical verification of bednet use has revealed satisfactory coverage but very poor condition with several holes and improper drying and washing of LLINs. A mixed compliance to repellent use and achievement of betterment with constant IEC was observed. Entomological collection using CDC Trap in a Jhum hut of Tripuri Tribe of Dhalai, Tripura was carried out.

Role of T cell exhaustion in conferring protection against cerebral malaria following *T. gondii* and *P. berghei* co-infection

This study showed differences in proportion of T cell subsets and their phenotypic expression of exhaustion markers or inhibitory receptors in *T. gondii* and *P. berghei* co-infected mice that might be conferring protection against the *Plasmodium* mediated neuropathogenesis during chronic *T. gondii* infection in experimental mouse model.

Surveillance of Chikungunya virus activity in Assam and Meghalaya

During the study period, clinical samples from fever cases and JE, Dengue negative AES cases from

Assam and Meghalaya revealed 6.62% (44/664) and 17.66% (119/674) positivity from the two states respectively. Phylogenetic analysis revealed that the Chikungunya virus genotype circulating in this region is East, Central, South African genotype (ECSA).

Effectiveness of single dose of live attenuated SA 14-14-2 vaccine against Japanese encephalitis (JE) in adults over a period of three years in two districts of Assam, India

The effectiveness of the single dose vaccine was found to gradually decline in Dibrugarh from 92% in 2014 (year of vaccination) to 81%, 77% and 71% in the subsequent years 2015, 2016 and 2017 respectively. In Sivasagar, vaccine effectiveness during the first year following vaccination was found to be 90% in 2012, followed by a fall in effectiveness to 82% in 2013. A second round of mass adult vaccination was undertaken in Sivasagar during the year 2014 following which the vaccine effectiveness went up to 84% during the year. However, the downward slide of vaccine effectiveness continued in the subsequent years as follows - 75% in 2015, 74% in 2016 and 68% in 2017.

A study on the bionomics of the potential vector species of JE virus transmission in Assam

The study revealed *Culex vishnui* as the most predominant species (32.13%). Of the 1124 pools screened for vector incrimination study, one pool of *An. hyrcanus*, three pools of *Cx. tritaeniorhyncus*, two pools of *Cx. vishnui* and two pools of *Cx. pseudovishnui* were found to harbour JEV.

Adenoviral Vector based diagnostics for Japanese encephalitis virus, (JEV)

In this study, synthesized peptides along with the NS1 and E2 were used as template to design a peptide-based ELISA for JEV with minimum cross-reactivity. It has shown encouraging result in differentiating JE serological group virus with other flaviviral infections.

A systematic study of Acute Encephalitis Syndrome (AES) in North-eastern states of India for clinical, etiological and epidemiological aspects

During the period of study, maximum numbers of AES cases were reported during July – September. Collection of samples from AES reporting sites is in progress and entomological survey in identified endemic zones has been initiated.

Monitoring of insecticide resistance in malaria vectors in endemic states of India

It was observed that both *Anopheles minimus* and *An. baimaii* were susceptible to DDT having 100% mortality. Bioassays for *An. annularis*, *An. nivipes/ An. philippinensis* also showed 100% mortality against DDT, malathion and deltamethrin.

A multi-centric study to estimate the Seroprevalence of dengue virus infection in India

Age-specific sero-prevalence of dengue virus in three NE states of India *viz.*, Assam, Meghalaya and Tripura (total 48 clusters: 24 urban; 24 rural) has generated reliable information for the implementation of vaccination programme in the states.

Bionomics of malaria vector(s), sibling species composition and to establish their role in malaria transmission in North East Region of India

Entomological surveys were conducted in 14 different ecotypes in 4 districts of two highly malaria endemic states of North Eastern India, Meghalaya and Tripura to study the bionomics of malaria vectors.

Newly initiated project

Study on impact of climate change on seasonality and distribution of insect vector borne viral and Rickettsial diseases in North-East India: A remote sensing and geographical information system approach.

LYMPHATIC FILARIASIS

Studies on Lymphatic Filariasis

Findings from this study indicate that the non endemic tea garden is harbouring 4.3 % microfilaria rate. The prevalence of antigenemia level in school going children is over 10%. Microfilaria status after eight rounds of MDA in tea garden is over 1% mf. These findings highlight that elimination programme in Assam specially in the tea garden workers population needs attention in terms of MDA coverage and drug compliance.

VISCERAL LEISHMANIASIS

An exploratory study of Visceral Leishmaniasis in endemic areas of Assam

In this study, two animal models (mouse and hamster) have been developed/maintained for screening of new agents (plant products/synthetic compounds) for their antileishmanial properties. The immunological study indicates maneuvering of the host immune system by the parasite for its survival as is evident from record of IL23 up regulation. The study also suggests the role of TOLLIP SNP association as a risk factor for leishmaniasis.

BACTERIAL DISEASES

Study of Genetic diversity and drug resistance pattern of *Mycobacterium tuberculosis* in the tribal state of Sikkim

The study revealed that the Beijing genotype (79.04%) is the most dominant genotype circulating in Sikkim which is known to be ecologically more fit and associated with MDR tuberculosis. 24-loci MIRU-VNTR phylogenetic tree analysis of Beijing isolates of MTBC from Sikkim revealed great genetic diversity and eight major lineages were found to exist in Sikkim. The most frequently mutated codon associated with anti-tubercular drug resistance were: codon 531 TCG > TTG (S>L) [88.9%], and codon 463 CGG>CTG (R>L) [33.3%] in *katG* gene.

Epidemiology, disease burden and vectors of Rickettsial diseases in the states of Nagaland, Meghalaya and Mizoram in Northeast India

Clinical samples were subjected to serological and molecular tests to investigate the presence of rickettsial diseases *viz.*, Scrub typhus group *Orientia* (STGO), Spotted fever group rickettsiae (SFGR) and Typhus group rickettsiae (TGR). Vector collection and GIS mapping of high risks areas are in progress.

To study the virulence factor and adhesins of uropathogenic *Escherichia coli* (UPEC) isolates from pregnant women with urinary tract infections

So far, it was observed that most of the *Escherichia coli* strains isolated from pregnant women with UTI cases belong to the B2 phylo-group.

Breast milk microbiome (BMM) and neonate's gut-flora enrichment: The possible predictors for survival of pre-term-birth associated Low Birth Weight (LBW) Infant

So far, it was observed that the BMM is dominated by *Bacteroidetes*, *Staphylococcus*, *Pediococcus*, *Streptococcus*, *Enterococcus*, *Pseudomonas* and *Rothia* within the first month while in the later stage of lactation it is dominated by the genera *Micrococcus*, *Bacteroidetes*, *Clostridia*, and *Ruminococcus*.

Influence of maternal microbiome (vaginal, breast milk, cord blood and amniotic fluid) and immunogenic factors for survival, growth and immune modulation of premature neonates via gut microbiota establishment

The study has comprehensively mapped the vaginal microbiome (n=27) and has observed that the diversity of vaginal microbiome (VA) is dynamically altered in third trimester and becomes homogeneous with advancement of gestational age (GA) and becomes minimum at the onset of labour. *Lactobacillus inners* identified as keystone genera for the study population.

VIRAL DISEASES

Impact of measles rubella (MR) vaccination campaign on population immunity in India

This study was conducted in Dibrugarh using MRHRU, Chabua platform to understand the prevaccination status of measles and rubella among children. After training of the staff members by ICMR, ICMR-NIE, Chennai, WHO India, New Delhi and John Hopkins Blooming School of Public Health, Bethesda, USA field work has been initiated in selected 30 clusters and sample collection has been completed in 6 clusters.

Enhancing Biorisk mitigation awareness in public health community and creating laboratory networks for enhanced diagnostic capabilities to deal with surveillance and outbreaks of high-risk group viral pathogens causing viral hemorrhagic fevers and respiratory infections

During the period, a total of 1368 cases (ARI & SARI) were enrolled of which, 40.5% (554/1368) samples were found to be positive for respiratory viruses. Human rhino virus was the predominant virus detected.

Immune exhaustion in chronic hepatitis B and malaria: focus on γδ T cells

The study demonstrated increased expression of exhaustion markers on $\gamma\delta$ T cell subset and total T cells in chronic hepatitis B patients, suggesting their impaired functions. In case of *P. vivax* infected patients and people from the endemic region, a significantly higher percentage of $\gamma\delta$ T cells was detected.

Establishment of a network of laboratories for managing epidemics and natural calamities

So far, 12100 numbers of tests were performed. Study revealed existence of distinct circulating strains of pandemic Influenza A/H1N1 with marked genetic variations. Molecular typing of Dengue virus revealed a shift in serotype dominance from DENV-3 in 2012 to DENV- 1,2,3,4 in 2014 to DENV-1 in 2016 to DENV-1,2,3,4 in 2017. Genotype D8 of measles virus was detected during an outbreak in Arunachal Pradesh. Genotype A2b of human metapneumovirus is found circulating in this region. A higher prevalence of human rhinovirus type C compared to types A & B is observed in Assam.

Upgradation of the virology division to modular molecular Virology Lab dedicated to focus on HIV, Hepatitis and Influenza viruses in Northeast India

During the period, HBV viral load assays were provided free of costs to patients and genetic basis of hepatitis B infection was studied by looking at genetic polymorphism of vitamin D receptor genes such as *fok1*, *apaI*, *bsmI*, *taq*1. An increased frequency of *ApaI* 'a' allele among HBsAg+ve cases than in healthy controls was observed.

BIOMEDICAL INFORMATICS CENTRE

The centre has identified three most promising lead molecules: Soulameanone (antimalarial), Kaempferol 7-o-glucoside (anti cholera toxin), Lupeol acetate (anti HBV RT). Study on the effect of curcumin, tetraoxaquines and xanthone derivatives as antimalarial and anti diabetic agent respectively was carried out. The centre has also developed a database called "Malaria Epidemiology Database".

DBT-ICMR animal house facility for Biotechnology Research in North-eastern Region

The process for construction of an advance animal house facility is under progress.

OTHER AREAS

A study to assess economic costs of harmful alcohol use in a sample of unorganized workers in Assam and Sikkim

So far, a total of 741 out of targeted 1314 population have been surveyed.

Outbreak investigations

During the period, 10 outbreak investigations were carried out.

REGIONAL MEDICAL RESEARCH CENTRE, PORT BLAIR

MAJOR PROJECTS UNDERTAKEN

Collaborators and research counterparts

Directorate of Health Services, Department of Tribal Welfare, Andaman adim Jan Jati Vikas Samiti, Andaman and Nicobar Tribal Research Institute, NVDCP, RNTCP, ICMR institutes VCRC, NIRT, NIMR.

Effectiveness and operational feasibility of mass DEC fortified salt as a supplementary intervention to mass drug administration towards elimination of the lone foci of diurnally sub-periodic *Wuchereriabancrofti* in Andaman & Nicobar islands

Diurnally sub-periodic W. bancrofti filariasis is on the verge of elimination from its lone focus in India *i.e.*, Noncowry islands as a result of supplementing ongoing MDA(DEC+albendazole) with double fortified salt (DEC+iodine). The impact assessment of DEC fortified salt distribution post 12 months (2016 - 2017) showed 93.8% reduction in *Mf* rate in study arm Vs 41.3% in control arm. The analysis further revealed that Microfilaraemia levels were reduced to less than 1% [0.4% - 0.56%]in all villages under study arm where as Microfilaraemia still persists more than 1% [1.3%-7.89%] in four villages under control arm. The Centre plans to roll out the programme of substituting iodized salt with double fortified salt (DEC+iodine) in all villages where Microfilaraemia still persists more than 1% as a step towards the elimination LF from the whole Islands.

Situation analysis of malaria in the Car Nicobar island of Andaman and Nicobar archipelago: Pre- elimination phase study

In Car Nicobar Island, malaria, which was rampant after tsunami and the joint efforts made to strengthen various interventions, viz., release of insectivorous fishes, strengthening the insecticidal residual spray and effective case detection and treatment. Further community awareness on malaria and its vectors undertaken through door to door visits and motivation of traditional knowledge practitioners through imparted training on detection of suspects of malaria and referring to health care facilitiesfor specific treatment. The inter-sectoral efforts resulted in substantial reduction of API (19.93 in 2008 Vs0.2 in 2017) and the efforts are being continued towards the elimination of malaria from Car Nicobar Island.

Estimate the burden of TB among the tribal population and develop an innovative health system model to strengthen TB control towards risk reduction

The Centre undertook periodic surveys for estimating tuberculosis prevalence and Initiated joint efforts towards elimination of Tuberculosis from Car Nicobar showed declining trend in the incidence. The first survey conducted during 2001 and the estimated prevalence was 735.3/ 100000. 2012survey showed decline in the prevalence and was found to be 241.6/100,000 and recent survey showed further decline and was 191/100,000 (95% CI: 89.9, 404.3). However emerging MDR TB is a challenge.

Disease Surveillance and Health profiles of Particularly Vulnerable TribalGroups (PVTGs) of the Andaman & Nicobar Islands

The Andaman & Nicobar Islands are home to six indigenous tribal communities viz. Nicobarese, Onges, Great Andamanese, Shompens and Sentinelese. Although the disease and health status of Nicobarese is known, it is not known for Onges, Jarawas, Shompens and Sentinelese (PVTGs) As per the request of Tribal Welfare Andaman &Andaman and Nicobar Administration, Initiated a multi-sectoral project for assessing the complete health profile of each individual of the particularly vulnerable tribal groups (PVTGs) The data contains information on demography, nutritional anthropometry, blood group, haemoglobinopathies, G6PD deficiency, chronic NCDs and communicable diseases. This is the first systematic collection of data and documentation and facilitates the health care providers to provide highest patient care. Health profiling of the Ongesand Great Andamanese have been accomplished. Such health profiling will also extend to other tribes viz. Shompens and Jarawas which is ongoing.

Immunization of Jarawa tribe

As per the request of Directorate of Health Services, Immunological status of Jarawas was assessed by the Centre. Based on the recommendations ofRMRC, Vaccination for Jarawa is in-place and covers the BCG, OPV and Pentavalent vaccine. Recently, MR vaccination is also included in the program.

