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Annual Report 2017–18

NIMR

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ICMR-National Institute of Malaria Research
Sector 8, Dwarka, New Delhi–110 077

Annual Report
2017–18

Department of Health Research
Ministry of Health and Family Welfare
Government of India

ICMR-National Institute of Malaria Research

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Published by the Director, on behalf of ICMR–National Institute of Malaria Research, Sector 8, Dwarka, New Delhi–110 077;
Typeset, designed & printed at M/s. Royal Offset Printers, A-89/1, Phase-I, Naraina Industrial Area, New Delhi–110 028.

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Preface

I am delighted to present the Annual Report of the ICMR–National Institute of Malaria Research (ICMR–NIMR) for the year 2017–18. During this year, the Institute has made tenacious advancement to achieve its goals in research and development for supporting malaria eradication/elimination. Headway attempts are in continuation to accomplish the mandate of performing basic and applied research towards the delivery of outstanding results and in addition, for developing human resource by providing training and technical support to the National Vector-Borne Disease Control Programme (NVBDCP), Government of India. Over 40 scientists, 70 Ph.D. students/Post-doctoral scientists and more than 400 staff in New Delhi and 10 Field Units are the key driving force behind the progress of this Institute.

During the period, along with the ongoing programmes, the Institute took some major initiatives towards infrastructure build-up which include guest house, international hostel, auditorium, conference room and staff recreational facilities. A long-awaited animal research facility will open shortly and will be accessible to the researchers for conducting animal experiments that have the potential to advance for clinical testing in future.

This report presents a glimpse of the key research accomplishments, technical advances, scientific innovations, research supports, inter-institutional collaborations, training programmes, institutional activities, human resource development, community engagement initiatives, and the exceptional role and contribution of the Institute towards improving health outcomes related to malaria as well as other vector-borne diseases like dengue, chikungunya and zika.

The Institute has been identified as a Centre of Excellence for Impact of Climate Change on Vector-borne Diseases. Besides, the Institute, being WHO recognized Centre for Phase-I Pesticides and Malaria RDT Lot-testing Laboratory, continued to provide services to beneficiary institutions.

ICMR–NIMR is determined to support the NVBDCP in the drive to eliminate malaria from India by 2030 in line of WHO's initiatives and Government of India commitments. An initiative has been taken by the Institute to conceive and develop a trans-institutional research platform 'MERA India' (Malaria Elimination Research Alliance–India) to bring all the stakeholders working for malaria elimination in India under single umbrella.

Different Divisions of the Institute have demonstrated impressive progress and commitment towards the control and elimination of vectors and important vector-borne diseases. This year, the Institute has published over 50 research papers in peer-reviewed and reputed journals with several new findings and developments. Some patents were also filed.

In a study involving a comprehensive RNAseq analysis of Olfactory system of mosquitoes, the scientists of the Institute unravelled the synergistic actions of Odorant Binding Proteins (OBPs) and Odorant Receptors (ORs) in disease-transmitting mosquitoes. Scientists are also trying to identify novel dual target inhibitors which can effectively block the growth of malaria parasites by targeting cysteine and aspartic proteases. In this regard, scientists identified an allosteric inhibitor of parasite proteases, which can be combined with other classes of compounds as effective antimalarial chemotherapy. Using the allosteric inhibitor, especially in malaria, can serve as a new mechanism-based approach which could be less prone to drug resistance.

In this year, a pilot project 'Comprehensive Case Management Programme (CCMP) for control of malaria in Odisha' was the major watch. The project demonstrated up to 85% pre- and post-CCMP decline in monthly average malaria positive cases in each intervention health subcentre as compared to 32% in control. The results led to the scaling-up of the demonstrated interventions in the form of another programme 'DAMaN' in Odisha.

The Institute is also working on aedine-borne viral diseases like dengue, chikungunya and zika. A major project on zika surveillance is underway. NIMR scientists have also found multiple knockdown resistance mutations including a novel mutation that has a strong association with pyrethroid resistance to disease vectors. Besides, NIMR is publishing an open-access journal *"Journal of Vector Borne Diseases"*. The journal has received a global attention and is preforming well in its field. Approximately 60% of the manuscripts being published in the journal are from outside India.

I must thank all the scientists, students and staff of NIMR for their relentless contribution during the year. I am also thankful to the Director-General of ICMR for consistent support to the Institute.

Neena Valecha
Director

Executive Summary

Vector Biology and Control

- A comprehensive RNAseq analysis of olfactory system unravelled that synergistic actions of Odorant binding proteins (OBPs) and Odorant receptors (ORs) drives mosquito's host- seeking and blood-feeding behaviour.
- A study identified and characterized a unique multi-domain *attractin* (*Ac-atrn)* protein that is suggested to play dual role of managing neuro-olfactory associated physiological functions as well as courtship engagement behavioural responses in the mosquito *Anopheles culicifacies*.
- A meta-transcriptomic study identified and catalogued gut-specific genes as well as gut associated microbes, to further decode tripartite gut-microbe-parasite interaction in the mosquito *An. culicifacies*.
- In a study carried out in a tribal district of Chhattisgarh on the implications of insecticide resistance in malaria vectors on malaria transmission it was established that (i) LLINs provided significant protection against malaria infection and disease, even in areas with pyrethroid resistant malaria vector *An. culicifacies*, (ii) LLINs performed neither worse nor better either in areas with higher vector resistance or lower resistance, and (iii) LLINs may lose effectiveness, if resistance frequency or resistance intensity increases. New formulations based on neonicotinoids, a new class of insecticides having novel mode of action are under evaluation in combination with pyrethroids or as synergists for insecticide resistance management.
- Four knockdown resistance mutations (*kdr*) were identified in *Aedes aegypti* in Bengaluru City, *i.e.* F1534C, F1534L, S989P and V1016G. F1534L is a new mutation not reported elsewhere.
- New allele-specific PCRs (AS-PCRs) were developed for detection of *kdr* mutations S989P and V1016G in *Ae. aegypti* populations.
- Vector surveillance studies on Zika for detection of Zika virus in numerous pools coming from several localities of Delhi and Ahmedabad showed that none of the pools were positive for Zika; though 11 pools were found positive for dengue. This information has been sent to competent authorities for priority intervention.

Parasite Biology

- A study demonstrated that targeting allosteric sites in falcipains can serve as a new mechanism-based approach in malaria, which could be less prone to drug resistance. Allosteric inhibitor binds at the 'hot-spot' interactions at the allosteric site and maintains the naturally favoured zymogen state of falcipains. This is the first report to elucidate the restriction of an auto-processing event in falcipains through allosteric regulation. Two compounds NA-01 and NA-03 are not the active site inhibitors but rather blocked the auto-processing event when falcipains exist in their pro-forms.
- A study found metacaspases cysteine proteases as a potential antimalarial target for malaria control. Effector caspase inhibitor, Z-FA-FMK was found to be a potent inhibitor of an unusual cysteine protease metacaspase-2, which blocked the malaria parasite growth. Metacaspase-2 cleaves its natural substrate, TSN and Z-FA-FMK which inhibit enzyme-mediated TSN fragmentation. Metacaspase-2 is a potential antimalarial target due to its role in programmed cell death, and especially present in the parasite.

- Molecular characterization studies on *Plasmodium falciparum phosphoethanolamine methyltransferse (Pfpmt)* gene for development of potential and novel antimalarial drug targets led to identification of two compounds, ASN.1 and ASN.3 that have significant gametocidal activity against *P. berghei* and were observed as competitive inhibitors of *Pfpmt* gene.

Epidemiology

- In a pilot project "Comprehensive Case Management Programme (CCMP) for control of malaria in Odisha" there was 85% decline between pre- and post-CCMP in average monthly positive cases notified per Subcentre in the intervention blocks, while the decline was 32% in control blocks
- In view of launch of malaria elimination programme in India, the state of Punjab has qualified for malaria elimination as per National Framework of Malaria Elimination, 2016–2030. The Department of Health and Family Welfare, Government of Punjab is collaborating with the ICMR-National Institute of Malaria Research, New Delhi in order to validate the data of malaria of the state and to provide technical expertise to consolidate the efforts in elimination of malaria.
- The recommendations of a study on health impact assessment of Sardar Sarovar Project (SSP) in Command areas of Rajasthan were made to the State Health Department which included interventions like, biological control of mosquitoes through introduction of larvivorous fishes in newly constructed diggis and sump wells, repairing and de-weeding in canals etc.
- Phase III studies on the health impact assessment of Narmada basin dams and resettlement and rehabilitation colonies in Madhya Pradesh covered 20 dams and its components under three Field Units, one each at Indore (6 dams and 1238 villages), Sanawad (7 dams and 834 villages) and Bhopal district (7 dams and 224 villages). The mitigation measures and detailed recommendations were submitted to Narmada Valley Development Authority (NVDA) and State Health Department for necessary action for control of vector-borne diseases.
- Efficacy study on use of innovative ovitraps made by using cellulose comb for control of Aedes breeding in west-zone, New Delhi suggested that these ovitraps are very effective for surveillance and monitoring of mosquito vectors. Their control efficacy can be maximized through community participation if the data of surveillance indicators are shared with each and every house.

