From the Director's Desk

Dear Readers,

With great pleasure I present the second issue of Plasmodium—the fifth issue of NIMR Newsletter. Like previous issue, the current issue embodies the gist of activities of NIMR in general and related information on malaria research in particular. The most significant of these activities in the past six months, among others was the official inauguration of a new NIMR campus at Dwarka, New Delhi by the then Director General of ICMR, Prof. N.K. Ganguly. NIMR would now be able to function as a coherent and one-stop research centre for malaria and other vector borne diseases in India once we shift to the new campus by mid-2008.

Notwithstanding to various hindrances due to fragmented set-ups, research activities of NIMR have never been compromised. This is reflected by generation of huge extramural projects, quality research publications, international recognition to NIMR scientists, new drug trials, etc. during this period. I would like to take this opportunity to thank all concerned who have helped us in achieving some of these targets and understanding malaria in Indian perspective.

Over the years, NIMR has been a source of imparting training in generating awareness on malaria. In recent times, in addition, NIMR has become an academic institute for training students of various institutions across the country on modern biology techniques like molecular biology, immunology, genomics, proteomics and bioinformatics. To aid this, a Central Instrumentation Facility has been created that is currently equipped with a 96-capillary automated DNA sequencer, Real-time PCR, HPLC along with other related instruments. Further, the NIMR scientific family is enriched by joining of Dr. Ruchi Singh as scientist C during this period.

I hope this issue of Plasmodium will aid in disseminating knowledge in malaria to a greater extent. Wish you a happy and prosperous new year 2008.

AP Dash
**Transgenic mosquitoes and the fight against malaria: managing technology push in a turbulent GMO world**

Gene modified organism (GMO) technology, if applied to mosquitoes, offers unique opportunities for controlling malaria by reducing transmission of the disease, according to a team of scientists from Austria, the Netherlands and Kenya. Even though insecticide treated nets (ITNs) are now widely used, insecticide resistance will continue to increase, necessitating alternative vector control strategies, according to the authors. Integrative approaches are needed to move genetic control trials forward with the greatest chance to properly assess the merits in terms of public health benefits. Resolving translational and implementation challenges may prove more complex and time consuming, but they will ultimately determine the power of transgenic mosquito development, according to the paper’s authors.

**New interventions for malaria: mining the human and parasite genomes**

The sequencing of the human genome provides a new opportunity to determine the genetic traits that confer resistance to malaria infection, as detailed by a team of international scientists. The identification of these traits can reveal immune responses, or host-parasite interactions, which may be useful for designing vaccines or new drugs. The parasite genome sequence is currently being explored to accelerate the development of new antimalarial interventions - for example, identifying parasite metabolic pathways that may be targeted by drugs. The genome sequence of the malaria parasite *Plasmodium falciparum* and its human host create new opportunities to solve the malaria problem.

**Microbially derived artemisinin: a bio-technology solution to the global problem of access to affordable antimalarial drugs**

Despite considerable efforts by multiple governmental and non-governmental organizations to increase access to artemisinin-based combination therapies (ACTs), these life-saving antimalarial drugs remain largely unaffordable to the most vulnerable populations. A new collaboration, described by a group of California researchers, is setting out to develop synthetic ingredients to help decrease the cost of the high price of these treatments. The project has the potential to reduce malaria mortality rates and to decrease the pervasiveness of counterfeit drugs. By providing the market with safe, low-cost ACTs, potential profits generated by criminal counterfeiting activities could be substantially lowered.

**Scientists make important discovery in battle against malaria**

At Johns Hopkins Malaria Research Institute, scholars recently identified a sugar in mosquitoes that helps explain, for the first time, the mechanism of the malaria parasite invasion. The sugar is essential in the parasite’s movement within the midgut section of a mosquito’s body. But the scientists say it is difficult to treat the mosquitoes in nature. They suggest a human vaccination with antibodies that would block sugar production in the mosquito. When a mosquito feeds on human blood, it would ingest the antibody.

The new finding brings scientists one-step closer to developing effective malaria vaccines. The best hope we have is that we have a combination of transmission blocking vaccine that the antibody works in the mosquito stage, combined with infection blocking, so that people are protected.” The finding could be a key element for a vaccine development in the fight against malaria. Experts report the understanding and control of the malaria parasite is one of the most serious scientific challenges of all time.