DESERT MEDICINE RESEARCH CENTRE, JODHPUR

Desert Medicine Research Centre, Jodhpur made significant progress in two major research programmes viz; Early Detection of Breast Cancer & Sickle Cell Anaemia. Other studies on Assessment of Nutritional status of vulnerable population, Health of Elderly Population etc. are at the completion stage, while an important study on Iodine Deficiency Disorder is ongoing.

Strengthening State Non Communicable Disease Programme For Early Detection of Breast Cancer Involving Strategic Education And Awareness Among Women: A Joint Programme of State Govt And ICMR- Desert Medicine Research Centre, Jodhpur

The aim of the study is to strengthen state breast cancer screening programme and develop a referral system for diagnosis and treatment of suspected cases at state medical colleges/ District Hospitals. A total of 27 Medical officers were assessed about their knowledge on cancer. Only about 19% were aware about the incidence of cancer in world whereas about 41% were aware about incidence in India. Medical officers were poor (16%) in their knowledge that breast cancer is common among women. They were having appreciable knowledge (75%) about symptoms of Breast Cancer and their knowledge about most specific symptoms of Cervical Cancer was even better (89%). Around 30% were aware of warning signs of Oral Cancer whereas 59% were aware of common risk factor of Breast Cancer.

A total of 99 ANM/LHV were assessed about their knowledge on cancer. All paramedicals heard about cancer whereas 62% were aware of meaning of cancer and 92% were aware that breast cancer is common cancer among women. About half (48%) of the Para Medicals were aware of symptoms of breast cancer and two third (72%) were aware of most specific symptoms of cervical cancer. Paramedicals were having poor knowledge (18%) about correct age and frequency of clinical breast examination as well as time of doing breast self examination (34%). Around 75% paramedicals however, were aware of primary prevention for cervical cancer and importance of community participation (91%).

A total of 2411 households from 17 Villages covered and information about awareness of community about symptoms of cancer and risk factors were collected from 2556 women. Out of 2556 women covered, analysis of information on 1577 women have been completed. It was found that around 90% women heard about cancer. Among women who were aware about cancer, around 50.42% were of the age group 30-45 years and 49.58% were of the 46-65 years. Among women who heard about cancer, 45%, 25% and 18% were respectively aware of oral breast and cervical cancer. Those who were aware of breast cancer (n=359) were asked about symptoms of breast cancer. They were having good knowledge (59%) that lumps in the breast is symptoms of breast cancer and may be cause of breast cancer. But their awareness about other symptoms like change in size and shape of Breast (3%), swelling in the armpit or collarbone (1%) and similarly about breast dimpling as well as nipple retraction pain was very poor. Only 8% women were aware that swelling in armpit may also be cause of breast cancer. Among those aware about breast cancer (n=359), 87% were not aware about the risk factors of the breast cancer. Similarly 82% were not aware of self breast examination technique.



Fig. 7: Village level camp at Nimbla, Jalore on 02nd February 2018.



Fig. 8: Capacity Building Workshop for Medicals & Para Medicals held on 4th & 5th Feb., 2018 at DMRC, Jodhpur.



Fig. 9: Women practicing evaluation of the symptoms of breast cancer with the dummy models during the capacity building camp at Gudarama Village on 21st February, 2018.

SICKLE CELL ANAEMIA

A study on screening of tribal residents for Sickle Cell Anaemia (SCA) and intervention through Information Education and Communication (IEC) is being carried out in two blocks of Udaipur zone i.e. Kotra block of Udaipur District and Sajjangarh block of Banswara District. A total of 7100 students have been screened from Kotra Block and 1215 (17.11%) students were carrying sickle cell trait and 29 (0.41%) students having sickle cell disease.

Nutrition: Improving Health and Nutritional status of vulnerable segment of population by implementing multi-component health &

nutrition education intervention as a sustainable model of intervention

The objective of the study was to improve health and nutritional status of vulnerable segment of population by implementing multi-component health & nutrition education intervention.

The baseline has been completed and intervention has been imparted. During last one year, impact evaluation has been completed. A total of 5000 households were covered including lactating women, infant 1 to 5 years children and adolescent girls.

Study on the health of elderly population of rural Rajasthan

Study was carried out with joint collaboration of State Medical & Health Department, Dr. S.N. Medical College, Jodhpur and CNRT Laboratory, New Delhi with the objectives of Clinical assessment of the elderly population; assessment of micronutrient deficiencies viz Iron, zinc, vitamin A and E, calcium, Selenium and also analysis of blood sample for lipid profile. Analysis of 400 elderly subjects showed that overall 65.3% elderly had poor vision, 31.3% hearing difficulty, 33% had disturbed sleep, and breathlessness in 32.3% population. Overall knee and back pain were high i.e. 51.5% & 46.2%, comparatively higher in case of females than males. Chest pain was recorded in 14.5% population. Other problems recorded were frequent headache (12.3%), fever in last 1 month (5%) and falls in last 6 months (4%) and depression (2.5%). The overall prevalence of hypertension (23.3%), COPD (5.5%), diabetes mellitus (4.5%), asthma (4.3%) and IHD, (1.7%) were mentioned in parenthesis. Analysis of Mini Nutritional Assessment Scale showed that 58.5% were found to be at risk of malnutrition whereas 27.5% were malnourished (Score >23.5). Overall 82.8% anaemia was observed which was higher in females (91.1%) than males (69.3%). Moderate & severe anaemia was 23.5% & 3.5% respectively, higher in females than males. Main micronutrient deficiencies observed were serum calcium 53.6%,

serum zinc deficiency 44.2%, serum iron 22.8% and serum retinol deficiency 13.1%. Hyperlipidemia (>200 mg/dI) among elderly population was 10.7%, higher in females (13.9%) than males (5.6%). High triglycerides (>150mg/dl) were observed among 37.5% whereas 71.6 percent elderly population had HDL lower than 40 mg/dI. Dietary intake analysis (24 hours recall method) revealed that their diet was deficient in fibres (28.1% in males & 32.4% in females), vitamin C (64.4% in males & 54.5% in females), folate (6.7% in males & 24.9% in females), beta carotene (84.7% in males & 88.1% in females), energy (12.1% in males & 12.5% in females), zinc, vitamin 6 and niacin.

Development of IEC modules for the promotion of three local pearl millet preparations to improve the knowledge w.r.t. Pearl Millet consumption among the rural population of Nagaur district of Rajasthan

It is an extramural project of Translational Research Cell, ICMR, with primary objective to develop an IEC modules for promotion of three local pearl millet preparations viz. Rab1 (Pearl millet Grains), Kadhi and Sogra and also to improve the knowledge of the rural population; The study was initiated in Nagaur a desert district of Rajasthan. Two clusters i.e. two tehsil of Nagaur district have been selected randomly i.e. Merta and Khinvsar tehsil out of 10 tehsil of Nagaur district. One cluster, Khinvsar tehsil, is intervention group and 2nd cluster, Merta tehsil, selected for control group. Respondents are women aged 15 years and above, who is cooking food. A comparative Analysis have been done after six month of period of intervention and found that knowledge regarding the 'Bajara used as staple grain in households' increased from 75.4% to 91% after intervention. Frequency of preparing Rab1 with bajra grains increased from 22.8% to 60.7% after six months intervention. Frequency of preparing Kadhi with bajra (2-3 times) increased from 25.3% to 50.6 %. Frequency of preparing Sogra with bajra flour (daily) increased from 86.9% to 99% whereas 'Frequency of preparing Rab2 with bajra flour' (Once a week) decreased from 28.7% to 19.5% after intervention. The

method used for preparing *Rab1*, the practice of using 'Soak, pound, dehusking ' has been increased from 20.9% to 52.4% after intervention whereas the practice of using 'grind to flour' decreased from 70.5% to 45%. Knowledge about the beneficial effects of PM products especially Rab1, Kadhi and Sogra increased up to 84.8%, 50.9% and 77.6% respectively. Knowledge regarding 'Iron Tawa has higher retention of iron than Mud tawa' increased up to 94.9% after intervention. This shows a good impact of intervention among the respondents as retention of Zinc and iron is more in *rab1* (Pearl millet Grains) preparation i.e. 4.40 mg/100g and 10.5mg/100g in comparison to Rab2 (iron 5.99mg/100g & Zinc 3.64mg/100g).

Sero-prevalence of dengue, chikungunya and Japanese encephalitis virus infection in Rajasthan

As a part of the ICMR multi centred study, DMRC assured sero-prevalence of dengue, chikungunya and Japanese encephalitis virus infection in Rajasthan. As per the study protocol the census enumeration and randomization was conducted for the four districts of the state which includes 16 census enumeration blocks (CEB). Eight urban and eight rural Census Enumeration Blocks were selected as per the PPSLSS statistical methods. A total of 7836 individuals were censured in 1282 abridged houses. After randomization of the population, 760 persons given their blood samples for the study. Among the samples 55.8% were positive for dengue IgG and 2.36% were equivocal. However, 25% and 23% subjects were positive and equivocal for the Japanese Encephalitis IgG respectively. The report of the positive for Japanese Encephalitis IgG in such a high percentage is reported for the first time in Rajasthan. All the JE cases were reported from the Churu district. Less number of cases were recorded for Chikugunya compared to Dengue.

IDD

ICMR has initiated a Task Force study on "Assessment of Iodine status among pregnant women in selected districts of India" during 2017 at 10 locations in the country with an objective to carry

out cross sectional study to assess the urinary iodine level among pregnant and non-pregnant women at six centres; and to carry out longitudinal study to assess the serum/plasma micronutrient level, thyroid profile and urinary iodine level of pregnant women during first, second and third trimester as well as at the time of delivery, at 6 months and at one year after delivery; and to also assess the new borns for birth weight and growth up to one year of age at four of the total ten participating centres. DMRC, Jodhpur is one of the participating centres of longitudinal study under which Jaisalmer District, Rajasthan is being covered. So far, the centre has recruited 181 pregnant women in first trimester and is being followed. Around 280 blood samples and 250 urine samples of pregnant women and 250 salt samples from their houses have been collected and analysed.

SUPPORTING FACILITIES

uring the period under report, the National Institute of Epidemiology (NIE) at Chennai and the National Institute of Medical Statistics (NIMS) at New Delhi provided statistical assistance to various ICMR institutes. Health systems research (HSR) and social and behavioural research (SBR) were intensified by starting new projects and with the completion of previous projects. Various new agreements and letters of intent were signed with different national and international organizations. Publication and information Division showcased the achievements of ICMR organization in various significant exhibitions throughout the country. The new division ISRM strived to move the organization towards new goals of technology and digitization.

INTRAMURAL RESEARCH

NATIONAL INSTITUTE OF EPIDEMIOLOGY, CHENNAI

ICMR SCHOOL OF PUBLIC HEALTH

• NIE has been conducting Master of Public Health program since 2008. Till date, 123 Medical Officers from 26 states have graduated.

SERO-PREVALENCE OF DENGUE VIRUS INFECTION IN INDIA

• NIE is coordinating a study to estimate the sero-prevalence of dengue in India. The survey has been conducted in 240 clusters (120 rural, 120 urban) in 60 districts from 15 Indian states

from five geographic regions (Fig 2). Blood samples have been collected from 12,300 individuals aged 5-8, 9-17 & 18-45 years.

• Samples are being tested for IgG antibodies against Dengue, Chikungunya and Japanese Encephalitis virus. A sample of sera will also be tested for serotype specific antibodies using Plaque Reduction Neutralization Test at NIV, Pune.

Integrated Road Traffic Injuries (RTIs) Surveillance-India (IRIS-INDIA): Chennai

• This multi-center task-force study proposes to establish a hospital based (both private and public sector) surveillance system and pilot feasibility of community based surveillance system for RTIs to capture unreported minor RTI.Team has collected data from private sector facility (Jan-Mar 2018). Of the 303 events captured, 71% were fatal in nature and almost 44% of them involved two wheelers. Team is yet to initiate surveillance from tertiary care referral facility in government medical college.

Health system preparedness for interventions for diabetes, hypertension, chronic respiratory diseases, cardiovascular diseases and cancer and deaths due to noncommunicable diseases among the tribal population in India

• This study, conducted in 7 tribal districts in India indicated that non-communicable

diseases accounted for 7 out of 10 deaths. Deaths due to injuries, suicide and diseases of digestive system were higher among young adults. Among infectious diseases, tuberculosis was leading cause of death. The study also identified several gaps in the delivery of services for NCD management in public health facilities.

In-country data verification for Elimination of Mother-to-Child Transmission of HIV and Syphilis in 6 States in India, 2017

• NIE conducted sub-national pre-verification exercise in 6 states with the objectives to (i) review the data recorded and reported in the programme monitoring system and (ii) understand the data reporting and recording systems and processes followed at the field level. Results highlighted high reporting status, consistency over time and across records; poor documentation for Syphilis. The recommend strategies and mechanisms would help to inform the further strengthening of information systems and overall data quality at the state and district levels. This is imperative to progress towards achieving EMTCT of HIV and Syphilis in India.

Process evaluation of Integrated Management of Neonatal and Childhood Illnesses program in India

- Process evaluation of Integrated Management of Neonatal and Childhood Illnesses was done in eight selected states representing different regions of the country. This evaluation obtained information from 34 program managers, 285 health facilities, 990 facility based service providers, 3,031 community-based service providers and 4858 beneficiaries.
- The study found that the proportion of trained frontline health workers (AWW, ANM and ASHA) was higher, relative to that of trained service providers in each of the selected states. The majority of mothers of neonates in all

eight states reported they had received home visits from ASHAs as mandated. Levels of awareness of exclusive breastfeeding were high in beneficiaries from eight states. More of the 75% of mothers in five of the eight states reported that they had received counselling at facilities. Program coordination involving the establishment of a coordination group was lacking in most districts.