Clinical Research

- Monitoring the therapeutic efficacy of antimalarial medicines was continued. Both the ACTs, artemether lumefantrine and artesunate + SP were efficacious in north-eastern and other states, respectively in falciparum malaria, while chloroquine was efficacious in vivax malaria.
- A multi-centre, phase-IIIb, single arm trial was carried out in Ranchi and Mangaluru to assess the safety, tolerability and efficacy of Eurartesim oral film coated tablet formulation in children and adolescent patients with acute uncomplicated *Plasmodium falciparum* malaria. A total of 100 patients fulfilling screening criteria were enrolled in the study. The combination was efficacious, safe and well-tolerated.
- A National Malaria Slide Bank (NMSB) was established with aims to impart trainings and assessments for malaria microscopist at national level.
- At fever clinic, 144 malaria cases were diagnosed in the year 2017, which included 140 *P. vivax* and four *P. falciparum* cases.
- A total of 1609 dengue and 161 chikungunya cases were diagnosed in 2017 at NIMR which is a sentinel surveillance site for diagnosis of dengue and chikungunya. Dengue serotyping was performed in 24 samples and all belonged to DEN-3 serotype.
- A pilot study indicated presence of haemolysis following parenteral artesunate in severe malaria. ❑

Vector Biology and Control

1

1.1 Vector Biology

1.1.1 A synergistic coordination of olfactory derived factors manages complex behavioural responses in the mosquito *Anopheles culicifacies*

Decoding the genetic relationship of sense of smell is central to design new molecular tools to disrupt mosquito-human interaction. Immediately after mosquito emergence, an exposure to diverse environmental/chemical cues facilitate the maturation and learning of the olfactory machinery components (sensory appendages, maxillary palps and proboscis) to govern common innate behavioural activities such as nectar sugar feeding and mating in both the sexes. However, it is yet unclear whether the mating events have any direct impact on the initiation of host seeking and blood feeding behavioural responses. Our recent finding suggested that *quick-to-court* protein may have a crucial role to meet the conflicting demand of sexual mate partner finding and/or a suitable vertebrate host finding by regulating the expression of unknown olfactory genes in adult *An. culicifacies* mosquito.

In fact, the organization of the olfactory components is morphologically similar in both the sexes but carries unique structural differences which are responsible for discrete temporal peaks of activities to sense swarm and identify sex partner for a successful mating event. However, in case of adult female mosquitoes, we opined that the evolutionary forces might have driven an extra specialization of the olfactory components such as proboscis, enabling rapid host seeking and blood feeding behavioural adaptation. In other words, we termed this highly sex-specific extra specialization as an "evolutionary speciality" which not only evolve adult female mosquitoes as a fast blood feeder but make them a potent vector for many disease pathogens. Once, a mosquito takes first blood meal it needs to manage major physiological activities linked to blood meal digestion and egg maturation. These physiological changes possibly may have another level of impact on olfactory perception to guide oviposition site finding behaviour. We further hypothesize that first blood meal exposure must have a priming effect on the olfactory responses expediting the consecutive host seeking and blood feeding behavioural activities more rapidly than previous one.

To test and decode this evolutionary speciality, we performed, compared RNA-Seq data of the complete olfactory system of pre- and post blood meal adult female *An. culicifacies* mosquito, a dominant Indian malarial vector. A comprehensive molecular and functional annotation of RNA-Seq data unraveled a limited but remarkable change in the nature and regulation of unique sets of olfactory gene repertoire in response to distinct feeding status of the mosquitoes as described in earlier report (2016–2017). Here, we further extended our studies to fully decode the complexity of olfactory management strategy deriving complex behaviour response of host seeking, blood feeding and ovipositon site finding *etc.*

We demonstrated that a synergistic and harmonious action of olfactory encoded unique factors govern the successful 'prior and post' blood feeding associated behavioural complexities. A quick recovery of the actions of odorant binding proteins immediately after blood feeding, and delayed re-activation of olfactory receptor proteins after blood meal digestion completion are unique to manage diverse behavioural responses. However, an extended blood meal follows up experimental data analysis further hypothesize that first blood meal exposure is enough for prime learning, satisfying the motivational search of mosquitoes for the completion of their gonotrophic cycles. Thus,

it is plausible to propose that apart from the innate odor responses, adult female mosquitoes might take an advantage of prior odor (vertebrate) exposure, which leads an exclusive evolutionary specialty, allowing them to learn, experience and adapt as a fast blood feeder in nature (Fig. 1).

1.1.2 Transcriptional responses of *attractin* gene in the mosquito *Anopheles culicifacies*

Attractin, initially identified as a soluble human plasma protein is a large multi-domain protein of therapeutic potential, having regulatory functions in multiple physiological processes. In invertebrates, it was first identified as a water-borne protein pheromone that plays important role in chemical communication and coordinates reproductive activities. But their role in insects especially mosquitoes is not known. Our unexpected discovery of *attractin* homolog from the olfactory tissue of *Anopheles culicifacies* mosquito prompted us to investigate the possible role of *Ac-attractin (Ac-atrn)* in diverse behavioural responses, e.g. feeding, mating and other non-genetic stress. *Ac-atrn* is a 3942 bp long transcript, encoding a 1313 AA protein, having multiple domains including CUB, EGF, Keltch *etc.* and showed 80–90% homology to other insect/mosquito homologs (Fig. 2). As expected, phylogenetic data showed a conserved relationship among blood feeding as well as non-blood feeding insects and animals, hypothesizing a similar multi-physiological role of *attractin* in mosquitoes.

1.1.3 Food source stimulates *attractin* response in early larval development

A real-time PCR analysis showed relatively higher expression of *Ac-atrn* in the young L1 larvae when compared to egg and other developmental stages (Fig. 3a). This data indicated that an increase in *attractin* expression in emerging young larva may be important to taste, smell and move towards food

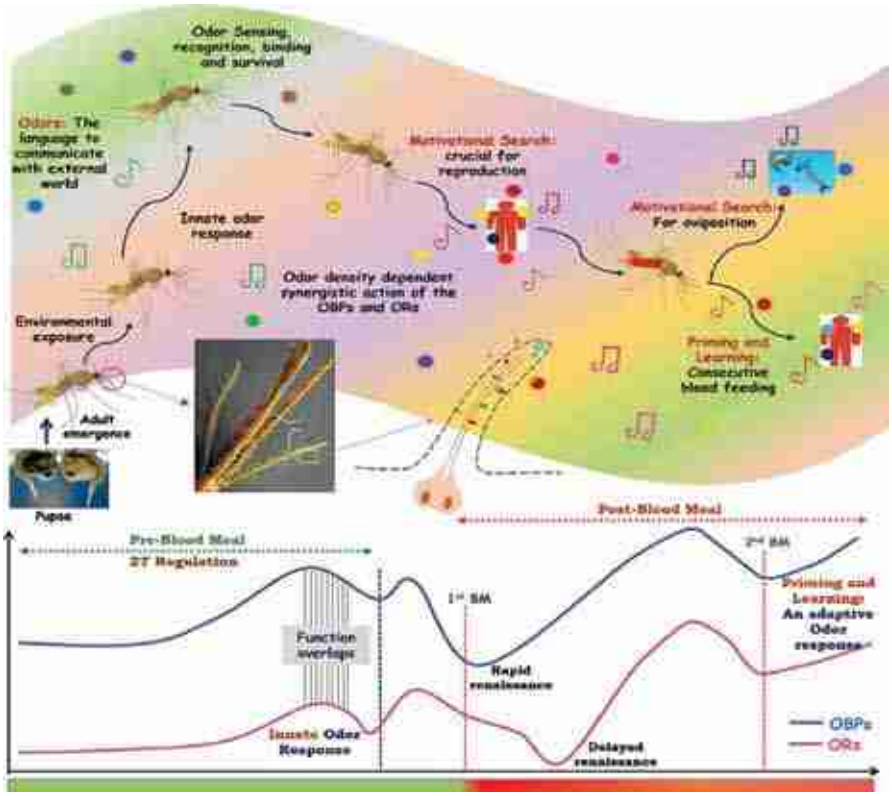


Fig. 1: How smartly olfactory system manages blood feeding associated odor response: an evolutionary speciality of adult female mosquitoes. After emergence from pupae adult mosquitoes are exposed to the overwhelmed odor world, where odorant chemicals act as a language of communication with the external world. The sophisticated innate olfactory system of mosquitoes enables them to recognize and differentiate this wide variety of odorants which are crucial for their every life cycle stages. Inner physiological motivation, as well as the age and exposure of mosquitoes towards the external world, promote them for host seeking and blood feeding event. After taking blood meal mosquitoes initiate next level of physiological-cum-behavioural events, *i.e.* oviposition. Apart from that, first exposure to vertebrates facilitates learning and second blood feeding events. These whole odor mediated response is tactfully managed by the synergistic actions of Odorant binding proteins (OBPs) and olfactory receptors (Ors). The overlapping circadian rhythm dependent functions of OBPs and Ors govern the pre-blood meal events of host fetching events. As soon as the mosquitoes take blood meal the functions of OBPs and Ors ceases for some period, but the recovery of OBPs action occurs early as compared to Ors to perform the next level of behaviours. Mosquitoes, then take advantage/adapted from priming and learning of the first blood meal exposure for the more rapid consecutive blood feeding.