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**Forthcoming conferences**

**Fourth annual BioMalPar conference on the biology and pathology of the malaria parasite**

The European Network of Excellence BioMalPar is organising its fourth annual conference on the Biology and Pathology of the Malaria Parasite at Heidelberg, Germany on 14–16 April 2008. The scientific aims of the network are to address, in an integrated, collaborative manner, fundamental questions of the biology of the malaria parasite, its vector, and the disease, allowing optimal exploitation of the resulting knowledge to impact on public health. BioMalPar places a particular emphasis on its training role, and has established a high profile PhD scholarship. BioMalPar aims also to ensure a broad dissemination of research results and enhance the public awareness through the implementation of a website www.biomalpar.org, and the organisation of annual conferences, training courses and meetings.

**International forum for sustainable management of disease vectors**

Beijing 2008
Chinese Preventive Medicine Association (CPMA) and Chinese Center for Disease Control and Prevention (China CDC) plans to organize the Second “International forum for Sustainable Management of Disease Vectors” in 2008 in Beijing, China, followed by the First Forum in 2006 in Beijing. This Forum was launched by Society for Vector Biology and Control (SVBC), CPMA. The principal goal of this event is to promote further international communication and cooperation on sustainable management of disease vectors, to improve the ability of vector surveillance and control, and to promote the vector research and management network in the world.

Date: 2–4 November 2008
The latest information can be found at http://www.chinavbc.cn/forum
World Antimalarial Resistance Network (WARN)

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The world has seen emergence and spread of drug resistance in *Plasmodium falciparum* over the last few decades. This has resulted in treatment failure, recurrent malaria, anemia, increased transmission potential and mortality as well as the economic burden on health care. Thus, there is a need for an effective mechanism to detect drug resistance and ensure effective treatment of malaria. The information on resistance to most widely used drugs namely Chloroquine and Sulfadoxine-pyrimethamine has been documented but is widely dispersed and inaccessible. Now the important challenges are to use the information to understand selection and spread of drug resistance. Another area is to employ the tools developed and lessons learnt in mobilizing the system for effective, worldwide surveillance of resistance to the newly introduced drugs. To respond to the challenges, The Bill and Melinda Gates Foundation sponsored a meeting in October 2006. At that time, outlines were agreed by an ad-hoc group under the name, World Antimalarial Resistance Network (WARN). In cooperation with the WHO, a central repository of information on resistance to antimalarial drugs could serve to integrate and make accessible the important information being generated by different programs that study and monitor drug efficacy and resistance.

The WARN has now been funded by the Bill and Melinda Gates Foundation to plan for the implementation of the WARN. Dr. Neena Valecha, National Institute of Malaria Research is a member of the Board of Directors of the WARN and Dr. Hema Joshi and Dr. Saroj Mishra have both been active in the planning process, as well.

The available data on antimalarial drug resistance highlight many problems like diverse sources of data, lag between the time of study and accessibility to data. Knowledge on the efficacy of new as well as old drugs from many areas is still unavailable. There is a need for approaches to correlate pharmacokinetic and dynamic properties of drugs and molecular markers of resistance to therapeutic responses. Thus, we need to organize the available information and ensure that all members of the community have access to the data. This will need to be a collective effort involving the whole malaria community.

*In vitro* culture of *P. falciparum* is used to assess responses of parasite isolates to individual drugs free from host and pharmacokinetic factors. Even a small decrease in sensitivity of the parasites would be reflected in the outcome of an *in vitro* test on isolates from a particular region. These *in vitro* tests can yield early warning of parasite resistance long before clinical failure is manifested and will be crucial for detecting, confirming and characterizing resistance to the artemisinins. Currently, a wide range of *in vitro* test protocols are in use which creates difficulty in comparison.

Polymorphisms in parasite genes are used as molecular markers of resistance to some antimalarials and as an adjunct to *in vitro* and clinical measures of resistance. Although molecular markers for resistance to the artemisinins and some of their newer partners are not yet well defined, for the ‘old’ drugs, trends in prevalence of these resistance markers are useful predictors of treatment responses and can help to guide treatment policy.