CONGENITAL RUBELLA SYNDROME SURVEILLANCE IN INDIA

• NIE initiated sentinel surveillance for CRS in six sentinel sites since 2016. Till date, these sites have enrolled 488 suspected CRS patients so far. Based on the clinical details and laboratory results, 22.8% patients were laboratory confirmed CRS, 2.1% were congenital rubella infection while the remaining were discarded cases.

HIV SENTINEL SURVEILLANCE (ANC) 2016-17

NIE, as the Regional Institute, has been coordinating HIV sentinel surveillance in 7 southern states. In the current round of surveillance, a total of 99434 blood samples were collected from the states of Andhra Pradesh, Karnataka, Kerala, Orissa, Tamil Nadu, Pondicherry and Telengana. The HIV positivity rates in these states ranged from 0-0.38%.

Risk factors for acquisition of Scrub Typhus among children in Deoria and Gorakhpur districts, Uttar Pradesh, India, 2017

• Scrub Typhus (ST) is associated with outbreaks of acute encephalitis syndrome in India. A case-control study (155 cases; 406 controls) identified residence within/ adjoining fields, storing firewood indoors, open defecation and playing/visiting in fields had higher odds of developing ST. Messages should focus on behaviors and importance of early administration of antibiotics.

Hospital Based Sentinel Surveillance for Pneumonia and other Invasive Bacterial Diseases

 NIE is coordinating the sentinel surveillance for pneumonia and other invasive bacterial diseases to assess the burden and distribution *Streptococcus pneumoniae* in children aged 1 month to 59 months. During 2017-18, 1216 patients of pneumonia, 671 patients of meningitis and 312 patients of sepsis were enrolled. The molecular investigations are ongoing.

Strengthening Tuberculosis and HIV detection and management through intensified case finding in Central Jail, Aizawl, Mizoram

 NIE implemented the intensified screening for tuberculosis and HIV among inmates of Central Jial, Aizawl, Mizoram. Intensified screening identified 14 new tuberculosis cases (overall tuberculosis positivity 1.9%) and 41 (9.5%) new HIV infection among the inmates. These findings have implications in developing strategies for TB/HIV case finding in prison settings in India.

NATIONAL INSTITUTE OF MEDICAL STATISTICS, NEW DELHI

The Clinical Trials Registry – India (CTRI) (www.ctri.nic.in) is a national online register for registering clinical trials being conducted in India. Since, CTRI is a Primary Registry of the WHO's International Clinical Trials Registry Platform (ICTRP), it also registers trials being conducted in countries which do not have a Primary Registry of their own. CTRI registers all types of therapeutic area trials, i.e., interventional, observational BA/ BE, surgical, lifestyle, devices, Ayurveda, herbal etc. Moreover, as the global mandate is to register trials only prospectively, CTRI has also moved towards only prospective registration from 1st April 2018 and working in the direction of result disclosure. Till 31st March, 2018, there are 12906 trials registered on this platform.

The Institute has undertaken comparing methods of assigning causes of death study supported by MoHFW and WHO to field test the WHO harmonized verbal autopsy tool and compare PCVA and CCVA methods. The study findings will be utilised for recommending the methodology of a routine national verbal autopsy programme for ascertaining the cause of death in India.

The Institute has been involved in the estimation of disease burden through its various studies, viz, "Malaria elimination and estimation of disease burden in Punjab with collaborative efforts with State Government"; "National Non-communicable Disease Monitoring Survey (NNMS) in India" and "Burden of Non-Communicable Diseases and Associated Risk Factors for India (BOD-NCD) -Methodology group".

ICMR-NIMS designated as the nodal Institute by NACO to provide estimates of HIV burden of India and its states using updated globally accepted methodology since 2003.

A study on gender inequity in health seeking behaviour and utilization of health services among Santhal tribes of Jharkhand is currently underway.

A research project on Improvement in the Utilization of RCH Services through Male Participation among the Saharia Tribes in Gwalior District, Madhya Pradesh is in progress. The study findings will facilitate the better utilisation of RCH services.

PUBLIC HEALTH IMPORTANCE

The CTRI brings all clinical trials to public domain which empowers patients to participate in relevant clinical trials pertaining to their conditions particularly life threatening diseases. It is a free and online searchable database in the country which can be tapped by academicians, researchers, social activists and parliamentarians among others. It brings transparency, accessibility and accountability of clinical trials and their data which helps in enhancing public trust in clinical research. By negating publication bias, CTRI would help ensure implementation of evidence based medicine for the general public.

HIV estimates and prevalence data will help in identifying regions with high disease burden which in turn will direct the programme strategies for control and prevention of disease. It also provides Antiretroviral Therapy (ART) to people who are living with HIV.

The malaria elimination and estimation project data would help in understanding the extent of endemicity and disease burden in Punjab. The study findings will give directions to malaria eradication programme in the state.

Studies on tribal health in Madhya Pradesh and Jharkhand states will facilitate health care delivery programmes to marginalised sections of the society.

EXTRAMURAL RESEARCH

SOCIO-BEHAVIOURAL AND HEALTH SYSTEMS RESEARCH

HEALTH SYSTEMS RESEARCH (HSR)

During the year, the Division has funded some adhoc projects on understanding and strengthening of health systems in the country. Some of these projects have been concluded during this year. In addition, two national task force projects on Road Traffic Injuries have been initiated in 10 cities. Following is the brief description of the ad-hoc projects funded during the current year.

Study on health systems responsiveness during mass gathering with reference to Kerala's Sabarimala temple is concluded. It warranted that an effective Mass Gathering and Safe pilgrimage (MGSP) policy. This policy requires an evidence base from a multi-dimensional platform, a committed and flexible monitoring mechanism, and a body that is ready to take suggestions. Pilgrims' responses form an essential starting point for developing an MGSP policy. The data shows that cardiac care is the most important service required during the pilgrimage, and some services are available. Apart from cardiac care, food hygiene needs to be strictly enforced to prevent major outbreaks of diarrheal diseases. Crowd management is certainly an issue, and a multi-sectoral approach is required given the data reported in this study. The study further found that safety and security are certainly important issues. A study has been conducted in Karnataka to assess the effectiveness of Panchayat Raj Institutions (PRIs) in managing the rural health care system, with special reference to the implementation of the National Health Mission (NHM) programmes. The study concluded that health decentralization brings governments closer to people thereby allowing them to respond more effectively to the local health needs and preferences. However, there are contrasts and disagreement in the views expressed by the independent stakeholders on the issue along with certain causal bearing with their individual attributes and behaviour. It is further concluded that there are enough reasons to suggest that the PRIs engagement in improving the key health indicators will become a reality in India.

A study to understand the perceptions of physicians, pharmacists and patients about the prescription of generic drugs is going on in Gujarat. It identified the factors that prevent the prescription of generic drugs. Data obtained in this project will help policymakers to understand the perspectives of stakeholders for designing strategies to promote the use of generic drugs. Another study has been concluded in Jammu to monitor hand hygiene compliance of health-care workers in government medical college hospital. The intervention, a combined multimodal hand hygiene improvement strategy was carried out, on the basis of the WHO guidelines for hand hygiene in healthcare. The study provides valuable information regarding hand hygiene compliance and its effect on healthcareassociated infections. During this year, nine HSRrelated adhoc projects are continuing. A study on advancing equity in primary health care has been initiated in Telangana state. This study, with the anthropological approach, is being examined Social Determinants of Health (SDH) and attempted to establish the chain of causality between SDH and equity in the context of community participation initiatives of NHM Ten themes for carrying out qualitative inquiry are identified during this year. The first phase of the study came up with a detailed and thematic plan to explore reasons for health inequity owing to cultural norms conditioning health practices. A community-based intervention for community engagement in control of some Vector-Borne Diseases (VBDs) is going on in Alappuzha urban area, Kerala. The formative research could bring out the status of existing health system under Alappuzha Municipality, its responsiveness to control VBD, characteristics of the community, the perception of the community regarding the health system, community engagement, etc. On the basis of formative research, an intervention program is underway. The basic concept of the intervention is to empower the community through an engagement programme and to make them aware of the strength and weakness of them to tackle a public health issue like VBD. The intervention will shortly be evaluated. Moreover, the Municipality of the Alappuzha proposed to scale-up this intervention to other parts of the town with municipality resources.

A study to evaluate the impact of an educational intervention among primary health care providers regarding prevention of hypertension and associated co-morbidities is underway in West Bengal. The patients diagnosed with hypertension and associated comorbidities following an risk factor screening by primary health care providers are being targeted. Several interventional activities are underway. These results have implication on National Programme for Prevention and Control of Cancers, Diabetes, Cardiovascular Diseases and Stroke. Impact of awareness programme symptom management among advanced on cancer patients and their caregivers is underway in Karnataka. This study is hospital-based and patients with breast or head or neck cancer and have undergone radiotherapy or chemotherapy or surgery or combination of them are targeted. The family caregivers are also included. The study demonstrated that a structured education on symptom management will improve the patients' quality of life. It further demonstrated the importance of promotion of non-pharmacological methods of pain management and the role played by family caregivers in supporting terminally ill cancer patients.

A yoga programme for caregivers of schizophrenia was validated by a study undertaken in National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru. It further developed and validated self-help yoga manuals and CDs. This study tested the efficacy of this manual on burden, stress, quality of life and anxiety-depression of caregivers of persons with schizophrenia. Now, these manuals can be used in various community settings. The structured training manuals would act as a guide for mental health professionals and yoga therapists in the future. Another study from Rajasthan for assessing and managing mental health problems through frontline health workers is underway on a pilot basis. Improving the capacity of health workers with regard to knowledge and skills in assessing mental health has been initiated through a series of training workshops. Another study has been initiated recently in Karnataka to assess the mental health literacy and referral practices among high school teachers. This study further screens adolescents, 14-16 years, attending high schools for mental health conditions.

Another study was initiated in Karnataka to help nursing students to make aware of their perceptions on Reproductive and Sexual Health (RSH) issues and build the skills and abilities of adolescent or young adult nursing students to introspect and address personal and clientele RSH issues effectively. Various nursing institutes have been identified and interventions are going on among the nursing students. In Uttarakhand, a mixed-methods study has been initiated to study the causes that lead to work-related stress among the police officers and its impact on their health. It is found that stress amongst the police staff is leading to various health issues and chronic morbidities. The finding will have implications for strategies to reduce the stress and improve the health and well-being of the police officials.

NATIONAL TASK FORCE STUDIES ON ROAD TRAFFIC INJURIES (RTIs)

Two Multi-Centric National Task Force Projects are ongoing in 10 cities. The first study is to establish

an electronic-based comprehensive and integrated RTI surveillance system. Since RTA are more common on urban roads and on roads connected to the urban area and it has been seen that majority of the cases are referred to tertiary care hospitals, hence a passive surveillance system in tertiary care hospitals is established. It is possible that most of the critical and immediately fatal cases are recorded and those who die in government hospitals also enter the official statistics through police network. As more than 60% of the fatalities occur in rural areas, it is possible that a larger number of cases go unreported, particularly non-fatal and minor injuries. Also, a significant proportion of fatalities that occur some days after the crash in rural areas are missed. Even some deaths escape from police. In addition to all these, many non-fatal and minor injuries were treated in smaller nursing homes and

clinics. In view of these realities, the present study is developed and integrated an active surveillance system to cover police stations, community-based health facilities like primary health centres and community health centres and private nursing homes and clinics. Active surveillance is also placed in communities to track missing cases. Necessary mechanism is integrated into the software system to avoid duplications. Thus, this study establishes both passive and active surveillances comprehensively to capture all RTI and related deaths in a particular geographical area. This study is underway in five places in India, viz., Chennai, Chittoor, Dehradun, Delhi and Jaipur. After establishing the system and demonstrating the feasibility of establishment within the public health system, it can be taken over by the government for scaled-up.



Fig. 1: Community engagement activities in VBDs control in Kerala



Fig. 2: Vector control activities in VBDs control in Kerala



Fig. 3: Vector control activities in VBDs control in Kerala

The second issue is timely and quality care of RTI patients as many deaths occur either at the scene or in route to the hospital. There is a clear survival and functional benefit for critically injured patients to receive appropriate care within the first 60 minutes of injury ('golden hour'). Hence, this multi-centric study has been initiated to standardize structured evidence-based intervention for safety, efficacy and quality of post-crash pre-hospital and in-hospital trauma care services to improve the outcome in RTI victims. This study is implemented in five cities, viz., Bengaluru, Delhi, Karamsad, Lucknow and Thrissur. An Android-based trauma registry is built and is used to collect pre and post-intervention data.

Improving and establishing prehospital care is one of the objectives of this study. The intervention on prehospital care includes education and training for prehospital care and prehospital notification, standardized hospital selection, a mandatory checklist for persons attend RTI and prior notification of arrival. In trauma resuscitation management of immediately life-threatening injuries requires rapid identification and management of threats to airway and breathing, bleeding, cardiac and brain function. With sufficient notice, trauma hospitals can usually mobilize a team with the relevant expertise to be present and ready for patient arrival. Another interventional activity undertaken was to educate and train the first-responders for prehospital notification. The training included i) American Heart Association's basic life support training ii) basic education on the initial assessment of a trauma patient; iii) compliance with the basic necessities of any trauma patient; and iv) standardization of hospital selection.

The intervention was made to ensure the availability of ambulances to transport the critically injured patients according to prior set criteria. The list of all the qualifying hospitals per type of injury or the injured patient was made available to the firstresponders and posted in all the ambulances. It is ensured that the recipient hospital will be notified about patient's basic injuries and vitals. This is to minimize the delay in definitive care that the patient requires to optimally utilize the golden hour. The effectiveness of the prehospital care is assessed using the data collected through trauma registry. The intervention included the strengthening of the quality of care within the hospital, through relevant Quality Improvement (QI) activities according to WHO guidelines. These activities include WHO's trauma QI training for key clinicians followed by mentoring of developing the necessary structures and processes to conduct regular morbidity and mortality meetings, preventable death reviews, audit filters, risk-adjusted benchmarking of key performance indicators where relevant and loop closures. The impact of the QI is assessed through various outcome indicators including death, morbidity and length of hospital stay that are collected through trauma registry.