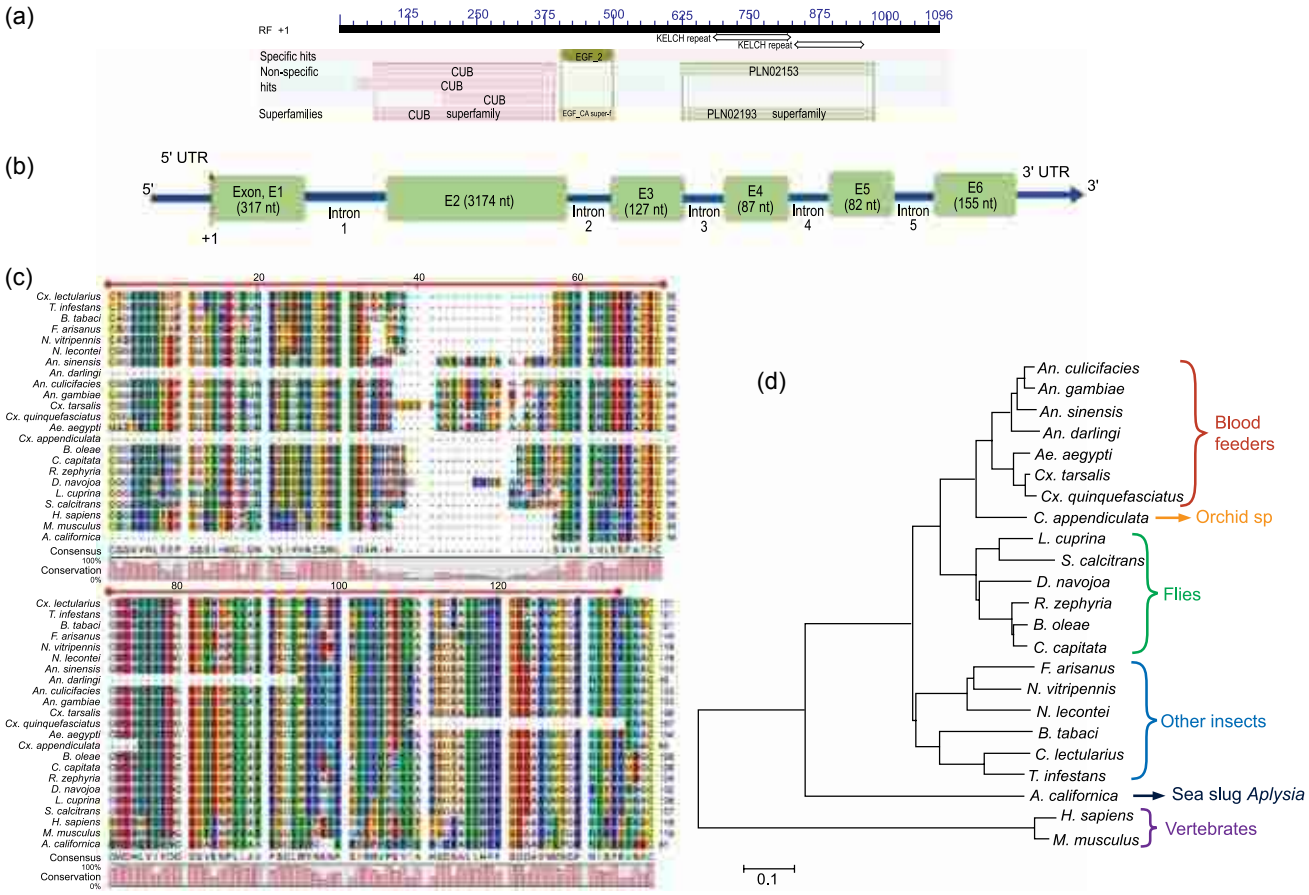


Fig. 2: Molecular analysis of *An. culicifacies attractin (Ac-atrn)* gene: (a) Domain architechture of *Ac-atrn* gene; (b) Schematic representation of the genomic architecture of the *Ac-atrn* gene. Five green coloured boxes indicates the exons, blue line denotes the introns and +1 mark the transcription initiation site. The size of the exons and introns correspond to the size of the boxes and lines; (c) Multiple sequence alignment of a segment of *An. culicifacies attractin* with other mosquitoes, flies, invertebrates and vertebrates homologs showing high degree of conservation in the amino acid sequence. One of the CUB domain is highlighted with horizontal red line; and (d) Phylogenetic relationship of *Ac-attractin* indicating that *An. culicifacies attractin* is clustered within the mosquito domain and have much greater similarity with mosquito *attractin* than flies and other insects. *Attractin* sequences of human, *Mus musculus* and invertebrate *Aplysia californica* were also considered in this analysis for out-group clustering (a) within the mosquito domain and have much greater similarity with mosquito *attractin* than flies and other insects.

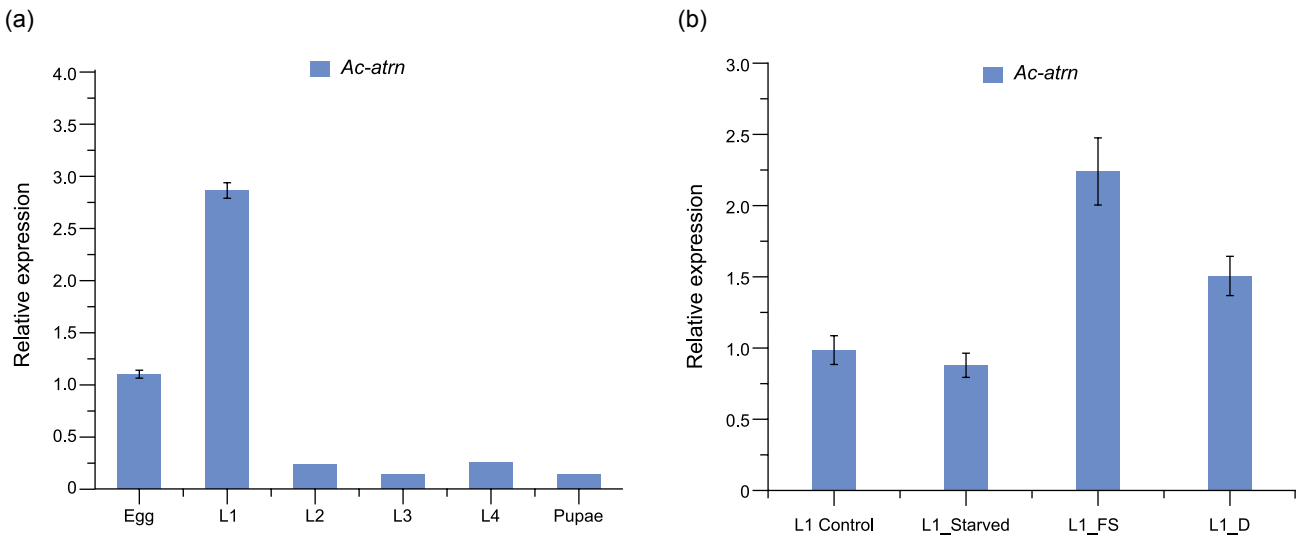


Fig. 3: Transcriptional profiling of *attractin* gene in *An. culicifacies* developmental stages—(a) Real-time PCR mediated developmental expression of *Ac-atrn* in *An. culicifacies;* and (b) Relative expression analysis of *Ac-atrn* under food stressed conditions in I instar larvae; L1–L4: Larval stage 1–4.

sources. Ten hours of food deprived larvae did not alter *attractin* expression, when compared to freshly emerge un-starved larvae of the same age, suggesting that nutritional stress do not influence the expression of *attractin* in the larvae. However, surprisingly, we observed a two-fold ($p < 0.01$) up-regulation of *attractin* in the naïve as well as the starved larvae, when given fresh food supply prior and after starvation, respectively (Fig. 3b). Together, these data suggested that a food supply may stimulate *Ac-atrn* expression, possibly to regulate the larval movement towards the food source. Dominant and elevated expression of *Ac-atrn* in the young larvae and increased transcriptional level in response to the fresh food supply of the starved larvae suggested its role in mediating chemical communication towards the food source. Furthermore, a temporary arrest of *Ac-atrn* expression in response to cold stress, indirectly suggested that *attractin* may have role in thermal regulation in young larvae.

Cold stress arrest attractin expression: Next, to test whether external/environmental stress influence the *Ac-atrn* expression, we exposed the young larvae to an overnight cold stress and compared its expression with unstressed larvae Though, cold stress did not affect the survival of the larvae, but we noticed the depletion of *Ac-atrn* to a negligible level ($p < 0.002$) in the cold treated larvae (Fig. 4). We also observed that cold treatment temporarily arrested the motility of the larvae, which was recovered to the normal active stage when kept back at room temperature for 3–4 h. Along with the recovery of larval movement, *Ac-atrn* expression also reached to normal level after 3–4 h of the recovery phase. However, 4–5 h of

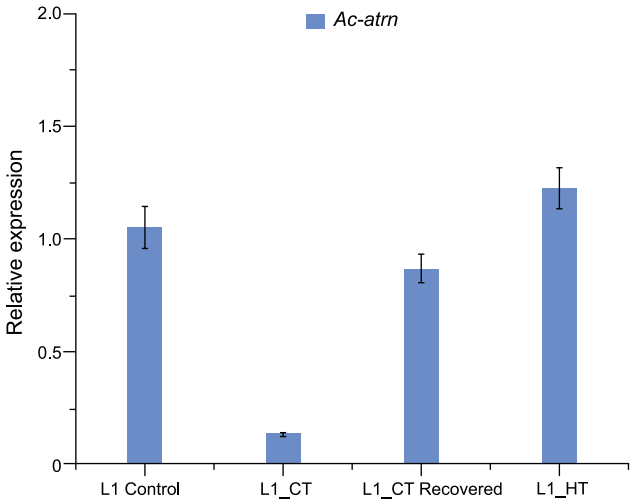


Fig. 4: Differential gene expression analysis of *Ac-atrn* gene in the I instar larvae under temperature stressed conditions.

heat exposure of the larvae at 42 °C did not alter *Ac-atrn* expression significantly ($p < 0.1$). Though it is yet to be clarified the exact role of *Ac-atrn* in the regulation of thermal stress, however, these data indicated that cold stress may temporarily arrest *attractin* expression, a response necessary to cease the motility in order to minimize the energy loss.