For providing evidence to initiate immediate response on emerging resistance, the current data should be available in an open access format. The database should include tools to make data coding and entry in standardized format, output in various formats including map based to show regional and temporal trends. The WARN database will be modular, with data from four linked components: clinical efficacy trials, *in vitro* measures of parasite chemosensitivity, clinical pharmacology and molecular resistance markers.

The data on clinical and parasitological drug efficacy will be generated from clinical efficacy trials. WARN will use patient data to enable direct comparisons between studies and provide more comprehensive and accurate estimates of regional efficacy. The issues of confidentiality and intellectual property will be adhered adequately. For comparing the drug efficacy, tools like primary outcome, survival analysis will be used. There are already hints of reduced efficacy of artesunate-mefloquine and artemether-lumefantrine. In addition, some genetic changes have been observed in parasite populations following artemether-lumefantrine treatment. Genetic tools to follow ACT resistance

(Contd on p. 4.)
Malaria severity remains one of the major causes of the mortality worldwide. To understand the cause of the severity, research has been focused on parasite virulence phenotype and host genetic factor. One such virulence phenomenon of *Plasmodium falciparum* is rosetting of infected RBC with uninfected RBCs, which causes vascular obstruction and impaired tissue perfusion leading to multi-organ failure. Several studies in Africa had suggested that rosetting has been associated with severity of malaria although no such association has been observed in Southeast Asia or Papua New Guinea. Rosetting is mediated by the binding of *P. falciparum* Erythrocyte Membrane Protein 1 (PfEMP1), expressed on the surface of infected RBC with variety of uninfected RBC receptors including complement receptor 1 (CR-1). PfEMP1 is a 200 kDa polymorphic immune regulatory protein (single polypeptide chain) present on erythrocytes, neutrophils, eosinophils, monocytes, macrophages, lymphocytes, mast cells, and glomerular podocytes. Functionally, CR-1 helps in clearance of immune complexes, regulates the activation of complement cascade by preventing formation of classical and alternative pathway convertases and by acting as a cofactor for Factor I mediated cleavage of C3 (Fig. 1). Expression of CR-1 on RBCs vary from individual to individual, the differences might determine susceptibility of an individual towards developments of cerebral malaria and severe malaria associated anemia (SMA).

Three types of CR-1 polymorphisms exist, viz. structural, density and Knop’s blood group. The density polymorphism (determined by co-dominant allele H for high and L for low expression on erythrocytic surface) arises due to an intronic single base change of d1d2 segment within the LHR-D (long homologous repeat) region, resulting a polymorphic Hind III site. Studies in Indian subjects reported that the gene frequency in normal individual of 0.23 and 0.77 for the L and H allele, where as percentage distribution of HH, HL, LL genotypes were found to be 63, 29 and 8%, respectively. Comparative studies show that the genotype frequencies observed in Indian populations is similar to that of Pacific Asians and Cambodian populations.

From the findings of a collaborative study between NIMR and All India Institute of Medical Sciences, New Delhi, it has been observed that the distribution of HH, HL and LL genotypes are 25.6, 54.8 and 19.6% in normal and 40, 52 and 8% in *P. falciparum* patients, respectively, however, frequency of H and L alleles were 0.53 and 0.47 in normal and 0.66 and 0.34 in *P. falciparum* patients, respectively. Based on the study, it was observed that a significant association of HH genotype with the occurrence and severity of the falciparum malaria.

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![Fig. 1: Schematic diagram depicting CR1 mediated cleaning of Immune complexes and SMA. M-Ag: Malaria Antigen; α-M-Ab: Antimalarial Antibody; Mø: Macrophage; C3b: complement 3b.](Image)

(WARN: contd. from p. 3)

have not yet been defined and an early-warning system is needed urgently to identify parasites resistant to either partner drug when they first arise.

There is a need to greatly reduce the disparities among the various *in vitro* test sites by agreement on culture conditions, time of incubation, starting parasite density etc. Then, the assays should include common standard strains with known drug responses. Thus, the *in vitro* network will be able to provide data that can be compared over time and across countries. It can also give early indications of resistance.

We also need to add pharmacokinetic surveillance to the clinical-efficacy studies in this ACT era. It is also proposed to estimate the drug level in individual patients in the context of clinical efficacy studies, so as to study the influence of pharmacokinetic properties of drug on therapeutic response. There should be a system of regional pharmacology reference laboratories to assure quality control.