Fig. 4: Web tool used in electronic-based comprehensive and integrated RTI surveillance system.

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| Survey Sections | | | | Community base | road accider | nt recording for |
| Application is | running in Test m | odel | | Application | is running in | Test model |
| Personal Identification | | | | Question: 1/28 | | |
| (To arrouge confidentiality, identifiers will not be inc | | | | Centre Code | | |
| Socio-demographics Socio-demographics | | | | (Select Any One) | | |
| Accident Identification Details Accident Identification Details | | | Chennal Chiltoor | | | |
| Person Related Data Person Related Data | | | Delhi Tahri Garboul | | | |
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Fig. 5: Controlling data from hospitals and community using android tablets.



Fig. 6: Training programmes in road traffic injuries projects.

SOCIAL & BEHAVIOURAL RESEARCH (SBR)

During this year, three adhoc projects and one fellowship were completed; eighteen adhoc projects and one research associateship are continuing. Eleven adhoc projects have been funded jointly with Indian Council of Social Science Research (ICSSR).

During this year, a study was carried out to understand the barrier to eye donation. The research involves cross sectional survey of the family members of deceased. The study highlights that the barriers to eye donation are not cultural or religious, but the misinformation regarding disfigurement of body and proper utilization of the donated tissue. The study warrants addressing both the emotional and medico-legal issues associated with eye donation. There is a need to formulate actionable nationwide strategies addressing these barriers to boost up the eye banking movement. A study was undertaken to understand the impact of discriminatory behaviour against disability on various psychosocial concomitants. It involved various categories of differently abled people. The study concluded that perceived discrimination differed for type of disability, duration of disability, gender and age variations and anxiety insomnia, social dysfunction dimensions and overall general health were liable to variations due to gender, showing the lower wellbeing of females. Another study assessed micro economic costs of alcohol use in a sample of unorganized workers from north eastern states (Assam and Sikkim). There is an urgent need primarily to understand how much revenue can be saved by investing in evidence-based intervention. With a projected age-adjusted prevalence of almost 60% alcohol consumption, approximately 7,00,000 workers in tea gardens of Assam are prone to adverse consequences of harmful alcohol use. Assam also has an integral culture of production and consumption of unrecorded or traditional alcohol. Further in Sikkim the consumption of unrecorded or traditional alcoholic beverages is an integral part of daily dietary habit and cultural practice and more than ten types of ethnic, home

brewed alcoholic beverages are consumed in Sikkim, which is one of the highest in India. The study found that more than 50% of the respondents engaged in unorganized sector have either harmful/ hazardous pattern or dependent pattern of drinking leading to adverse effect on health and financial position.

An Inter-divisional pilot study with and Division of Basic Medical Sciences - 'Programme on Creating Awareness amongst Stakeholders on Rightful and Ethical Use of Stem Cells in Medical Practice' was Concluded. This study was conducted to explore various dimensions on use/practice of stem cell therapy, knowledge, attitude and perception, stress of stakeholders. The findings revealed that majority (92%) of the stakeholders heard about stem cell therapy and most of them (70%) felt that stem cell can do wonders also agreed that stem cell therapy is costly. The patients expressed need for stem cell therapy. Stakeholders also emphasized for more research/clinical trials. Majority also agreed that stem cell related all issues should be dealt under govt. umbrella for better regulation and administration. The study also found that the patient and their caregivers are not averse to the whole practice, if the cost of treatment is not to exorbitant and cure is reality (not mirage). The scientific premise of the stem cell therapy is shaky and does not stand test of time. It is evident from the study that dissemination of correct knowledge and information to all section of population (affected or otherwise) regarding stem cell applications is the need of the hour.

INNOVATION AND TRANSLATIONAL RESEARCH

TECHNOLOGIES TRANSFERRED TO INDUSTRY

- Development of IgM assay for detection of anti CHPV antibodies developed by National Institute of Virology, Pune – Transferred to M/s Cadila healthcare pvt. Ltd, Ahmedabad
- Measles diagnostic IgM kit technology developed by National Institute of Virology,

Pune – Transferred to M/s Cadila healthcare pvt. Ltd, Ahmedabad.

- Development of Anti-CCHF Human IgG ELISA assay developed by National Institute of Virology, Pune – Transferred to M/s Cadila healthcare pvt. Ltd, Ahmedabad.
- Development of Anti-CCHF Human IgM ELISA assay developed by National Institute of Virology, Pune – Transferred to M/s Cadila healthcare pvt. Ltd, Ahmedabad.
- Technology for drinking water testing for enteric viruses developed by National Institute of Virology, Pune – Transferred to M/s Cadila healthcare pvt. Ltd, Ahmedabad
- ELISA for Rotavirus developed by National Institute of Virology, Pune – Transferred to M/s Cadila healthcare pvt. Ltd, Ahmedabad.
- Measles diagnostic IgM kit technology developed by National Institute of Virology, Pune – Transferred to M/s Cadila healthcare pvt. Ltd, Ahmedabad.
- AV –Magnivisualizer for detecting cancer lesions developed by National Institute of Cancer Prevention and Research, Noida – Transferred to Smileoracles Dental and Allied Services Llp. In addition to M/s Soothe Health Care, Greater Noida.
- Loop mediated isothermal amplification (LAMP) assay for detection of multiple Leishmania species, developed by National Institute of Pathology- Transferred to M/s NextGen Invitro Diagnostics Pvt. Ltd., Delhi

TECHNOLOGIES LAUNCHED FOR COMMERCIALIZATION

- Diagnostic kit for Crimean-Congo Haemorrhagic Fever (CCHF) Sheep and Goat developed by National Institute of Virology, Pune.
- 2. Diagnostic kit for Crimean Congo Haemorrhagic Fever (CCHF) in Cattle developed by National Institute of Virology, Pune.

 Diagnostic kit for Japanese Encephalitis Virus (JEV) from Mosquito developed by National Institute of Virology, Pune

HARVEST GROUP

A Harvest Group was created as per the recommendations of the High Power Committee to identify leads from the Extramural research projects funded by the ICMR towards making products, processes and other deliverables which are of use for Indian Public Health System and other countries who may need them. The leads having potential for translation were to be identified from the completed extramural projects reports of all the technical divisions funded from 2010.

DRONE FOR VACCINE DELIVERY: LAST MILE COVERAGE

The national immunization program continues to face challenges in terms of making safe and potent vaccines available in remote areas. A 2013 study from India found that two thirds of vaccines were damaged by freeze exposure in the cold chain between State stores and administration sites across ten States. Technologies like Drones can be used to cover the gaps in cold chain system. In view of this ICMR and IIT KGP have initiated a project 'Drones for Vaccine Delivery: last mile coverage". The overall aim is to develop a drone system that can be instructed to fly autonomously using GPS points to sites administering immunization under National program in far flung remote areas and deliver vaccine pay load under temperature controlled condition. The drone would normally fly above safe height from known obstacles like trees and buildings. The drone will be developed by Aerial Robotics Kharagpur (ARK) a student research group under the Centre for Excellence in Robotics at IIT Kharagpur. Since the GPS has errors of \pm 3m on average, precise tasks like landing cannot be carried out with GPS as the position feedback. The drone technology being developed at IIT KGP has successfully tested landing on fiducial marker based landing pads.

IMPACTING RESEARCH INNOVATION AND TECHNOLOGY (IMPRINT)

This is a flagship national initiative of the Government, launched by the President, Prime Minister and Human Resource Minister on November 5, 2015. The program aims at addressing and providing solutions to the most relevant engineering challenges faced by the nation by translating knowledge into viable technology. Healthcare is one of the 10 technology domain identified under the IMPRINT. ICMR along with MHRD has provided support to 24 projects in healthcare domain. The projects range from Bioresorbable Drug Eluting Coronary Stents, Artificial Pancreas for Closed Loop Blood Glucose Control of Type-1 Diabetic Patients and Development of Microneedle Array for Paediatric Applications.

UCHHATAR AVISHKAR YOJANA (UAY)

The Uchhatar Avishkar Yojana (UAY) was launched to promote industry-specific need-based research so as to keep up the competitiveness of the Indian industry in the global market. The UAY is a joint collaboration between MHRD, participating ministry and industry. Under the UAY, MHRD funds 50% of research project, 25% is borne by the industry and the balance 25% by participating ministry. During 2017-18, 10 projects were funded by ICMR. These projects included 3D Printing of Metallic Orthopaedic Implants, Silicon nanoporous membranes (SNM) and membrane arrays for Continuous Ambulatory Peritoneal Dialysis (CAPD), a comprehensive framework for treatment of stroke of upper extremity by combining computational modeling, movement behavior and gaming, hydrogel platform for 3D cell culture application and a kit distinguish mixed malaria infection. These research projects are designed to provide path breaking new knowledge.

MEDTECH INTERNSHIP: CLINICAL, TECHNOLOGY AND MANAGEMENT EMERSION

To tackle health needs of the country, to reach the marginalized population in remote areas, technology can become a huge enabler in ensuring delivery of quality and affordable healthcare. ICMR in collaboration with IIT KGP and IIM Ahmadabad organize summer MedTech Internship program since 2016.

Sixteen medical-technology-business interns were trained in year 2018 in a strategic area of health (maternal and child health). The interns observe the clinical facility, physician, frontline health worker and/or a patient for a period of one week at MRHRU, Tigiria and/or SCB Medical College, Cuttack, AIIMS Bhubaneswar. The MRHRU and medical college provided support for medical technology need assessment. The IIT KGP faculty guided the interns through the process of technology development whereas the IIMA faculty helped in mentoring the business model development part of the technology. The observations collected during their stay at MRHRU/Medical College were useful in building new ideas or reshaping the initial project proposal. This was followed by design development for identified technology at ICMR institute, IIT KGP and IIM A laboratories. The interns were also trained in evaluation of the Intellectual Property, regulatory compliance, stakeholder validation, methodology for preclinical and clinical testing of the prototype or methodology for validation of the health system model and marketing strategy.

The ideas on which this year's interns worked included backrest cum squat-stool to help pregnant female during delivery and decreasing pain, device for early screening of congenital heart defects in neonates and metallic degradable fracture fixation devices. The proposals with some potential will be supported further for prototype development.

A patent on "Rapid detection of bacteria susceptibility against drug in a microfluidic platform" has been filed by an intern from ICMR's NIRT, Chennai from 2016 batch.

RESEARCH METHODOLOGY CELL (RMC)

Research Methodology cell (RMC) has been established in ICMR to propagate the research

at peripheral level in Govt Medical Colleges. The objective of the Research Methodology Cell in the ICMR Headquarters is to train the young faculty, professionals and students of bio-medical science, especially those belonging to state medical colleges and other academic institutions located in the periphery of different states through research methodology workshops for writing a good research proposal, which includes formulating valid hypothesis, drafting appropriate study design, collecting, documenting and analyzing data as well as communicating the research findings in a scientific journal.

CAPACITY BUILDING WORKSHOP

Call for the concept proposals was undertaken to identify young and middle level faculty members/ researchers working in medical colleges and health research institutions to participate in Research Methodology Workshop from Northern and Southern India was done in August 2017 with the objectives of explaining the basic concepts of research methods, training in designing biomedical and health related studies among human participants; and providing a hands on exercise for a refined prior shortlisted concept proposal empowering them to develop a full proposal adequate for possible funding submission. A total of 380 concept proposals were received among which 120 were from northern India, 199 were from southern India and 61 were among the others. All proposals receiving ≥ 60 score were invited to submit a full length proposal online for a review. For the proposals receiving between 59 - 41 score, Research methodology workshops will be planned separately for Northern and Southern India. These all proposals will be encouraged for resubmission after the Research methodology workshop. Proposals receiving ≤ 40 score and age > 45 were regretted.

STUDY UNDERTAKEN

To assess high risk behavior and HIV prevalence among truckers of Haryana. The study aimed to find out the sero-prevalence and other socio – cultural factors among truck drivers in Haryana state. In this cross sectional study, a total of 4072

truckers were contacted of which 4016 consented and 4000 gave blood sample for the study. 77% of the sample population was below 40 years of age. 73.3% of the population was married and in stable relationship, 0.6% were either separated or widowed and 26.1% were unmarried. 47.9% were drivers and 30.4% were co-drivers. Mean duration of occupation of 13.04 years with 26.8% were in this profession since less than 5 years duration. 13.7% were illiterate, 23.7% were middle level 22.8% were metric level educated. 14.9% population subjectively reported of non-injectable drug use and 0.4% reported of injectable drug use. Around 40% stayed away from home for more than 3 week per month. A significantly low HIV/ AIDS awareness was noted among the illiterate population than the literate one, with 85.2% of awareness gained from the driving license authority. 81.3% were not aware of their HIV status. 52.3% experienced extra marital sexual relationship and 71.6% were with the unpaid female partners. 17.2% positively responded of experiencing sexually transmitted infection symptoms in lifetime and 54.2% mentioned of not taken any treatment for it. 0.75% of the population tested reactive for HIV on serology testing which was 3 times more than general adult population in India (0.26%). About 60% cases of HIV either did not use condoms or used occasionally. Truckers being vulnerable for the sexually transmitted diseases showed 3 times more seropositive status than general population.

Seroprevelance of TORCH infection among pregnant women. The aim of this study was to assess the prevalence of TORCH infection complex (Toxoplasma gondii, Rubella virus, Cytomegalovirus (CMV) & Herpes Simplex) in pregnant woman. With a cross-sectional study design, this study was conducted in 22 sub centers of Attabira block, the rural field practice area of the department of Community Medicine in Bargarh district. A total of 402 antenatal mothers were interviewed for the study by simple random sampling. Mean age of the study subjects was 24.53 years (+3.63). Fig. 7 shows the prevalence of the targeted infection in the sample and Fig. 8 shows the age distribution. Considering either or both IgG and IgM as markers it is observed that Rubella is the

most prevalent (69.1%) followed by CMV (66.7%), Toxoplasma (39.8%), HSV 1 (23.6%) and HSV2 (13.2%) infection. Syphilis seroprevalence is least common, constituting only 2(0.5%). Toxoplasma and CMV were more prevalent at age groups 26-30 years and above whereas Rubella HSV 2 was more prevalent in the age groups below 26 years. However IgM seroprevalence is very high in ANC below 26 years. The most of the infections have occurred before the 20years of age.