Nutritional stress may influence attractin response in the adult mosquito brain: A tissue specific expression analysis indicated that *Ac-atrn* constitutively expresses in the olfactory tissues, central nervous system and the reproductive organs of both male and female mosquitoes (Fig. 5a). But, ~2.5 fold higher level of expression was observed in the neuro-olfactory system than the reproductive tissues of both the sexes of naïve adult mosquitoes, suggesting its possible role in mosquito's behavioural biology and stress management. An initial gene expression analysis of sugar fed versus blood fed olfactory system did not show any significant alteration in the *Ac-atrn* expression (Fig. 5b). Furthermore, *Ac-atrn* expression level in the sugar fed and starved (24 h) mosquito's olfactory system remains un-altered (Fig. 5c). Together this data indicated that *attractin* protein may not be associated with the regulation of feeding behaviour in adult female mosquitoes.

But surprisingly, a time dependent starvation significantly modulated *Ac-atrn* expression in the brain tissue of adult mosquitoes of both sexes (Figs. 5 d and e). The male mosquitoes brain showed an early transcriptional response (6 h after starvation) of *Ac-atrn* gene ($p < 0.0001$) under nutritional stressed condition (Fig. 5d), whereas, female mosquitoes brain showed a delayed elevation of *Ac-atrn* at 30 h of starvation ($p < 0.0001$) (Fig. 5e). These data indicated that male brains are more susceptible to starvation induced neuronal damage as compared to female brains because in theses experiment, we also observed that the mortality rate of male mosquitoes is much higher than their female counterpart (Fig. 5f).

With these observations, we hypothesize that an early up-regulation of *Ac-atrn* in the male brain may be an attempt to protect the brain cells from fasting induced oxidative damage and consequently neuronal degeneration and death. Whereas, >10-fold elevation of *Ac-atrn* in the female brain during later stage of starvation suggested that female mosquitoes can survive a longer period of time (Fig. 5f) without any food source and thus are more

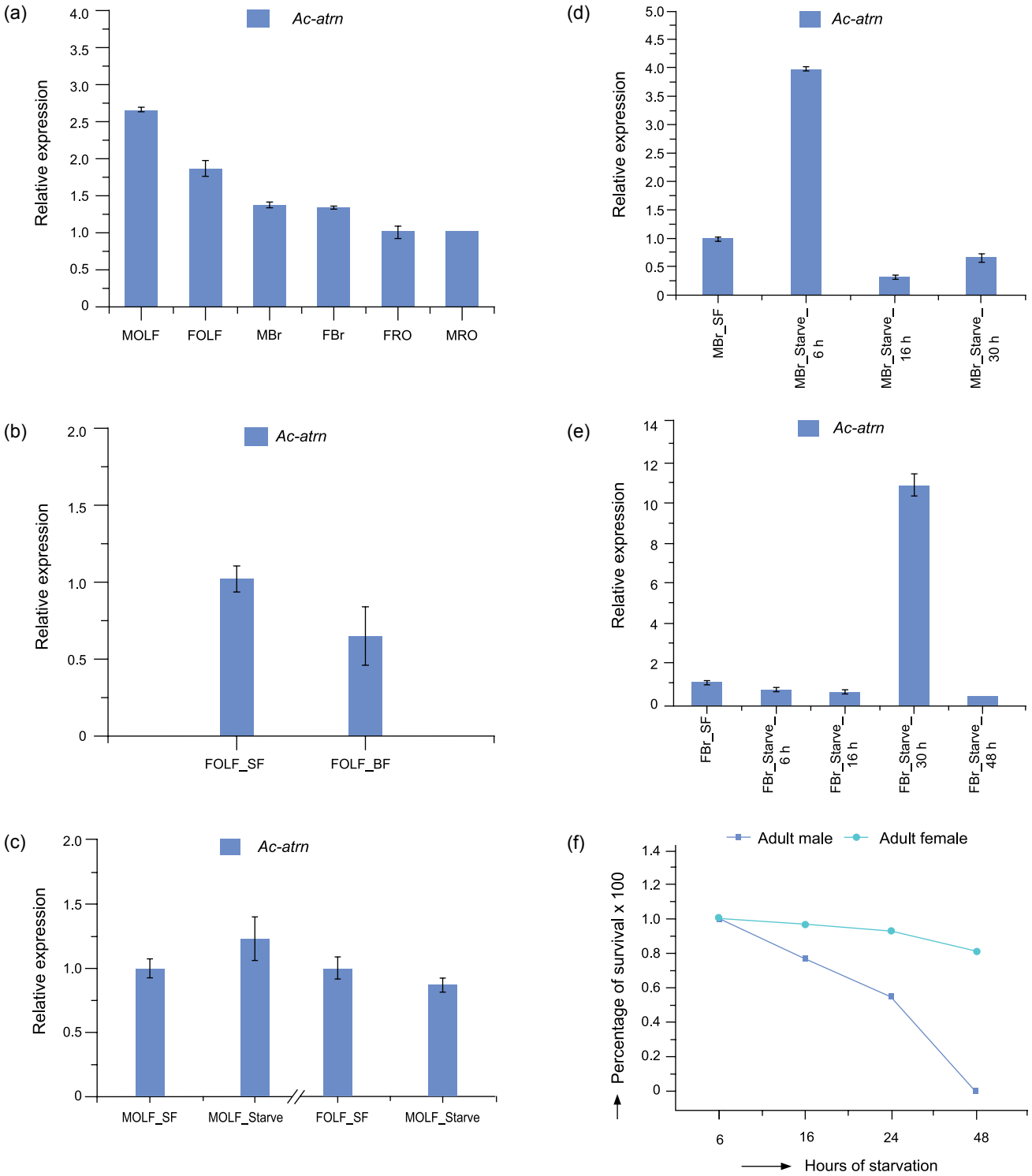


Fig. 5: Tissue specific transcriptional behaviour of *Ac-atrn*—(a) Tissue specific relative expression analysis of *Ac-atrn*; MOLF: Male olfactory tissue (Antennae, maxillary palp and proboscis); FOLF: Female olfactory tissue; MBr: Male brain tissue; FBr: Female brain tissue; FRO: Female reproductive organ; MRO: Male reproductive organ; (b) *Ac-atrn* expression pattern in sugar fed and blood fed olfactory tissues; FOLF_SF: Sugar fed female olfactory tissue; FOLF_BF: Blood fed female olfactory tissue; (c) Transcriptional response of *Ac-atrn* in the olfactory tissues of both male and female mosquitoes under food deprived condition; MOLF_SF: Sugar fed male olfactory tissue; MOLF_Starve: 24h starved male olfactory tissues (Same for the females); (d) A time dependent transcriptional profiling of *Ac-atrn* in the brain tissues of male *An. culicifacies* mosquitoes under food deprived condition; MBr_SF: Male brain dissected from sugar fed mosquitoes; MBr_Starve_6h: Male brain dissected after 6 h of starvation (Same in case of other time points); (e) A time dependent transcriptional profiling of *Ac-atrn* in the brain tissues of female mosquitoes under food deprived condition; FBr_SF: Female brain dissected from sugar fed mosquitoes; FBr_Starve_6h: Female brain dissected after 6 h of starvation (Same in case of other time points); and (f) Survival curve of 3–4 days-old adult male and female mosquitoes under food deprived conditions.

adaptive to adverse environmental conditions which favor its evolution and existence.