**Conclusion**

Today, we have tools that can enable the mobilization of current information about drug resistance in *P. falciparum* and extend these advances to study the resistance in other *Plasmodium* species, especially *P. vivax*. These tools can be used to respond to the challenge presented by the rapid deployment of ACTs, track the path of resistance to the old drugs and to detect early signs of emerging resistance to the artemisinins. If and when artemisinin resistance does appear, WARN can emerge to be a global resource for confirming, characterizing and containing this resistance before it spreads globally.

**Further reading**

New projects launched

A phase II, randomised, open label, multicentre study to assess the antimalarial efficacy and safety of arterolane (RBx11160) maleate and piperazine phosphate co-administration and Coartem® in patients with acute uncomplicated Plasmodium falciparum malaria.

Assessment of efficacy, safety and population-pharmacokinetics of the fixed-dose combination of Artesunate-Mefloquine in the treatment of acute uncomplicated falciparum malaria in India.

A Phase III multicentre, randomised, double-blind, double-dummy, comparative clinical study to assess the safety and efficacy of a fixed-dose formulation of oral pyronaridine artesunate (180:60 mg tablet) versus chloroquine (155 mg tablet), in children and adult patients with acute Plasmodium vivax malaria.

A Phase III comparative, open-label, randomised, multicentre, clinical study to assess the safety and efficacy of fixed dose formulation oral pyronaridine artesunate (180:60mg tablet) versus mefloquine (250 mg tablet) plus artesunate (100 mg tablet) in children and adult patients with acute uncomplicated Plasmodium falciparum malaria.

HRP-2 and pLDH based diagnostic kits for the differential diagnosis of malarial parasites.

Application of attracticide (oviposition pheromone in combination with insect growth regulator) for surveillance and control of dengue and chikungunya mosquitoes.

In vitro sensitivity of Indian P. falciparum isolates to antimalarial agents.

Monitoring and epidemiological assessment of lymphatic filariasis in Kamrup district of Assam.

Promotion of Plasmodium research and training in India.

Workshops and training courses organised

NIMR Field Unit, Rourkela organised a workshop on “Environmental management of vector borne diseases” on 10 August 2007 in collaboration with Public Health Department of Rourkela Steel Plant.

NIMR Field Unit, Rourkela organised an awareness training programme on 9 October 2007 for 12 volunteers of a local NGO on vector borne diseases.

NIMR Field Unit, Jabalpur organized a meeting on “Preparation of a field site for malaria vaccine trial in and around Jabalpur” from 8 to 9 September 2007.

NIMR Field Unit, Jabalpur organised an International workshop on “Molecular epidemiology and immunology of malaria and other vector borne diseases” in collaboration with Regional Medical Research Centre for Tribals, Jabalpur from 16–19 October 2007.

New scientist joined

Dr. Ruchi Singh joined NIMR as Scientist ‘C’ on 27 August 2007. Before joining NIMR, she was a Post-doctoral Fellow at Centre for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, USA. Dr. Singh had obtained her Ph.D. in Microbiology from Jiwaji University, Gwalior and Institute of Pathology (Indian Council of Medical Research), New Delhi. Her research interest includes understanding the molecular basis of disease pathogenesis due to intracellular parasites Leishmania and Plasmodium.


Das A attended the International symposium on ‘Chromosomes to Genome’ at CCMB, Hyderabad from 3–5 July 2007.

Das A attended the meeting organised by TIFR and Institute of Pasteur, France on proposed research collaboration at the TIFR, Mumbai from 5–7 September 2007.

Das A, Singh V, Mallik P, Seth R and Prajapati S attended ‘International Workshop of Molecular Epidemiology and Immunology of Malaria and Other Vector Borne Diseases’ at Jabalpur from 16–19 October 2007 and presented papers.


Dash AP attended a meeting to discuss climate change on health under the Chairmanship of Principal Scientific Adviser to Govt. of India at New Delhi on 6 August 2007.

Dash AP attended 1st Conference on ‘Medical Arthropodology’ at CRME, Madurai on 31 August 2007.

Dash AP attended Indo-German workshop on ‘Genetic Susceptibility’ under ICMR-HGF at Braunschweig, Germany from 30 September to 2 October 2007.