This study showed that most of the TORCH infections in the pregnant mothers have occurred by 20 years of age and before or during 1st pregnancy. It is less common in the educated group and with spouse serving in private or government sectors.



Fig. 7: Bar diagram of IgG and IgM seroprevalence (in %) of different TORCH infections.



Fig. 8: Bar diagram showing the age wise distribution of the TORCH seropositive cases.

Monitoring and Surveillance of Hypertension Control in Slum through Community Ownership Program. This study aimed to explore the factors affecting compliance in the management of hypertension in urban slum population. The objectives in this study were to assess prevalence of hypertension in urban slum; to evaluate physical and behavioral risk factors among individuals suffering from hypertension; to assess the treatment adherence among those who were prescribed drugs for hypertension; to involve stakeholders in monitoring and surveillance of hypertension control; to assess the feasibility of community cluster members involvement in monitoring and surveillance of hypertension control; and to evaluate effect of community ownership program in hypertension control and adherence. This study was able to document that involving the community members in monitoring the hypertension would be able to provide beneficial results in terms of blood pressure control as well as improving the drug compliance. However, the compliance rates in this study improved initially and almost remained stagnant throughout with variations in between. At the end of the follow-up period the compliance rate was 65%. Involving multiple stakeholders and other healthcare providers, in addition to physicians, may help reduce the time and cost involved in the management. It was concluded from the results of this study that the Community members' involvement in hypertension control is feasible and can be successfully implemented, even in uneducated population, for their self monitoring of blood pressure control. Educated individuals can be convinced to monitor their blood pressure at home improving the drug compliance among them. Community Catalyst Activists can be trained to measure blood pressure thus can be utilized in hypertension management to enhance the acceptance and regularity of anti hypertensive drug intake.

DIVISION OF HUMAN RESOURCE PLANNING & DEVELOPMENT (HRD)

A. FELLOWSHIPS

 JRF (Junior Research Fellowship) - Annual ICMR JRF Fellowship Exam was conducted in collaboration with Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh at the 12 Centers viz. Bengaluru, Bhopal, Bhubaneswar, Chandigarh, Chennai, Delhi, Guwahati, Hyderabad, Kolkata, Mumbai, Srinagar (J&K) and Varanasi, in July 2017. Frequently Asked Questions (FAQs) for JRF fellowship were added this year on the ICMR website. In 2017, a total of 138 JRF were selected and presently, 73 JRFs who qualified the 2017 exam have joined in different institutes.

- ICMR Centenary PDF (Post-Doctoral Fellowship) - ICMR offers 50 PDF fellowships every year for working in 26 ICMR Institutes/ Centers with state-of-art R&D facilities. A total of 116 PDF's proposals were received by the Division during 2017-18, of the 116 proposals, 76 were considered for personal discussion and 36 were approved for funding and 30 PDF's are currently ongoing for 2017-18.
- MD-MS/Ph.D. Fellowship Currently, 3. this programme is being carried out at three Centres viz; King George's Medical University (KGMU), Lucknow, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru and Sri Ramachandra University (SRMU), Chennai. The selection of the candidates is made on the basis of a competitive National level examination consisting of a written test conducted at 3 or 4 Centers in the country. The candidates passing all MBBS examination in the first attempt with 60% or more aggregate marks are eligible for the examination. Under this programme, the selected medical graduates are provided financial assistance for 4-5 years and a total of 15 fellowships are available per year. During 2017-2018 out of 15 allotted slots a total of seven candidates were selected (KGMU-03; NIMHANS-01 and SRMU-03).

4. ICMR Chairs for Sr. retired Medical/ Biomedical Teachers/Scientists

i. Dr. C.G. Pandit National Chair - These prestigious Chairs of ICMR have a provision of remuneration of Rs 1.00 lakh per month and contingency grant of Rs. 7.50 lakh/year per Chair. The duration of Dr. C.G. Pandit National Chair is for five years (three years extendable by another two years after assessment of the progress and plans). Retired medically qualified persons are eligible for one Chair and retired non-medical/ bio-medical/ professors/ bio-medical teachers are eligible for the other Chair. The persons should preferably be the Fellows of all the National Science Academies. At a given point of time, only two such Chairs will exist. At present one biomedical Dr C.G.Pandit National Chair is ongoing.

- ii. **Distinguished Scientist Chair of ICMR-**Distinguished Scientist Chairs are open to retired scientists/ medical teachers who may belong to Medical/Bio-medical/Life Sciences with the excellent track record in the field of medical application. All the perks/ remuneration of Distinguish Scientist Chairs of ICMR will be at par with the existing Chairs of ICMR i.e. Rs. 1.00 lakh per month as a remuneration and Rs. 7.50 lakhs per year as a contingency grant. The duration of Chair will be for five years (three years extendable by another two years after assessment of the progress and plans). Usually two Chairs will be established at one point of time; their number will not cross five at any given point of time. Presently, two slots are occupied.
- 5. Adjunct Professors/Scientists of Universities/ Colleges/Institutes - This is a new Scheme of HRD, launched in 2016, which aims to enhance, strengthen and improve the quality of teaching, training and research in the ICMR network of institutes by utilizing the services of superannuated academics, reputed scientists including skilled professionals, both serving and retired. Ideally, they should be medical professionals, scientists, doctors and researchers in service or retired from national and international agencies/universities/

institutes. An acceptance letter is required from both the organizations *i.e.* from where the Adjunct Faculty is working and the place where he/she would like to give his/her services [ICMR Institute/Centre]. Presently, 10 Adjunct Faculties have joined ICMR Institutes/Centres in various areas of research.

STS (Short Term Studentship) - The main **6**. objective of this program is to provide an opportunity to MBBS students to familiarize themselves with research methodology and techniques by being associated for a short duration with their seniors on ongoing research program or by undertaking independent projects. This may serve as an incentive for them to take up research as a career in the future. The value of the studentship is Rs. 5,000/- per month for 2 month's duration (Rs. 10,000/- only) and is meant to be a stipend for the student. This is paid only after completion of research and approval of final report. The Guide/Institution is expected to provide the student with all facilities (kits, reagents & other requirements) for carrying out research. Cost of research must be borne by Institution/ Medical College where research is conducted. A certificate is issued and posted to the Principal's/Dean's office after 6-8 months of completion of research.

During the year 2017-18, a total of 4545 MBBS students had sent their proposal, out of which 1060 students had qualified for carrying out the STS-2017 research fellowship. A total of 911 students had successfully submitted the STS 2017 report in which 106 were rejected by ICMR as per STS guidelines. Therefore, 805 reports were successfully reviewed, out of which, 765 were declared qualified for the year 2017 by the reviewers (having Grades A- Outstanding; B- Excellent; C- Good and D-Satisfactory).

Also the number of overall female students (489) who qualified for STS 2017 was more than overall male students (276).

7. Medical Scientists)-EMS (Emeritus Scientists, who have retired or are about to retire and who hold/have held before their retirement, the posts of the status of a Professor/Associate Professor in a medical college or of Director/Deputy Director, in a Institute of an all India character or scientists with comparable scientific experience and achievements in an organization of the Council and have been actively engaged in biomedical research of a high standard are eligible for appointment as Emeritus Medical Scientists. Meeting for award of EMS is generally held twice in a year *i.e.* January/July. In the last five vears (2012-2017) 20 EMS have beenworking for ICMR in different areas of biomedical research.

B. FINANCIAL SUPPORT

- 1. MD/MS/DM/MCh/MDS thesis support-This scheme is primarily aimed at promoting good quality research in medical colleges through students pursuing post-graduation courses as well as to improve visibility and accessibility of their research work to larger research audience. Out of 273-thesis protocols, 86 protocols/candidates were awarded financial assistance for the year 2017-2018.
- 2. International Travel Grant to non-ICMR Scientists- A total of 1698 applications were received, out of which 389 were approved for funding, with a total budget of Rs. 250 lakhs.
- 3. Support for Seminars/Conferences/ Workshops- The sanction of grants by ICMR depends on the importance of the topic /subject of the Seminar/Symposium and its relevance to ICMR. Out of total 1324 applications received, 612 were approved.

C. MISCELLANEOUS PROGRAMS

1. ICMR Awards & Prizes- ICMR offers an array of awards in biomedical sciences. Majority of awards are while few are given on alternate years. In addition to the awards given for the meritorious work done by the scientists in a particular field of science, there are number of awards also given to recognize and adorn the scientific talent of the young scientists. A total of 262 applications were received for 2015 & 2016 and 42 awardees were awarded in different award categories.

- **ICMR-Induction** Training programme-2. ICMR has a nationwide network of 26 institutes which employ approx. 600 scientists from different fields of biomedical science. The ICMR scientists work in different disciplines and have varying degree and quality of research experience prior to joining the cadre. ICMR expects them to do research autonomously under supervision from their institutional heads and contribute to achieving goals of ICMR as an organization. Hence ICMR scientists are expected to have competencies to design, conduct, analyze and write reports of their scientific investigations. As ICMR did not conduct any formal orientation or induction training towards imparting competencies in research methods and research administration, therefore in this context ICMR conducted the first ever Induction Training Workshop for their newly recruited Scientists B and C. The First Workshop was conducted at ICMR-NIE, Chennai from 3rd-7th April 2017 on "Research methods and research administration" with 25 participants and second Workshop was again held in Chennai from 10th-14th July 2017 for the remaining batch of 30 Scientists. There were motivational talks by eminent biomedical scientists as well as lectures by different Directors' of ICMR institutes. The feedback was very encouraging.
- 3. In order to create awareness on the Menace of Predatory Journals, one-day Symposium was organized jointly by RMPPC and HRD Divisions at ICMR Hqrs, New Delhi for Delhi and NCR-based ICMR institutes. Another programme was organized at ICMR-RMRC, Bhubaneswar.

INTERNATIONAL HEALTH DIVISION

The International Health Division (IHD) in ICMR 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/DHR with international organizations/ institutions such as INSERM in France, German Federal Ministry of Education and Research (BMBF) and Helmholtz Association (HGF) in Germany; National Institutes of Health(NIH) in USA; University of Minnesota (UoM), USA; International AIDS Vaccine Initiative (IAVI), USA; Swedish Research Council for Health Working Life and Welfare (FORTE) in Sweden; Canadian Institutes of Health Research (CIHR) and International Consortium on Anti-Virals (ICAV) in Canada; National Health and Medical Research Council(NHMRC) and University of Sydney in Australia; London School of Hygiene and Tropical Medicine (LSHTM) and Medical Research Council (MRC) in UK; Foundation for Innovative New Diagnostics (FIND) and Drugs for Neglected Diseases Initiative (DNDi) in Switzerland; Academy of Finland (AF) in Finland; Global Alliance for Chronic Diseases (GACD); Research Council of Norway (RCN) in Norway; Russian Foundation for Basic Research (RFBR) in Russia; National Institute of Infectious Diseases (NIID) in Japan; The Department of Health Research (DHR) has signed a Memorandum of Understanding with National Institute of Health & Care Excellence (NICE), UK; International Vaccine Initiative (IVI), South Korea.

PURPOSE OF INTERNATIONAL COOPERATION

The purpose of these Memoranda of Understanding (MoU) and Joint Statements 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.

JOINT WORKING GROUP (JWG) AND JOINT STEERING COMMITTEE (JSC) MEETINGS

The regular 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.

In addition, the International Health Division (IHD) has also represented ICMR in various bilateral/multilateral Joint Committee Meetings coordinated by MEA, DST and MOH & FW, GoI for cooperation with various countries.

Following JWG/JSC meetings under various MoUs and Joint Statements have been held and were attended.

- Joint Steering Committee meeting under Indo-US Diabetes Research Collaboration at NIH, USA during 10-11th April, 2017.
- Joint Working Group (JWG) meeting under Indo-US Collaboration in Environmental and Occupation Health at CDC Atlanta, USA during 13-14th April, 2017.
- India-Egypt 4th Joint Committee Meeting (JCM) on S&T Cooperation at New Delhi (organized by DST) on 21st April, 2017.
- Organized Global Alliance for Chronic Diseases (GACD) Board meeting at ICMR Hqrs., New Delhi on 7th November, 2017.
- 1st Joint Working Group (JWG) meeting between India and Croatia on cooperation in the field of health and medicine at MOH&FW, New Delhi on 9th February, 2018.
- Participated in the Knowledge Summit of the First Indo-French Forum Gathering Major

Representatives from the Higher Education, Research and Innovation Sectors at New Delhi. The duly signed MoU between ICMR and Inserm, France was also exchanged during the Summit on 10th March, 2018.

The International Workshops/meetings held and attended under Bilateral/multilateral programmes.

- India-Africa Health Sciences Collaboration Expert Working Group meeting at Indian National Science Academy (INSA), Delhi during 6-7th April, 2017
- ICMR-INSERM-DBT Symposium on Ethical and Scientific Issues of Gene Editing Using CRISPR-CAS9 Technology at National Institute of Immunology, New Delhi during 27-28th April, 2017.
- Consultation meeting on Health Sector Cooperation and Asia Africa Growth Corridor (AAGC) at Japan, Tokyo during 31st July-1st August, 2017.
- High-level committee meeting Chaired by DG, ICMR at ICMR Hqrs to review the progress and status on various issues related to development and up gradation of Regional Supra National Reference Laboratory in SAARC Tuberculosis & HIV/AIDS Centre (STAC) at Kathmandu on 25th August, 2017.
- Meeting regarding consultation on the Asia Africa Growth Corridor (AAGC) – The Way Forward and made a presentation on 'Health Sector Cooperation' under AAGC at, New Delhi on 25th August, 2017.
- Meeting of 2nd INDIA-U.S. Health Dialogue at Nirman Bhawan during 26-27th September, 2017.
- Meeting on Indian National Commission for Co-operation with UNESCO (INCCU) at Vigyan Bhawan on 10th October, 2017.
- 1st World Conference on 'Access to Medical Products and International Laws for Trade and Health in the Context of the 2010 Agenda for

Sustainable Development' at New Delhi on 21st November, 2017.