Age and sex specific olfactory response of attractin may influence mating behaviour: Given the multi-functional properties of *attractin*, next, we tested whether age dependent maturation affects the *Ac-atrn* response in mating behaviour of the mosquitoes. To examine this relationship, we performed an age and sex specific relative expression analysis of *Ac-atrn* in the olfactory and brain tissue of *An. culicifacies* mosquito. We observed a significant and continuous increase (~6 fold for female OLF and ~3.5 fold for male OLF) in *Ac-atrn* expression till the 7th day in the olfactory tissue of both virgin male and female mosquitoes

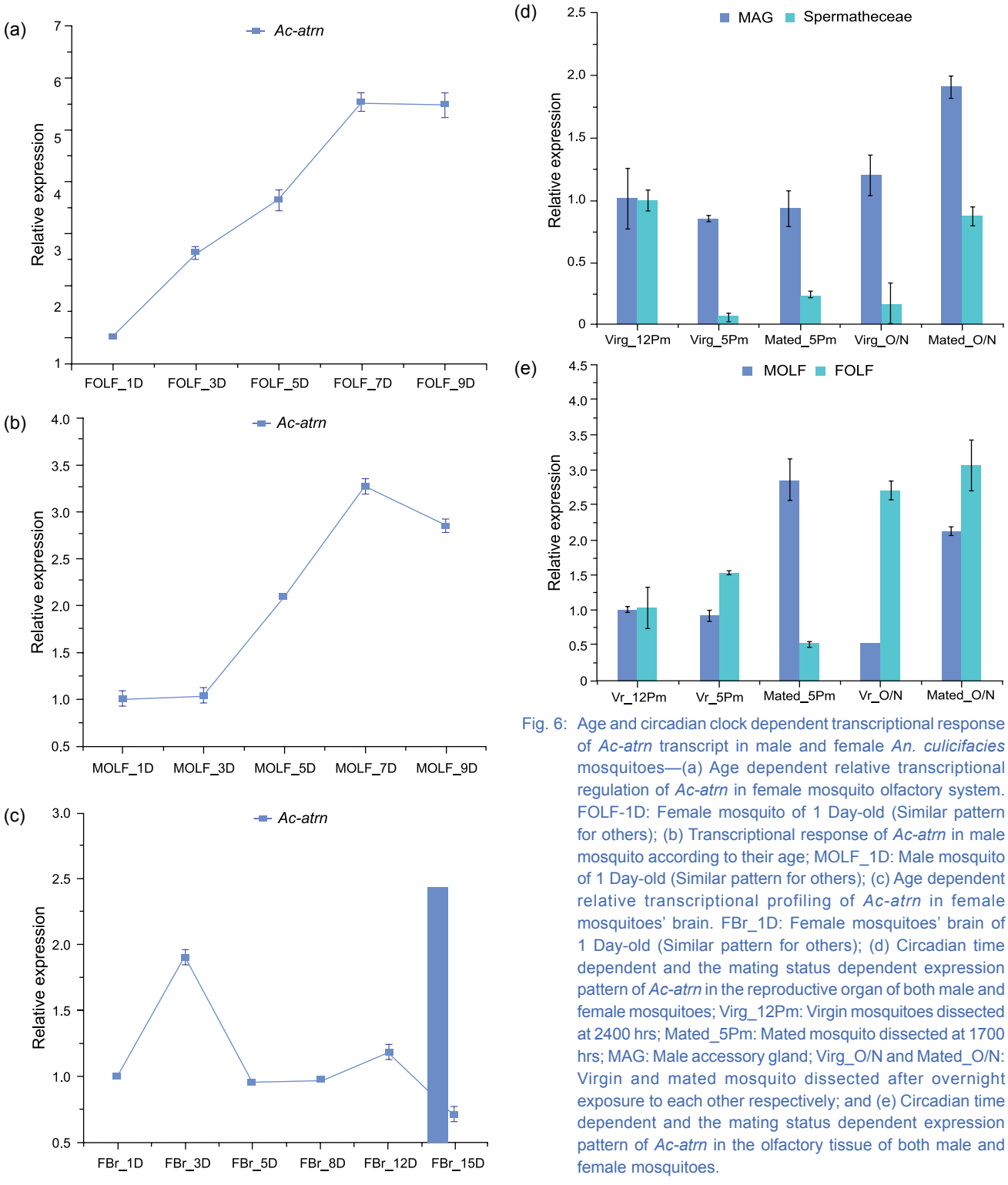


Fig. 6: Age and circadian clock dependent transcriptional response of *Ac-atrn* transcript in male and female *An. culicifacies* mosquitoes—(a) Age dependent relative transcriptional regulation of *Ac-atrn* in female mosquito olfactory system. FOLF-1D: Female mosquito of 1 Day-old (Similar pattern for others); (b) Transcriptional response of *Ac-atrn* in male mosquito according to their age; MOLF_1D: Male mosquito of 1 Day-old (Similar pattern for others); (c) Age dependent relative transcriptional profiling of *Ac-atrn* in female mosquitoes' brain. FBr_1D: Female mosquitoes' brain of 1 Day-old (Similar pattern for others); (d) Circadian time dependent and the mating status dependent expression pattern of *Ac-atrn* in the reproductive organ of both male and female mosquitoes; Virg_12Pm: Virgin mosquitoes dissected at 2400 hrs; Mated_5Pm: Mated mosquito dissected at 1700 hrs; MAG: Male accessory gland; Virg_O/N and Mated_O/N: Virgin and mated mosquito dissected after overnight exposure to each other respectively; and (e) Circadian time dependent and the mating status dependent expression pattern of *Ac-atrn* in the olfactory tissue of both male and female mosquitoes.

(Figs. 6 a and b). Together these data suggested that olfactory *Ac-atrn* may have an important role in the regulation of mosquito behavioural events. However, as compared to the olfactory tissue brain did not show any significant modulation, except an initial increase of *Ac-atrn* level in the aging adult female mosquitoes (Fig. 6c), suspecting its possible role in the regulation of mating behaviour during early adulteration age. Furthermore, an age dependent increase of *Ac-atrn* in the olfactory tissue of both the sexes, prompted us to test the possible role of *Ac-atrn* in mating behaviour.

A circadian dependent transcriptional profiling indicated that mating status did not alter the *Ac-atrn* expression in the reproductive tissue of both the sexes (Fig. 6d). However, a significant (>2.5 fold) change in the mated mosquito's olfactory system provides an evidence that *attractin* may facilitate pheromone guided male-female courtship behaviour (Fig. 6e). Though, it is yet to be clarified that how active swarm formation and courtship engagement is guided, but current data suggested that *Ac-atrn* may have a key role to attract the couples during swarm formation, which is actively commenced on the onset of the sunset (1700 hrs).

In summary, under multiple innate physiological status of mosquito, we evaluated the transcriptional response of *attractin* homolog *Ac-atrn*, originally identified from the olfactory system of *An. culicifacies*. A comprehensive *in silico* analysis and transcriptional regulation studies indicate that *Ac-atrn* not only supports neuro-olfactory associated physiological functions but may also play a crucial role in courtship engagement behavioural responses (Fig. 7).

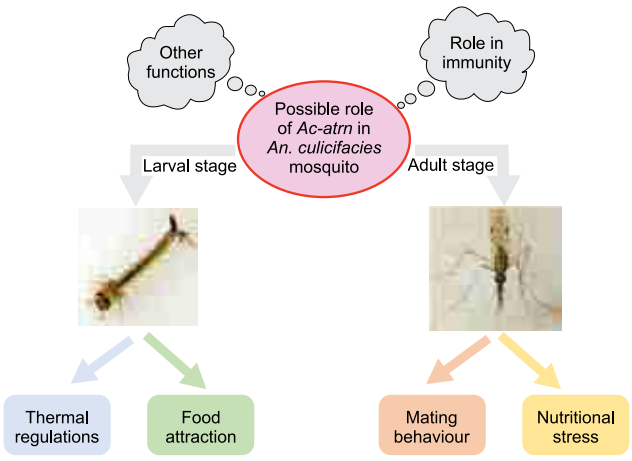


Fig. 7: Proposed hypothesis for the possible functions of *attractin* gene in the mosquito *An. culicifacies*.

Meta-transcritomic analysis of Anopheles culicifacies: Uncovering the functional relationship of gut-associated microbiome, may provide valaubale knowledge to establish paratrangensis strategies for vector control and parasite transmission. A comprehenive meta-transcriptomic study is in progress to decode the genetic make-up of the mosquito gut as well as catalogue the gut-assocaited microbes, in the mosquito *Anopheles culicifacies*. Briefly, here we report the preliminary data analysis so far carried out from the study.

Deep sequencing identifies diverse nature of gut proteins: Our Illumina Nextgen sequencing generated 2.5 GB data, containing 25,46,626 raw reads, which collapsed in total of 5,733 CDS during final assembly. A data stat is presented in Table 1. Initial annotation of total coding DNA sequence (CDS) transcripts data to non redundant (NR) database of NCBI using BLASTX, 5103 CDS matched to the insects most dominantly belonged to *An. gambiae* (95.33), *An. darling* (6.3), *Aedes aegypti* (2.39) and *Culex* (1.3%) etc. (Fig. 8).

A comprehensive gene ontology (GO) based functional annotation revealed mosquito encodes diverse nature of proteins, which could be catalogued to different categories at the molecular function level: organic (18%), heterocyclic compound binding proteins(18%) and carbohydrate derivative binding (8%) and approx. 20% belonged to hydrolase and transferase activity; Biological process belonging to metabolic process in which

Table 1. Assembly statistics for the transcriptomic sequencing of naïve mosquito gut of 3–4-day-old of *Anopheles culicifacies*

Description	AcMGC
No. of CDS	5,733
Total number of bases	42,93,360
Average transcript size	744
Maximum transcript size	3,237

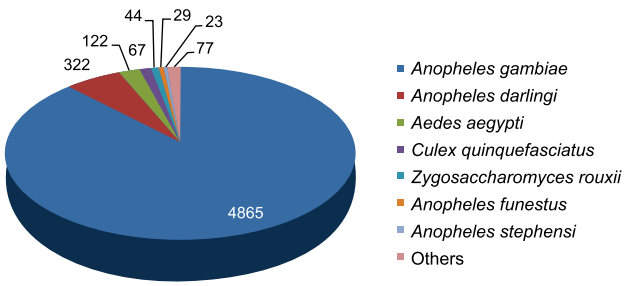


Fig. 8: Species distribution analysis (Blast hit) of the *An. culicifacies* transcriptome.