Dash AP graced the inaugural function as Guest of Honour at International workshop on ‘Molecular Epidemiology and Immunology of Malaria and Other Vector Borne Diseases’ and chaired a session at RMRC, Jabalpur on 16 October 2007.

Dash AP delivered oration lecture at 7th Joint Conference of ISMOCD and IAE on ‘India Poised Investment in Public Health for Health Security and Quality of Life’ at Jodhpur on 26 October 2007.

Dash AP chaired a scientific panel and delivered an invited talk at the India Conference 2007 on ‘Innovations and Technologies for India’s Public Health System’ on 2 November 2007.


Dash AP, Valecha N, Malhotra MS and Kumar A participated in the meeting on ‘Estimation of Malaria Disease Burden in India’ held at New Delhi from 21–23 November 2007.


Dev V and Mittal PK presented papers at ’7th Joint Annual Conference of ISMOCD & IAE’ held at Desert Medicine Research Centre, Jodhpur during 27–29 October 2007.

Dhiman RC participated in RSTMH Centenary Conference at London from 13–15 September 2007 and presented a Poster.

Dhiman RC participated in TROPACON workshop organised by Madras Medical College at Chennai on 6 October 2007 and delivered a lecture.


Dhiman RC participated in National workshop on ‘Climate Change and its Impact on Health’ at Lonavala by WHO and NEERI from 26–27 November 2007 and delivered a lecture.

Dhiman RC participated in National workshop on ‘Climate Change and Disaster Management’ organised by National Institute of Disaster Management, Delhi on 28 November 2007 and delivered a Lecture.


Ghosh SK attended the ‘Malaria Task Force’ meeting at New Delhi on 1 June 2007.

Gupta H, Phookan S and Baishya T participated in a National Seminar on ‘Communicable Diseases in North-East India with emphasis on HIV/AIDS and Malaria’ at Nagaon, Assam from 24–25 August 2007.

Mishra AK visited CDC, Atlanta, USA for Molecular Biology training on PCR and Sporozoite ELISA from 19 November–7 December 2007.


Singh N presented papers at 56th Annual meeting of American Society of Tropical Medicine and Hygiene at Philadelphia, USA from 4–8 November 2007.

Singh N attended ‘34th Annual Conference of Clinical Biochemistry of India’ at New Delhi from 17–20 December 2007 and presented a paper.

Sreehari U attended ‘Editors of Indian Biomedical Journals’ meeting at ICMR, New Delhi on 10 October 2007.

Valecha N attended a meeting of Expert Group on Chemotherapy of Malaria at NVBDCP on 6 September 2007.


Valecha N attended a meeting of India–Country Coordinator Mechanism for the Global Fund to Fight AIDS, Tuberculosis and Malaria at New Delhi on 17 December 2007.
Research papers published (July–December 2007)


Chapter in Books


**Hindi pakhwara celebrated**

The National Institute of Malaria Research celebrated ‘Hindi pakhwara’ from 14 September 2007. During this period, a Hindi workshop was organised for the administrative staff. Besides this, various competitions were also organised for staff members.

A debate competition for officers and prize distribution ceremony were organised on 25 September 2007. The topic of debate competition was “Vartman Piddhi Ka Bhavishya-Sarkari Yaa Nij”. To grace the occasion, well-known writer Shri Himanshu Joshi and Dr. Kusumvir, Director, Central Hindi Training Institute were invited.

All the field units of NIMR also conducted workshops and various competitions to celebrate Hindi Diwas.

**Brain storming meeting on malaria**

The National Institute of Malaria Research organised a Brain Storming meeting on malaria from 12–13 November 2007 at Bhubaneswar, Orissa in collaboration with WHO/SEARO. Twenty-seven participants attended this meeting. There were representatives from the National Institute of Malaria Research, Indian Council of Medical Research, National Vector Borne Disease Control Programme, State Health authorities including the Principal Secretary, Health, Regional Medical Research Centre, Bhubanewar, and WHO staff from GMPHQ, SEARO and WRO India. The group made practical recommendations for control of malaria situation in the state.

**Research block of NIMR inaugurated**

The newly built research block of NIMR in its Dwarka campus was inaugurated by Prof. N.K. Ganguly, the then Director General, ICMR on 8 November 2007. Also present were Dr. S.K. Bhattacharya, Additional DG, ICMR and Mr. Sanjeev Dutta, Financial Advisor, ICMR.