 Indo-German Workshop on 'Prophylaxis and Therapy in Antibiotic Resistance' at ICMR Hqrs during 18-19th January, 2018.

MOUS SIGNED DURING THIS PERIOD

MoU between ICMR; Department of Health and Family Welfare; MOH&FW and International Vaccine Institute, South Korea for enhancing the vaccine research and capacity building in vaccine area at New Delhi on 21st August, 2017.

MoU between ICMR and Inserm, France was signed on 10th March, 2018 at New Delhi during the visit of Hon'ble President of France to India. The MoU duly signed by Secretary, Department of Health Research & DG, ICMR, MOH&FW, GOI and CEO & Chairman, INSERM was exchanged during the Indo-French Knowledge Summit held at New Delhi on 10th March, 2018.

EXCHANGE VISITS

The IHD supports and coordinates the international travel of Indian scientists engaged in approved bilateral collaborative research projects under various MoUs and Joint Statements with other countries. A total of 63 exchange visits of scientists / officials to and from India were arranged under various international collaborative programmes / projects.

HEALTH MINISTRY'S SCREENING COMMITTEE (HMSC)

The 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 2017-18, 4 meetings of Health Ministry's Screening Committee were organized, wherein 161 projects were considered and out of which 146 projects were approved for international collaboration / assistance with agencies from USA, Germany, France, Canada, Australia, UK, WHO and several other foundations and foreign universities. Out of which, twelve projects are co-funded by ICMR under ICMR-RCN (Norway) and ICMR- GACD Mental Health collaboration.

ONLINE SUBMISSION OF INTERNATIONAL COLLABORATIVE PROJECTS AT ICMR

For facilitating online submission of International Collaborative projects for consideration of Health Ministry's Screening Committee (HMSC), a prototype for online submission of HMSC projects was prepared and the online submission of projects has been opened on ICMR website since March, 2017.

INTERNATIONAL VISITORS / DIGNITARIES

The Division also organized visits by various visitors to ICMR from foreign countries / agencies such as British High Commission; RCUK; HGF-Germany; BMBF-Germany; Royal College of Pediatrics and Child Health, UK; NIID, Japan; University of Melbourne, Australia; British Council; DFG; Kyrgyz Republic; USA; UK; France and Switzerland.

INTERNATIONAL FELLOWSHIP PROGRAMME

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 were awarded to six Senior and twelve Young Indian scientists during the year 2017-18.

Three Scientist under ICMR Intl. Fellowships for Developing countries were selected.

INDIA AFRICA HEALTH SCIENCES PLATFORM

The Government of India and the African Union Government under the Indian Africa Forum Summit (IAFS) III held in October, 2015 called for strengthened partnership in addressing health challenges of common interest to both Africa and the Indian sub-continents. This gave an impetus to the formation of an India Africa Health Science Partnership where the 1st Health Sciences Meet was organised in September, 2016 at New Delhi that was attended by senior policy makers, technocrats, scientists, medical specialists, researchers and industry leaders from the two regions.

This resulted in the development of a Memorandum of Understanding (MoU) between ICMR and African Union that is presently waiting modalities of finalization and formal signing between the Government of India and AU.

The first meeting of Expert groups was held in April, 2017 at New Delhi which prioritized disease areas of interest to both India and Africa.

Action plan between ICMR and AU-STRC is being finalized w.r.t the following:

- i. Training and capacity strengthening of health professionals, researchers, regulators and industry staff.
- ii. India-Africa Health research collaboration.
- iii. Enhancing pharmaceutical trade and manufacturing capabilities for drugs and diagnostics.

INFORMATICS, SYSTEMS AND RESEARCH MANAGEMENT (ISRM) DIVISION

Established in 2017, ISRM is the youngest Division of ICMR. The division has a mandate to nucleate, promote and support Biomedical Informatics through services, focused programs and Centers of excellence for promoting Biomedical Informatics in medical research. The Division is working in

three primary areas (i) developing accessible data systems and integrated research platform through cataloguing data systems, inducing standardization, data management plan, , data management services, sharing and access policy and controlled vocabulary (ii) Disseminate data and information of public health relevance to different stakeholders though websites, data and knowledgebase and social media and (iii) creating awareness about modern technologies (Biomedical Informatics, Genomics, Proteomics, Systems biology etc.) among medical professionals, multidisciplinary expertise and relevant infrastructure. During 2017-18, the Division has provided wide range of services to the scientific fraternity as well the administration and finance. The activities of the ISRM Division during 2017-18 can be grouped into three categories.

1. Data Management and Analytics

ICMR generates huge volumes of data through its extramural and intramural programs. Availability of this research data in a timely and responsible manner is essential for bringing accountability, responsibility and research acceleration. During 2017-18, the division has worked towards achieving the objectives of 'ICMR Strategic Plan and Agenda'. The Division established a Data Management Laboratory(DML) with the mandate of developing and providing professional data management solutions/applications to various programs of ICMR and medical fraternity from medical college / research institutes. During 2017-18, DML developed centralized data collection and analytics portals for following major programs of ICMR and Ministry of Health and Family Welfare.

- Leprosy Data Management System (Nikusht) available at http://leprosy.gov.in. It is a Web and Mobile based solution for systematic collection, management and real-time monitoring of Leprosy suspects and patients. The solution has been handed over to National Leprosy Eradication Program (NLEP).
- Antimicrobial Resistance Surveillance Network(AMRSN) available at http://iamrsn. icmr.org.in. It is a web based tool for collection,
management and analysis of data generated by the ICMR AMRSN. The tool has recently been used for contributing AMR data to Global Antimicrobial Resistance Surveillance System (GLASS).

- E-Partograph available at http://epart.icmr. org.in. It is a web and mobile based tool for monitoring progress of labour and for decision making for augmentation of labour, delivery by caesarean section and referral to a higher facility for further management. The tool is being implemented in Odisha state.
- Prevalence and Etiology of Hearing impairment available at http://hearing.icmr. org.in. It is a Web and Mobile based tool for collection, management and analysis of data on burden of hearing impairment collected by six Centres across the Country.

In addition, the division is also providing consultancy and services for systematic management of data and developing analytic dashboards. In line with the pillar 2 of the '*ICMR Strategic Plan and Agenda*', the division is providing hosting services to various programs of ICMR and non-ICMR institutions such as Indicleft available at http://indecleft.icmr. org.in, Indian Rare Disease Registry available at http://irdr.icmr.org.in/irdr/.etc. The Division is providing consultancy on redesign of Integrated Disease Surveillance Program (IDSP) portal. IDSP is a major flagship program of National Centre for Disease Control (NCDC).

The division is committed towards bringing standardization among various data sources. The Division has developed a Data Management Plan (DMP) Framework. A DMP is a formal document that outlines how data are to be handled both during a research project, and after the project is completed. Many Governmental, non-governmental, and private foundation sponsors of research are increasingly recognizing the value of research data. As a result, most funders now require that sufficiently detailed data management plans be submitted as part of a research proposal. The DMP

is proposed to be annexed with the applications for extramural funding. The DMP will be extremely useful in cataloguing data sources available with ICMR and further help in planning for data standardization and integration.

2. Extramural Research projects and fellowships in the area of Bioinformatics and Medical Informatics

During 2017-18, ISRM processed 27 adhoc projects and 63 SRF and RA fellowships. Majority of the projects are in the area of structural biology, however, recently the Division has taken steps to strengthen medical informatics and other areas of Bioinformatics.

3. Services to ICMR

• Research Management: ePPMS system: an entry point for electronic administration of ICMR funded projects promoting biomedical research, and hosts the service for managing the proposals throughout their lifecycle. The Council stands First in introducing a complete online system of its Extramural Project Processing among anyone of the Funding bodies of Science & Technology in India and is functional since January 2012.



Fig. 11: ePPMS system as of today.

In the year 2017-18, ICMR received 170 detailed adhoc proposals online. These proposals were completely reviewed online by an average of 3 experts and after normalization of scoring of all experts of each detailed proposal, a total of 134 proposals got \geq 60% scores and forwarded online to concerned division for further processing.

During the same period a total of 1255 SRF/RA fellowship proposals were received online (within 2 months- 1st June to 31st July 2017). These proposals were completely reviewed online by an average of 3 experts and after normalization of scoring of all experts of each proposal, a total of 959 proposals got \geq 50% scores and forwarded online to concerned division for further processing.



Fig. 12: Percentage Share of Fellowship Proposal, Division wise-2017-18.

An initial analysis of the data culled out from the system for proposals being submitted from the different parts of India, have clearly indicated change of productive institutions, subject areas being covered by investigators and the pattern of Cities and the 'Major Discipline' being chosen by investigators. Some of the remote cities, which have entered in the ICMR Extramural Project Scheme, are Sirmaur, Leh, Imphal West, Dindigul, Dimapur, Udham Singh Nagar, Tonk, Barpeta, Sirsa and Rupnagar. Seven 'Call for proposals' programmes were also launched during the year which resulted in receipt of 1157 proposals online and after verifying/checking the duplication/ incompleteness/Not in proper format/missing documents, all these proposals were forwarded to concerned division online for further processing. These included a). Call for concept proposals for identifying Young and Middle level Faculty to participate in Research Methodology Workshop (22-08-2017 to 31-10-2017 by RMC Division) (388 proposals), b). Call for proposal under North East Seed Grant Scheme (01-08-2017 to 30-08-2017 by RBMH&CH Division) (112 proposals), c). Call for Proposals for participation in National Registry for Rare Diseases (05-05-2017 to 15-06-2017 by RBMH&CH Division) (100 proposals), d). Call for Proposals for Research on Viral Hepatitis

in India (29-11-2017 to 15-02-2018 by ECD Division) (298 proposals), e). Call for proposals on Implementation Research (LOI) on Maternal and Child Health (07-04-2017 to 21-06-2017 RBMH&CH Division) (199 proposals), f). Call for Proposals on Indo-Norwegian Co-operation on Antimicrobial resistance (16-02-2017 to 26-04-2017 by ECD Division) (36 proposals), g). Call for Proposals on Tribal Health Research (09-01-2018 to 13-04-2018 by ECD Division) (24 proposals).

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Fig. 13: Home page of new revamped ICMR website.

- ICMR website: The division is maintaining the ICMR website at http://icmr.nic.in. The site hosts information about various ICMR programs/ activities, notifications and disseminates information to different stakeholders. The division has initiated a project for revamping the website with latest technology to enhance user-friendliness, enrich content dissemination, mobile application and security.
- ICMR Website revamping: The existing website was redesigned and several new features were added to it like audio-video section, publication section, ICMR News clipping section, expedition in day to day event reporting from HQ & other ICMR institutes, new guidelines' tabs, etc.
- ICMR e-English Bulletin: Total 7 issues have been designed, 5 for year 2017 and 2 for year 2018 (http://icmr.nic.in/bulletin.htm). Each issue is dedicated to a special cause, depending on the cause taken up world-wide during that particular period. These issues are completely compiled, designed and formatted in-house by online team. Apart from publishing regular features on topics of current

biomedical interest, the ICMR Bulletin also features articles from IJMR, bring out special issues commemorating important events and national and international days of relevance such as NO Tobacco Day, World AIDS Day, World Health Day, Breast Feeding Week, etc. Quite often the articles published in the ICMR Bulletin are those which are being featured as news stories in various newspapers, opinion articles, information regarding daily events/meetings at HQ, Seminar/Symposia/ Workshops sponsored by ICMR.



Fig. 14: ICMR e English Bulletins.

 Management of Social Networking sites e.g. Facebook, Twitter, YouTube, Instagram and LinkedIn of ICMR: The Division worked tirelessly to increase the virality and outreach of ICMR social media and successfully achieved it. The total likes in Facebook has increased 5 times during the year; as in Apr 2017 total likes was 2,066 and in Mar 2018 it got increased upto 9,953 in number. The number of followers in Twitter also has increased from 2,882 (Apr 2017) to 7,933 (Mar 2018).



Fig. 15: Outreach of Facebook during April 2017 – March 2018.



Fig. 16: Outreach of Twitter during April 2017 – March 2018.

- Initiated the process of ICMR Mobile Application development.
- Management of Direct Benefit Transfer (DBT)- Online team collects all transaction data from other divisions and Account section; then enter it on DBT portal on every month of all 6 registered schemes under this mission. ISRM division tried to develop the MIS of all schemes and integrated it with DBT App.
- Management of Public Financial Management System (PFMS)- During the year, a tremendous effort was made by ISRM division to implement PFMS module and complete all the entries at ICMR Hqrs. as well as its 32 Institutes/ Centers. To achieve the target tocomplete PFMS implementation, 13 training sessions were held in ICMR Hqrs. as well as its 32 Institutes/Centers with the support of Health Ministry.
- Management of Communication cell unit of ICMR to disseminate the goals, guidelines, events and research achievements of ICMR.
- Management of Annual Report compilation, editing, publishing, timely laying in parliament and distribution was successfully achieved by the Division. The Annual Report 2016-17 was designed keeping the principle of "Go Green" in mind depicting that ICMR is moving towards digitization and becoming paperless.



Fig. 17: Annual Report 2016-17.

- The Division continued providing the Internet, intranet and videoconferencing facilities to ICMR Headquarters and institutes. During the year the Division facilitated signing of MoU with the project ECHO wherein ICMR has been provided with software based Video Conferencing Licenses by ZOOM. The facility has been used extensively by ICMR for dissemination of educational and scientific session to wider-audience.
- The Division has initiated "Digital Swacchta Abhiyan" to eliminate piracy across the organization. The Division has conducted surveys to identify pirated software across the organization.
- The Division worked as a Nodal Point for all ICMR institutes and the Headquarters for e-Publishing of tenders on Central Public Procurement Portal of Government of India.
- The Division continues to provide programming services to different Technical Divisions. The division has developed an e-Recruitment portal for online submission and processing of applications for various posts/vacancies at ICMR.