11% belonged to nitrogen compound metabolism; Cellular Component level revealed proteins belongs to which compartment at the cellular level that whether the protein belongs to membrane bound or any other category of the gut cell of the mosquito (Fig. 9a).

Naïve mosquito gut encodes distinct immune proteins: Insect immuno DB species database based cataloguing classified to 27 clusters of the immune proteins, dominantly belongs to the CLIPs, APG autophagy, C-type lectins and peroxidase category (Fig. 9b). Molecular characterization of a few selected target immune genes such as AMPs and others is under progress for transcriptional profiling against blood meal time series in the mosquito gut.

Blood meal modulates the gut microflora of the mosquito An. culicifacies: The preliminary analysis of metagenomics data revealed that blood meal may enrich the abundance of many gram negative bacteria such as *Enterobacteriaceae* member *Serratia* 49.4% and *Pseudomonadaceae* member *Pseudomonas, i.e.* 46.3%. These data allowed us to hypothesize that blood meal may have significant influence in the modulation of the gut endosymbiont bacterial community. To test and verify that how blood meal uptake and digestion affect the gut flora, a time dependent real-time PCR was performed for the relative abundance of the bacteria in response to blood meal. For this the mosquitoes were fed on live rabbit blood and the midguts were dissected on different time points post blood meal. The 16S rRNA based real time PCR analysis revealed that bacterial population is most abundant in the larva as compared to other mosquito stages. Tissue specific 16S rRNA based data showed the highest abundance of bacteria in the naïve mosquito midgut as compared to other tissues, *viz*. salivary gland, ovary, head, spermathecae and male accessory gland. The blood meal dependent time course revealed endosymbiont level is highest between 18 and 36 h post-blood meal (Figs. 10 a, b and c).

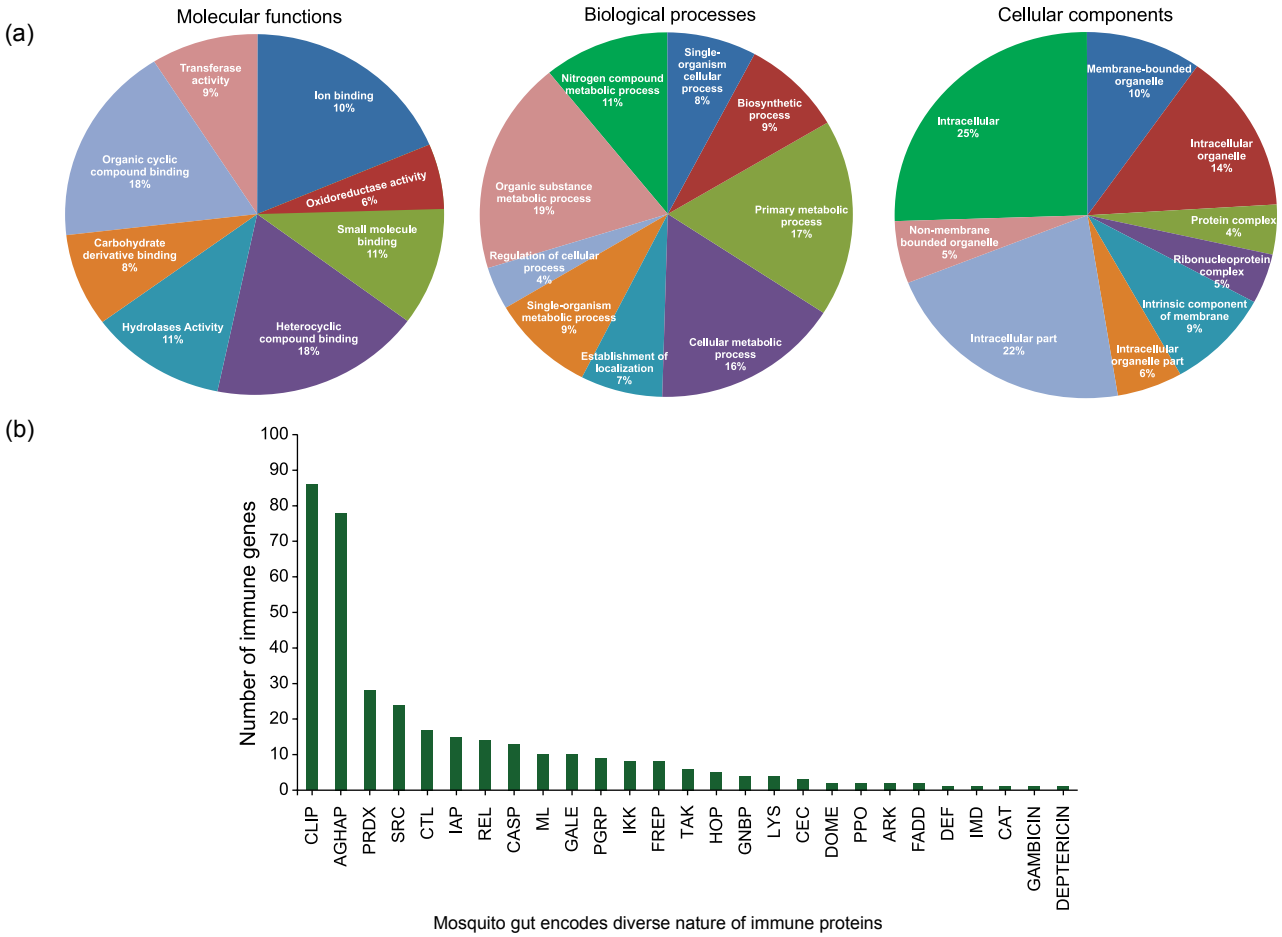


Fig. 9: (a) GO based annotation and cataloguing at the molecular function, biological process and the cellular component level; and (b) Immune cataloguing of the RNAseq data of the gut of the sugar fed *Anopheles culicifacies* mosquito.

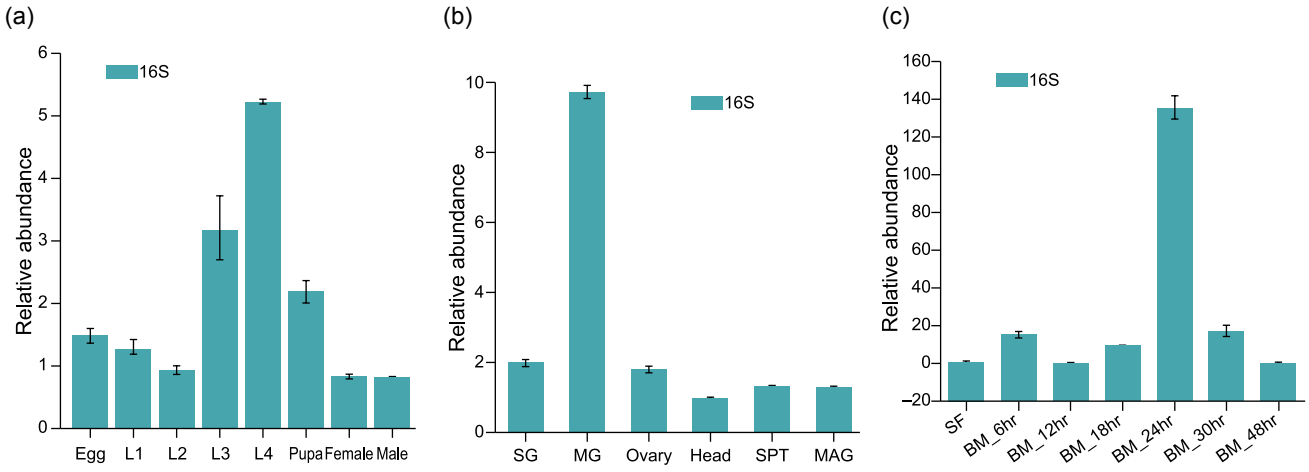


Fig.10: (a) Stage specific bacteria distribution in *An. culicifacies;* (b) Abundance of different microbes in the gut of *An. culicifacies* in sugar fed condition; and (c) Time dependent relative quantitative distribution of microbiota in the midgut of adult female in response to blood feeding in *An. culicifacies*.