MAJOR ACHIEVEMENTS

Reduction in Economic Burden & environmental pollution by complete digitization

• During the year ICMR received 170 detailed Adhoc Proposals and 1255 detailed Fellowship

proposals. Each proposal has an average of 50 pages including proposal's section A+B and C and all codal documents. ICMR insisted to submit all these proposals completely online, without a single hard copy submission and also evaluated these proposals completely online by assigning online to experts. Through this process. ICMR saved 71250 pages (170 adhoc +1255 fellowship = 1425 proposals X 50 pages each proposal = 71250 pages). ICMR helped to curb economic burden of PIs in the form of Cost cutting (Printing cost + Page cost + Speed post cost + Man power cost for each proposal) and environmental burden in the form of saving pages, saving trees, hence reducing environmental pollution.

- ICMR has moved one step ahead towards complete digitization of Annual Report of ICMR with cutting down hard copies from 1000 (500 English and 500 Hindi) to 400 (200 English and 200 Hindi) during the year 2017-18. Each Annual report has average 250 pages. Through this process, ICMR saved around 2 lakhs pages and cost of printing and postal charges of distributing the hard copies of Annual Report through speed post. Now, complete Annual Report is available online in ICMR website in pdf format.
- During the year ICMR published 7 issues of English Bulletin. Each bulletin has an average of 70 pages. These issues are completely online and available on ICMR website. These issues are compiled, designed and formatted in-house by online team. ICMR saved the pages as well as printing and distribution cost of these issues.

THE INDIAN JOURNAL OF MEDICAL RESEARCH

The Indian Journal of Medical Research (IJMR), a monthly biomedical journal has completed 104 years of its uninterrupted publication during this financial year (2017-2018). The IJMR is published in two volumes 12 issues every year and is covered by all major global abstracting and indexing services. The IJMR can also be read on IJMR App, both Android tablet and iPad. The IJMR is available full text free on www.ijmr.org.in and its Archive is available free on http://ijmr.in. The impact factor of IJMR for the year 2017 is 1.508.

The IJMR published high quality original research articles, descriptive review articles, systematic reviews/meta analysis, editorials, commentaries, research correspondences, letters to editor, Student IJMR, clinical images, *etc.* on a regular basis. In addition, perspectives, viewpoints, status reports, special reports, policy guidelines were also published occasionally. Supplements were also published on important topics of public health beside regular issues. A total of 14 issues were published during this financial year.

A total of 261 articles were published under various Sections/Categories; 59 per cent were original research articles, followed by 10 per cent review articles. Correspondences accounted for 9 per cent and clinical images 5 per cent (Fig.19).



Fig. 17: Articles published to IJMR under different categories (2017-2018).

Forty one per cent articles were submitted for consideration of publications from foreign countries. However, 17 per cent of articles published were contributed by countries other than India (Fig.2). Foreign countries with substantial contribution included United States of America, United Kingdom, Turkey, Italy, Brazil, Germany, *etc.* Figures 3 and 4 show distribution of contributors in two representative issues.

The IJMR has double blind and rigorous peer review process, and the quality was maintained by involving highly experienced reviewers from both India and abroad. Overall, during the period under report a total of 1068 reviewers peer reviewed for the IJMR and of these, 19 per cent were from countries other than India (USA, UK, Brazil, Turkey, Germany, Iran, Bangladesh, France, South Africa, *etc.*) (Fig.20).



Fig. 18: Indian and Foreign contribution in terms of number of articles submitted, published, and number of reviewers participated in peer review process during 2017-2018.

Two supplementary issues entitled, "Microbes & Health" and "Research in Non-Communicable Diseases" were brought out in July and November 2017 (Figs. 21 & 22). Eleven original articles were included in supplementary issue "Microbes & Health" while 13 original articles were published in the supplementary issue "Research in Non-Communicable Diseases".



Fig. 19: Supplementary issue on Microbes & Health.



Fig. 20: Supplementary issue on Research in Non-Communicable Diseases.

Beside articles, selected books on recent contemporary topics were reviewed by senior experts from the biomedical research. A total of 37 book reviews were published during the year under report.

MEDICINAL PLANTS DIVISION

ONGOING ACTIVITIES

• 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 which serve as comprehensive, informative & reliable source of information providing information on new leads, thus helping in systematic and planned evaluation of Medicinal plants, including drug design, basic and applied research.

During the year, volumes 17 (with botanical names Na-Ny) and 18 (with botanical names Oc-Ox) covering monographs on about 234 medicinal plants species carrying multidisciplinary information with 5222 citations were published.



Fig. 21: Indian Medicinal Plants.

Earlier, 16 volumes of Reviews on Indian Medicinal Plants (with botanical names starting with A-My) covering multidisciplinary research data on about 4342 plants, running into about 18630 printed pages and covering about 66364 citations were 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. Work on other volumes is in progress.

• Quality Standards of Indian Medicinal Plants

During the year the The Quality standards on 35 medicinal plants were developed, monographs prepared, finalized, technically reviewed and published as Vol. 15 as part of series on "Quality Standards on Indian Medicinal Plants".



Fig. 22: Quality Standard of Indian Medicinal Plants.

Earlier 14 volumes have been brought out containing quality standards on 484 plants. 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. Monographs on another 35 plants are being finalized for 16th volume.

• Safety Review monographs on Indian medicinal plants

A new initiative has been taken to bring out the compendium of safety of Medicinal Plants with the

objective to review and document the safety related scientific information on important medicinal plants which are commonly used by the industry Under this programme information related to botanical name, common name of the plant (Ayurveda, Hindi and English), family name, parts used in the traditional medicine (i.e. Ayurveda), historical use of the plant, scientific studies related to therapeutic uses (both prechinical and clinical), safety information derived from acute, subacute and chronic toxicity studies, safety information from pharmacological studies, information on genotoxicity, reproductive studies in animals, safety information derived from clinical studies (i.e. adverse drug reactions), case reports on toxic effects in human and herb druginteraction both in animals and humans for 75 important medicinal plants have been compiled and published as Vol I in this series.



Fig. 23: Safety reviews on selected Indian Medicinal Plants.

TASK FORCE PROJECTS WITH TRANSLATIONAL APPROACH

Development of A Standardized Formulation For Preventing or Delaying The Development of Type-2 Diabetes in Subjects With Pre-Diabetes.

The above entitled Multicenteric Task Force project on "Development of A Standardized Formulation of Medicinal Plant Seeds For Preventing or Delaying The Development of Type-2 Diabetes in Subjects With Pre-Diabetes" was approved by the Council. A MoU has been signed between the selected industry and for this project. The project comprises four different phases of work for development of a phytopharmaceutical product in the area of pre-diabetes and is for a total duration of 5 years enrolling 10 different centers across the country.

• Development of a formulation for treatment of sleep disorders

The above entitled Multicenteric Task Force project on "Development of a formulation for treatment of sleep disorders" comprises four different phases of work for development on this herbal/Ayurvedic product in the area of sleep disorders and is for a total duration of 5 years enrolling 8 different centers across the country.

• Development of a website exclusively dealing with Medicinal Plants

A website has been developed exclusively on the Divisions activities and hyperlinked with the ICMRs main website.

DIVISION OF RESEARCH MANAGEMENT, POLICY, PLANNING & COORDINATION

ICMR Performance Evaluation (PEC): The Performance Evaluation of ICMR was undertaken by an independent 5-member committee chaired by Prof. M.K. Bhan. During this review, the Committee analyzed ICMR's role and contribution as the principle agency and driver of the national health research system. This role includes a stewardship function, financing function, creating and sustaining research resources and producing and using validated research output. The council also plays a pivotal role in the translation and communication of research to inform health policy and practice. During 8 PEC meetings PEC members analyzed various activities/documents and other information of ICMR and its Institutes as provided by the identified Nodal Communication Officers from various ICMR Institutes and compiled at HQrs, which includes research output, HRD schemes, courses, training programs, fellowships, international collaboration, support to national programs, surveillance networks, technologies, diagnostic kits, devices developed and other achievements

of ICMR. Information was also provided on budget over the years, global trends and budget of other Indian S&T agencies, SWOT analysis, staff structure, vacancies on different positions, stakeholders consultations, etc. PEC members visited 13 ICMR institutes for review and assessment of ICMR performance. Also, PEC members interacted with Secretary Health, MoHFW, DHR officials and other external stakeholders to gain insights of their view of ICMR's activities, achievements and performance. The PEC noted the strength and gaps of ICMR and provided major recommendations, which includes capacity building, merger of some of the institutes, mission mode projects etc. The PEC Report was submitted to the Government of India in June 2017. The same was also considered during review of autonomous bodies by NITI Aayog and presentation was made by the Chairman in the NITI Aayog.

ICMR Strategic Plan- Agenda 2030: A strategic vision document that outlines the ICMR's agenda to deal with health challenges in the country was prepared and finalized. This document includes the new health research strategy of ICMR for next seven years, designed to improve health outcome in India. ICMR strategic document is aligned with National Health Policy, NITI Aayog 3 year Action Agenda and touches upon health related sustainable development goals as well as Government's Flagship Programs. The document is based on 5 major pillars which includes strengthening health research capacity, data systems and research data platforms, leveraging traditional medicine, enabling evidence to policy and program implementation through research with 15 major goals. Its core aim is to deal with new emerging challenges such as anti-microbial emerging and resistance. re-emerging infections, providing evidence to policy and do gap analysis for strengthening ongoing national health programmes. It was released on 11th Oct 2017 by Hon'ble Minister of State for Health & Family Welfare, Smt. Anupriya Patel in the presence of Dr V K Paul, Member, NITI Aayog.

- Evidence to Policy: With an aim to translating research in to impact, three workshops on writing effective Policy Briefs were conducted at NIMR, Delhi, NIRRH, Mumbai and NIRTH, Jabalpur to train ICMR scientists. Around 40 Scientists from ICMR institutes and headquarters participated in the workshop. Four Policy Briefs were finalized after external peer- review and published on the website & shared with the stakeholders.
- Setting up a new Regional Medical Research Centre (RMRC) at Gorakhpur, Uttar Pradesh: Gorakhpur is known for severe problem of JE and AES over the years. Though NIV field unit is working in the area but to expand the scope to address other health issues of the entire eastern UP, efforts were made for setting the RMRC by upgrading the existing NIV, Field Unit at Gorakhpur.
- Symposium on Science Communication & Predatory Journal: In order to sensitize ICMR Scientists towards importance of science communication & menace of predatory journals, one day symposium was conducted on 27th March, 2018 in collaboration with Division of Human Resource Development at ICMR Headquarters, New Delhi. Sh Eminent speakersdelivered informative and thought provoking talks.
- Biomedical Communications: In order to strengthen ICMR's communication capacity, training was imparted to ICMR leadership to effectively communicate information and evidence to media. Three regional Media training workshops were organized at NIOP, Delhi, NICED, Kolkata and NIRRH, Mumbai. A total of 90 scientists including the Directors, nodal officers and senior scientists from each ICMR institute. Communications unit also conducted the monthly media analysis to see the trends and visibility of ICMR. The analysis captures the tonality, count and key themes of the media articles along with a list of ICMR leaders who have been quoted.

ICMR Coffee Table Book-'Touching Lives' and Animation Film: Attempts were made to prepare a coffee table book "Touching Lives" on ICMR landmark achievements over the vears, which includes 16 of its most pathbreaking health research findings which has left a positive impact on the lives of Indians. Be it the invaluable contribution in developing the highly effective DOTS treatment module for tuberculosis (TB) or micro-nutrient fortification of food products or life-saving interventions like oral rehydration solution and vaccines or fluorosis treatment to documenting rare blood-groups, bioenvironmental control of malaria, integrated vector management for filariasis, leptospirosis, paragonimiasis, etc. ICMR has worked tirelessly towards achieving the vision for a healthy India. As a celebration of its more than a century-long journey and a recognition of the work performed by its researchers, an animation film on its major activities and achievements was also made.

PUBLICATION & INFORMATION

During the year under report, the Division of Publication & Information continued its routine activities to disseminate the information among not only medical scientists, students but common man also. The Division continued to bring out its periodicals like *ICMR Patrika*, Annual Report of ICMR *Varshik Prativedan* in Hindi. Dissemination activities were also continued by organizing a number of exhibitions at various places in the country displaying the activities and achievements of ICMR. The major work done by the Publication and Information Division during 2017-18 are as follows:

HINDI UNIT

ICMR PATRIKA

The articles on major health topics were included in the ICMR Patrika. *Mansik swasthya ke kshetr mein prathmik chikitsa* (April, 2017); *Manav Swasthya par Jalvayu Parivartan ke Prabhav; Rashtriya Yakshama Anusandhan Sansthan, Chennai ka* Gauravamayi Itihas evam Uplabdhiyan, Part I. (May-June, 2017); Rashtriya Yakshama Anusandhan Sansthan, Chennai ka Gauravamayi Itihas evam Uplabdhiyan, Part II (July, 2017); Bharat mein Swasthya aur Anusandhan ki Taza Sthiti (August 2017); Avasad : samvad karna zaroori (Sept.-Oct., 2017); Dengue – Tezi se ubharati ek jan svasthya samasya (Nov., 2017); HIV par niyantran : Ek sajha Prayas (Dec., 2017);Schizophrenia ke Chikitsa Prabandh mein Prathmik Suraksha ki Bhumika (Jan., 2018); Karysthal par Tanav-Mansik Swasthya ka ek Upekshit Pahlu (Feb., 2018); Zika Vishanu – Bharat mein Sthiti (March, 2018).

Varshik Prativedan 2016-17

Brought out the Hindi version of ICMR Annual Report 2016-2017 as *Varshik Prativedan* 2016-17.

Hindi Day Lecture : organized a Hindi Day lecture at ICMR Hqrs on 13th September, 2017. Prof Shridhar Dwivedi, Sr Consultant, Cardiology, National Heart Institute, New Delhi delivered a popular lecture on the topic "उच्च रक्त चाप: कारण, निवारण और उपचार". The programme was chaired by Dr Soumya Swaminathan, Secretary, DHR & DG, ICMR. A large no of scientists, officials and staff members attended the lecture.

ICMR AWARDS FOR POPULAR MEDICAL BOOKS IN HINDI (2014-1015)

Organized the award distribution function at ICMR Hqrs on 9th March, 2018. The Chairperson gave away the First Prize, whichwas given to Dr Dinesh Mani for his book *Genome evam Genomiki* whereas the Second Prize was conferred on Dr Sunanda Das for her book '*Pradushan Janit Rog*'. The First & the Second Prizes carried a sum of Rs 100,000/- and Rs 50,000/- respectively along with the Certificates and the Mementos.

DISSEMINATION OF BIOMEDICAL INFORMATION

ICMR carried out large number of education and extension activities during the year in different

> parts of India to disseminate the activities and achievements of ICMR at various platforms as well as to enhance the outreach of ICMR. The major outreach activities were as follows:

- Vibrant North-East 2017 at Guwahati a 3 day exhibition Vibrant North-East 2017 held during 4-6 May, 2017 at Guwahati Veterinary College ground, Guwahati. ICMR institutes namely, NIMR Field Unit, Guwahati; NIN, Hyderabad; RMRC, Dibrugarh also participated.
- Indian National Exhibition-cum -Fair 2017 at Kolkata organized by Bengal Human Resource Foundation, Kolkata at Dinabandhu Andrews College Ground, Garia, Kolkata during 17th to 20th August, 2017. Apart from the exhibits from ICMR Hqrs, the exhibits from NICED & ROCH, Kolkata displayed the activities and achievements of ICMR.
- Mega Science Exhibition held at Solan, H P during 24th to 26th Oct., 2017. A large number of people especially school children visited the ICMR pavilion.
- National Exhibition-cum-Fair & Seminar organised by *Bangiya Sewa Samiti*, Kolkata during 14th to 18th December, 2017 at Sonarpur, Kolkata. In addition to ICMR Hqrs, its two institutes located at Kolkata *i.e.* National Institute of Cholera & Enteric Diseases, NICED, and Regional Occupational Research Centre East (ROHCE) participated in the exhibition.
- Mega Exhibition at Udhampur during 29th to 31st Jan., 2018.
- **Exhibition 'Destination Goa 2018'** held at South Goa during 2nd to 4th Feb., 2018.
- Exhibition 'Bhopal Vigyan Mela 2018' held at BHEL Dussehra Ground Bhopal during 9th-12th Feb., 2018.
- Pride of India Expo 2018 at 105th Indian Science Congress held at Manipur University, Imphal during 16th-20th March, 2018. The 105th

Indian Science Congress was inaugurated by the Hon'ble Prime Minister Shri Narendra Modi at the Manipur University, Imphal on 16th March, 2018. Dr Harsh Vardhan, Hon'ble Union Minister of Science & Technology and Earth Sciences, Shri Radhe Shyam, Hon'ble Education Minister, Manipur and many dignitaries visited the ICMR stall. The ICMR team including the scientists from ICMR's NIN, Hyderabad, RMRC, Dibrugarh & ROHCE (NIOH), Kolkata also participated.



Fig. 24: The Hon'ble Prime Minister Shri Narendra Modi and other dignitaries during the inauguration of the 105th Indian Science Congress at Imphal University.

PARTICIPATION IN 26TH WORLD BOOK FAIR

ICMR participated in the 26th World Book Fair held in New Delhi during 6th-13th January, 2018 and had put up the display and sale of ICMR publications. ICMR stall was visited by large number of people and books on nutrition were in great demand.



Fig. 25: Dr Harsh Vardhan, Hon'ble Union Minister of S & T and Earth Sciences visited ICMR Stall.



Fig. 26: Dr R. Chidambram, Advisor (S&T) to the Prime Minister of India in the ICMR Stall.

PUBLIC RELATION ACTIVITIES

This year PR unit conducted a series of meetings with Media heads in Ministry of Health and Family Welfare, Ministry of Information and Broadcasting (Press Information Bureau, PM Unit, All India Radio and Doordarshan). Also meetings were conducted with private media houses and news agencies with the purpose to establish a continuous communication to inform them about the activities of ICMR. The PR Unit managed media interaction of Secretary DHR & Director General, ICMR Dr Soumva Swaminathan, which was attended by 25 media people from national print and electronic media; including government media. Important events such as Annual day 2017, Development of diagnostic kits for diseases, Release of global burden of diseases report, Development of diagnostic tools for TB, Kochon award were attended by the media and subsequently, press releases of the above events were also disseminated to the media. All the information disseminated was given due coverage by the media.

ICMR INSTITUTES/CENTRES

REORGANIZATION/MERGER OF ICMR INSTITUTION

ICMR has grown over the period of time and has been observed by various committees to re-look into institutional set-up owing to changing health priorities. A Performance Evaluation Committee (PEC) headed by Prof M K Bhan, Former Secretary DBT, undertook an independent review of performance of Indian Council of Medical Research (ICMR).

One of the major recommendations suggested by PEC was the merger of institutes and centers of similar nature of work or Less than 10 scientists, or Low productivity [less than 1 publication per scientist per year]. PEC suggested that the merger would provide ample benefits like overhead savings, flexible financial allocation, improved efficiency, proper resource utilization, shared clinical support and infrastructure rationalization. PEC identified 8 ICMR institutes on the basis of low scientific staff and/or low productivity and proposed them to be merged with their larger counterparts.

It was suggested that the merger of institutes would allow for a synergy in fields that have a relationship to one another, but more importantly in which the fields could complement and enhance one another's capacities. This would help to streamline human and other resources to achieve efficiency, reduce overheads and create enabling environment to carry out cross-cutting research in relevant and emerging areas. To implement PEC recommendations a committee was constituted by DG, ICMR to look in to the matter and take appropriate action. Following decisions were taken:

The details of the merger are listed below

- 1. Centre for Medical Entomology (CRME), Madurai has been merged with Vector Control Research Centre (VCRC), Puducherry and will now function as VCRC Field station. As both the institutes were working in vector borne diseases, the merger would help in appropriate resource allocation.
- 2. National Centre for Animal Sciences (NCLAS), Hyderabad has been merged with National Animal Resource Facility (NARF), Hyderabad as mandate of both the institutes was more or less the same and new Institute has much broader vision. Since, it will take 4-5 years for NARF to be fully functional, till then NCLAS will be known as NARF. Once NARF building is ready in the new campus, all NARF staff will be shifted there. NIN will retain the existing building and convert it to animal house for its own research.
- 3. Genetic Resource Centre (GRC), Mumbai has been merged with National Institute for Research in Reproductive Health (NIRRH), Mumbai & will now function as a laboratory of NIRRH. GRC was a very small Centre and having extremely low number of Scientists.
- 4. Entero Virus Research Centre (EVRC), Mumbai has been merged with National Institute of Virology (NIV), Pune & will now become a field station of NIV. Field station may be shifted to new building in Kharghar and may also start working on rubella, measles

etc. in addition to work on polio. As both the Institutes are working in the area of virology, a centralized approach will facilitate better management.

- 5. Food and Drugs Toxicology Centre (FDTRC), Hyderabad has been merged with National Institute of Nutrition (NIN), Hyderabad & will become a laboratory of NIN. Since FDTRC was a small Centre, it would be better to function it as a connected laboratory of NIN.
- ICMR Virus Unit has been merged with National Institute of Cholera & Enteric Diseases (NICED), Kolkata with all its assets & staff. It will become a laboratory of NICED. Virus Unit was a small unit and can be better controlled with the merger with NICED.
- Microbial Containment Complex (MCC), Pashan has been merged with National Institute of Virology (NIV), Pune with all its assets & staff. It will become a laboratory of NIV, Pune. MCC was a laboratory and would work better with the merger with NIV as nature of work is the same and coincide with the mandate of NIV.
- 8. Merger of National Institute of Pathology (NIP), New Delhi was suggested by PEC to be merged with National Institute of Cancer Prevention and Research (NICPR), Noida but the committee constituted to look in to this merger found major administrative and technical issues in addition to differences in work and mandate of both the Institutes. Hence, the Committee recommended that NIP and NICPR merger requires more discussion and the matter may be kept on hold as of now.

Hence 7 ICMR Institutes have now been merged with bigger Institutes and number has reduced to 26 from 32, with the addition of Regional Medical

ICMR INSTITUTIONAL NETWORK

Research Centre (RMRC), Gorakhpur which was announced recently with the up-gradation of NIV, Unit at Gorakhpur to a full fledged centre.

EXPECTED OUTCOME OF MERGER

- a. Increased quality in research activities: The potential improvement in academic quality would be derived from the pooling of academic talent and infrastructure, greater financial or staffing resources, and opportunities for interdisciplinary research with a wider variety of academic subject areas.
- b. Economizing financial and human resources: The public funding mechanisms generally favour larger institutions, notably as their critical mass increases, for instance in research. The potential to generate more revenues – whether from public or private sources – from a stronger and wider basis may also be a consideration.
- c. Consolidation of the system: The merger would benefit in overcoming fragmentation, achieving critical mass, avoiding duplication of programmes, creating synergies.
- d. Strengthening the institutional position: The smaller institutes would gain greater academic success and reputation through increased size and development of niche disciplines resulting from bringing different specializations to collaborate more intensively. This would help universities to attract more talented staff and students as well as giving added opportunities to undertake international collaboration.

This also fulfills the recommendations of the Committee to review the functioning of Autonomous bodies under the Chairmanship of Shri. Ratan P. Wattal, Principal Advisor, NITI Aayog and former Finance Secretary to the Government of India.

 ICMR National JALMA Institute for Leprosy & Other Mycobacterial Diseases Dr. M. Miyazaki Marg, PO Box 101, Tajganj, Agra - 282001 Uttar Pradesh.

- ICMR National Institute of Occupational Health Meghani Nagar, Ahmedabad - 380 016 Gujarat.
- ICMR National Institute of Traditional Medicine Belagavi, National Highway No.4, Belagavi - 590010, Karnataka.
- ICMR National Centre for Diseases Informatics and Research Nirmal Bhawan - ICMR Complex (II Floor), Poojanahalli Road, Off NH-7, Adjacent to Trumpet Flyover of BIAL Kannamangala Post, Bengaluru - 562 110 Karnataka.
- ICMR National Institute for Research in Environmental Health Kamla Nehru Hospital Building, Gandhi Medical College Campus, Bhopal - 462 001 Madhya Pradesh.
- 6. ICMR Regional Medical Research Centre Chandrasekharpur, Bhubaneswar - 751023 Odisha.
- ICMR National Institute for Research in Tuberculosis No.1 Sathiyamoorthy Road Chetput, Chennai - 600031 Tamil Nadu.
- ICMR National institute of Pathology Safdarjang Hospital Campus - 110029 New Delhi.
- ICMR National Institute of Epidemiology Second Main Road, Tamil Nadu Housing Board, Ayapakkam, Near Ambattur - 600 077 Chennai.
- ICMR National Institute of Medical Statistics Post Box No. 4911, Ansari Nagar - 110029, New Delhi.
- ICMR National Institute of Malaria Research Sector-8, Dwarka - 110077 New Delhi.
- ICMR Regional Medical Research Centre, NE Region Post Box No. 105, Dibrugarh - 786001, Assam.
- ICMR Regional Medical Research Centre Gorakhpur Uttar Pradesh.

- ICMR National Animal Resource Facility for Biomedical Research (NARFBR) National Centre for Laboratory Animal Sciences, NIN Campus, Jamai Osmania P.O. Hyderabad - 500 007 Andhra Pradesh.
- ICMR National Institute of Nutrition Jamai - Osmania (P.O.), Tarnaka, Hyderabad - 500 007, Andhra Pradesh.
- ICMR National Institute for Research in Tribal Health Nagpur Road, Garha, Jabalpur- 482 003, Madhya Pradesh.
- 17. ICMR Desert Medicine Research Centre New Pali Road, Jodhpur - 342 005, Rajasthan.
- National Institute of Cholera and Enteric Diseases P-33, C.I.T. Road, Scheme XM Beleghata, Kolkata.
- ICMR National Institute of Immunohaematology 13th Floor, New Multi-storied Building, KEM Hospital Campus, Mumbai - 400012, Maharashtra.
- ICMR National Institute for Research in Reproductive Health Jehangir Merwanji Street, Parel, Mumbai - 400 012, Maharashtra.
- ICMR National Institute of Cancer Prevention and Research (NICPR) I-7, Sector - 39, Noida - 201301 Uttar Pradesh.
- 22. ICMR Rajendra Memorial Research Institute of Medical Sciences Agam Kuan, Patna - 800007, Bihar.
- 23. ICMR Regional Medical Research Centre Post Bag No. 13, Port Blair - 744 101, Andaman and Nicobar Islands.
- 24. ICMR Vector Control Research Centre Indira Nagar - 605006, Puducherry.
- ICMR National AIDS Research Institute G-73, MICD Complex, Bhosari, Pune - 411026 Maharashtra.
- ICMR National Institute of Virology 20 A Dr Ambedkar Road, Pune - 411 001 Maharashtra.



ICMR CENTRES FOR ADVANCED RESEARCH

- Advanced Centre For Newborn Health Research, All India Institute of Medical Sciences, New Delhi.
- 2. Centre for Evidence Based Child Health Advance Pediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh.
- Centre for Advanced Research on Environmental Health: Air Pollution, Sri Ramachandra University, Chennai.
- Emerging Areas In Molecular Medicine, Jawaharlal Nehru University, New Delhi.
- Centre for Molecular Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow.
- Centre of Excellence In Molecular Medicine, All India Institute of Medical Sciences, New Delhi.
- 7. Centre for Advanced Research for Innovations in Mental Health and Neurosciences Manpower Development and Translational Research Phase-A, National Institute of Mental Health and Neurosciences, Bengaluru.