1.1.4 Identification of multiple kdr mutations in *Ae. aegypti* population from Bengaluru

DNA sequencing of partial domain II, domain III and domain IV of the VGSC of *Ae. aegypti* population collected from Bengaluru, India (77° 56–57' E, 12° 92–95' N), revealed presence of four mutations, *i.e.* S989P and V1016G in domain II, and F1534C and F1534L in domain III. No mutation was found in domain IV. The mutation F1534L is being reported for the first time in *Ae. aegypti*. Two mutations S989P and V1016G are being reported for the first time in Indian subcontinent. Mutations S989P and V1016G present in domain II were due to substitution on first codon (TCC→CCC) and second codon (GTA→GGA), respectively. In most of the cases, the identification of S989 and V1016 mutations were based on 1x sequencing data where forward sequence was used for identification of S989 alleles and reverse sequence was used for V1016 alleles. This was due to presence of ambiguous sequence in downstream sequence resulting from multiple indels present in intron between these two *kdr* locus. In course of study a total of 294 samples were sequenced for partial domain II of which 178 were homozygous wild for both residues, *i.e.* SS at residue S989 and VV at residue V1016, 92 were heterozygous (SP and VG) and 24 were mutant homozygous (PP and GG). Other two alternative mutations F1534C and F1534L present in domain III were due to T>C substitution on the first position of the codon, leading to Phe (TTC)→Leu (CTC) mutation, and T>G substitution on the second position of the codon leading to Phe→Cys (TGC) mutation. Of the 27 individuals sequenced for domain III, one was homozygous FF (TTC, wild), seven were homozygotes for CC (TGC), four were homozygotes for LL (CTC), four samples were heterozygotes for each of FC and FL and seven were having mixed peak for two bases in first and second position of the codon, *i.e.* with YKC, which could be either heterozygote for LC (CTC+TGC) or FR (TTC+CGC). The latter combination was ruled out as successful sequencing of 15 cloned PCR products from five such samples revealed presence of one haplotype with CTC and another with TGC. We also observed that F1534L mutation had a restriction site for *Eco88*I. Therefore, for further confirmation of all the seven heterozygote samples with the codon YKC were subjected to PCR-RFLP with *Eco88*I and all were partially cleaved indicating the presence of CTC+TGC codon combination. DNA sequencing of 12 samples for partial domain IV revealed absence of any non-synonymous mutation including D1794Y reported elsewhere. Additionally, 25 samples were checked for presence of D1794Y using PCR-RFLP and none was found positive for this mutation.

Development of PCR-based assay for genotyping of* kdr *alleles: For genotyping of F1534-*kdr* alleles, we modified PCR-RFLP developed by Kushwah *et al*, 2014, where additional restriction enzyme *Eco88*I was used for identification of new allele F1534L. For genotyping of S989- and V1016-*kdr* alleles, we developed allele-specific PCRs (ASPCR) for each locus. Detailed methods are described in section material and Methods. The genotyping result of PCR-based methods developed were well in agreement with DNA sequencing results of all corresponding samples described above (Figs. 11 and 12).

Fig.11: Gel photographs of allele-specific PCR for identification of S989-*kdr* alleles. Lane M represents 20 bp ladder; Lanes 1 and 2 represents genotype SS; 3 and 4 SP; 5 and 6 CC; and Lane 7 represents negative control.

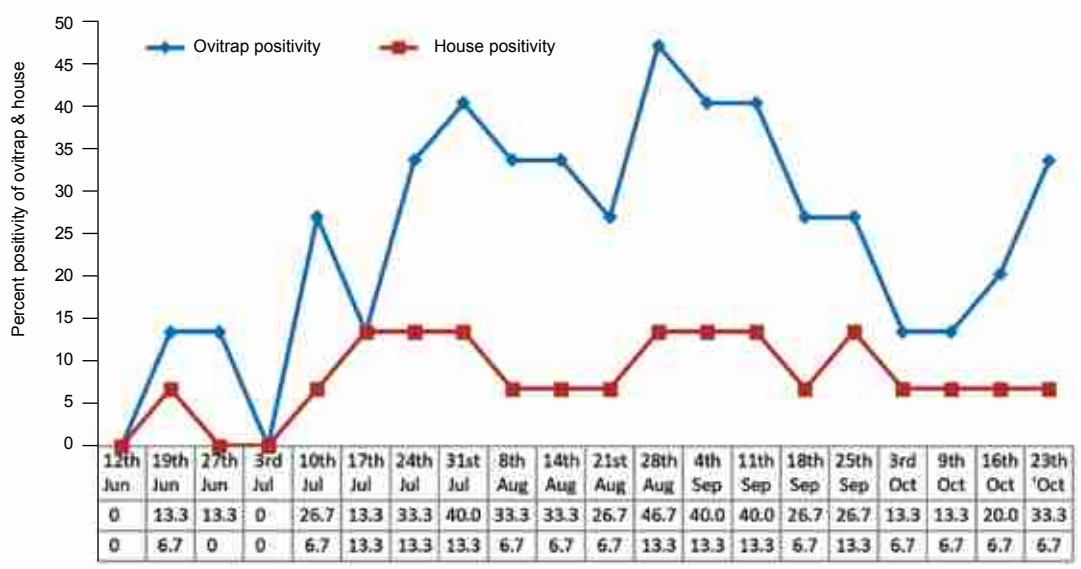
Fig.12: Gel photographs of allele-specific PCR for identification of V1016-*kdr* alleles. Lane M represents 20 bp ladder; Lanes 1 and 2 represents genotype VV; 3 and 4 VG; 5 and 6 GG; and lane 7 represents negative control.

1.1.5 Efficacy study on use of innovative ovitraps for control of *Aedes* breeding in west zone, New Delhi

The innovative ovitraps made by using cellulose comb which are up to 90.1% more effective than conventional types ovitraps were studied for the field efficacy in the Raj Nagar Part II area of Delhi. The ovitraps were installed in about 15 houses from June to August 2017 and tested with the control ovitraps by placing them at different locations in houses, *viz*. bed room, stores, drawing rooms, lobbies, toilets, *etc*. The positivity in the ovitraps varied from 13% in June to 46.6% in the month of August 2017 (Fig. 13).The positivity in houses without ovitraps was very less and it ranged from 0 to only 13.3% which suggests the ovitraps are very effective for surveillance and monitoring of mosquito vectors. The control efficacy can be maximized through community participation if the data of surveillance indicators are shared with each and every house.

The F-ratio value was 19.60545 and the *p*-value was 0.000132. The results were considered significant at $p < 0.05$. This means the positivity brought out by ovitraps is significantly higher than normal house positivity as done with routine methods.

With this study a uniform ovitrap evaluation protocol is also prepared for evaluating competent ovitraps. As the ovitraps were found effective and traps more eggs and bring out specifically *Aedes* breeding in houses, they can be evaluated further at other Field Units.



12th Jun	19th Jun	27th Jun	3rd Jul	10th Jul	17th Jul	24th Jul	31st Jul	8th Aug	14th Aug	21st Aug	28th Aug	4th Sep	11th Sep	18th Sep	25th Sep	3rd Oct	9th Oct	16th Oct	23th 'Oct
0	13.3	13.3	0	26.7	13.3	33.3	40.0	33.3	33.3	26.7	46.7	40.0	40.0	26.7	26.7	13.3	13.3	20.0	33.3
0	6.7	0	0	6.7	13.3	13.3	13.3	6.7	6.7	6.7	13.3	13.3	13.3	6.7	13.3	6.7	6.7	6.7	6.7

Fig. 13: Week-wise positivity of ovitraps (June–October 2017).

1.2 Vector Control

1.2.1 Vector surveillance of Zika/JE in selected high risk areas of India

Vector surveillance studies for Zika/JE virus launched as a comprehensive project in different sentinel parts of India were continued. In Delhi, NIMR was identified as nodal institute for screening of Zika virus. The project was focused on screening of adult *Ae. aegypti* mosquitoes collected from various localities of Delhi as well as the mosquitoes coming from other zika suspected areas through Government agencies. About 3388 *Ae. aegypti* were screened for detection of Zika virus in about 451 pools coming from 180 localities of Delhi and other cities (Fig. 14); none of the pool was found positive for Zika.

In addition to these, mosquitoes coming from Zika reported areas of Ahmedabad (369 mosquitoes in 50 pools) were also tested for the same; none of the pool was found positive for Zika. Among these pools, 11 were found positive for dengue as well. This information has been sent to MCD Delhi for priority intervention.

1.2.2 Feasibility of replacing modified lid of the "Tankas" (underground tanks) to reduce vector density and malaria in western Rajasthan: An intervention study

Under this project preliminary studies and selection of village has been done. Village Ajasar was selected on the basis of meeting with MO, Pokaran. The entomological as well status survey of breeding in underground tanks were conducted in the month of June 2017. About 29.1% (28/96) tanks were found positive for breeding; species composition included *An. stephensi*, *An. subpictus* and *Ae. aegypti*. The predominant breeding species in the underground tanks was *An. stephensi*. Involving Sarpanch of Ajasar village and the locals, a consensus was attained on the replacement of damaged lids. All the open tanks without lids and damaged lids of the tankas were marked for replacement with the modified polyvinyl lids (Fig. 15).

1.2.3 Generation of skilled task force for control of dengue

An initiative "First Seven Days-Skilled Workforce to Combat *Aedes*" was undertaken by the NIMR with

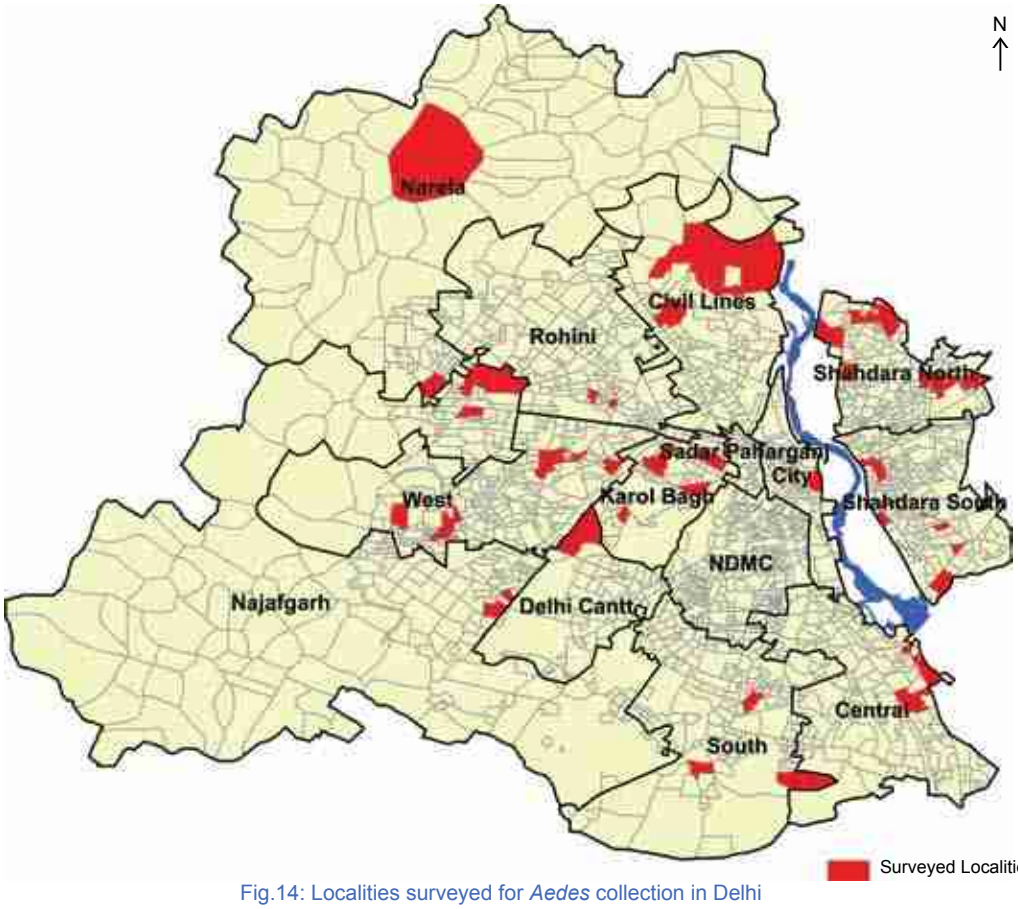


Fig.14: Localities surveyed for *Aedes* collection in Delhi

Fig.15: Evaluation and marking of lids for replacement.

an NGO to generate skilled task force for prevention and control of dengue. This initiative is in support of Government's initiative on the National Skill Development Mission which has been developed to create convergence across sectors and States in terms of skill training activities. It is an ambitious initiative to complement and strengthen government efforts by making self-reliant and trained workforce within organizations and community. The main objective is to train the nodal persons of government and private officials who are responsible for the maintenance of the office campus through formatted programme. Phase-I is focused primarily on organizations, both public and private establishments. In total 42 people from 10 different organizations including one from slum and two from a society in Delhi were trained in a month. With an informal follow up with participants of batch one, it is visible that they have further trained their teams, colleagues, family and neighbours. Such community-to-community dialogue is very important to generate faith in government campaigns and call for action from community. Our participants believe, with scientific facts and long experience of trainers, that chemical is not the solution but combined and collective efforts in the direction of vector source reduction is the only solution; and they are working within their campuses on the same lines and communicating it further. Out of 10 organizations, seven represent different CSIR laboratories from Delhi, Lucknow and Pilani, Academic institution, IIT Delhi, Hospital–King George's Medical University and private company Jindal Consulting Private Limited. Each participant has sensitized their staff and officials in their respective institutions and offices, and are efficiently maintaining their campuses.

1.3 Insecticide Resistance

1.3.1 Impact of insecticide resistance in malaria vectors on malaria transmission: Effectiveness of LLINS

A five-year study in a tribal District of Chhattisgarh on the implications of insecticide resistance in

malaria vectors on malaria transmission brought out the following important outcomes.

- 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 status to pyrethroids.
- LLINs with more then 80% coverage performed neither worse nor better in areas with higher *versus* lower vector resistance.
- LLINs may lose effectiveness, if resistance frequency or resistance intensity increases, and people sleeping under LLINs may still get malaria (albeit less than those who don't).

Hence, better tools are needed for preventing malaria. NIMR is evaluating formulations of neonicotinoids, a new class of insecticides with novel mode of action including mixtures with pyrethroids and combination LLINs of pyrethroids plus synergists for insecticide resistance management.

A new bottle bioassay technique for insecticide resistance monitoring is being standardized for large scale use. A study in tribal district, Gadchiroli in Maharashtra from 47 localities which include 7 localities with prevalence of *An. fluviatilis* and rest with *An. culicifacies,* showed that the later was found resistant to DDT and malathion with variable susceptibility to deltamethrin while *An. fluviatilis* was completely susceptible to deltamethrin though resistant to DDT and malathion.

Future plans

The insecticide and insecticide resistance lab designated as WHOCC is being upgraded for GLP compliance for phase-I testing and evaluation of public health pesticides. ACL2 facility is initiated, and studies on *Wolbachia* infection and malaria transmission control are underway.

Parasite Biology 2

2.1 Metacaspases, cysteine proteases as potential target for malaria

The increasing resistance of malaria parasites to antimalarial drugs is a major contributor to the re-emergence of the disease as a major public health problem. Among potential targets for new modes of chemotherapy are malarial proteases, as several of them are essential for parasite growth and development. Among the potential target for malaria, unique cysteine proteases termed as "Metacaspases" of *P. falciparum* has been explored in context of its role in regulation of cell fate of parasite. Metacaspases are novel cysteine-dependent proteases found in protozoa, fungi and plants which are distantly related to metazoan caspases. MCAs are structurally related to caspases, having Cys-His catalytic dyad which include active domains of caspases.

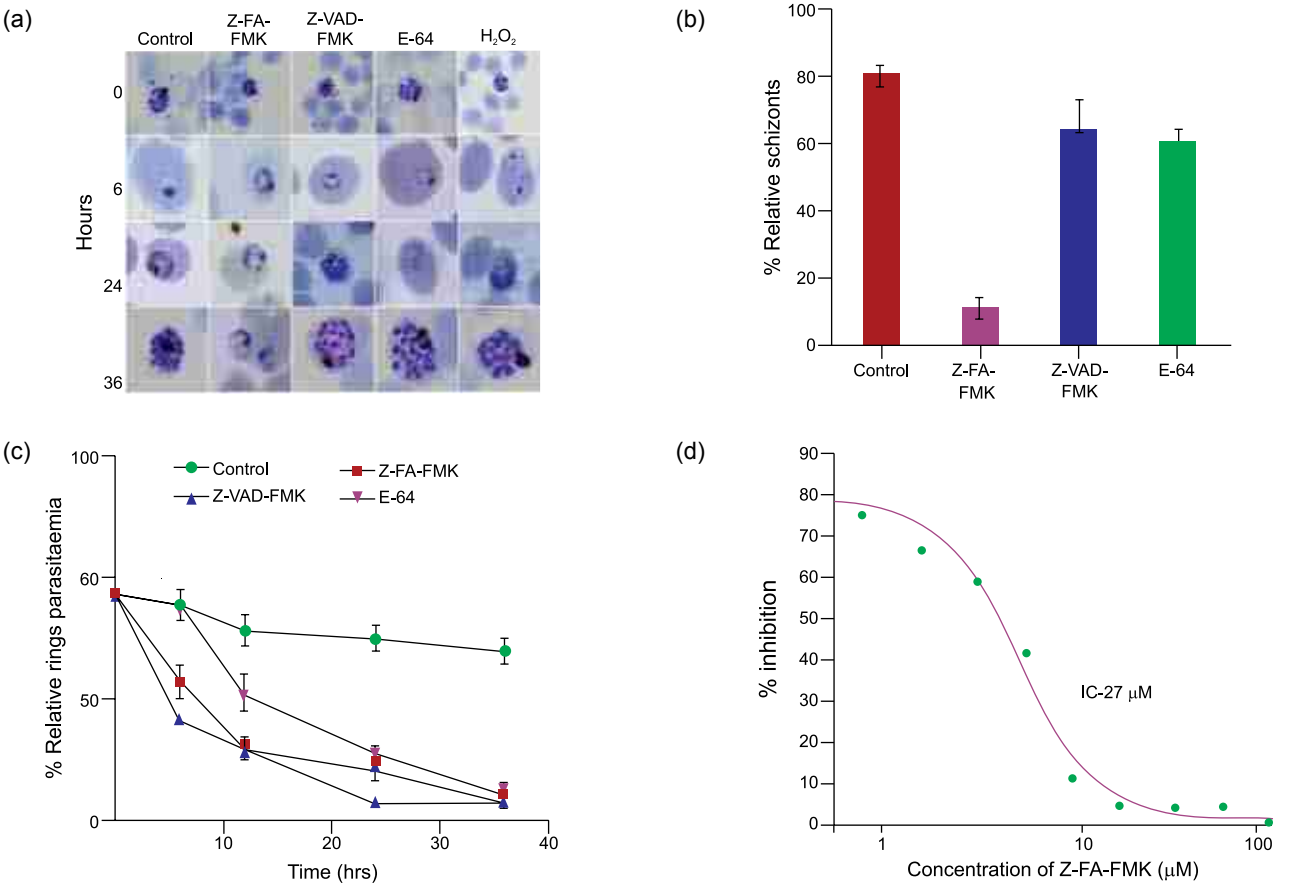


Fig. 1: Caspase-3 inhibitor Z-FA-FMK inhibits growth of the *P. falciparum:* Giemsa stained bright field microscope images showing the predominant parasite phenotype at different time interval in presence of inhibitors (second vertical panels) and control (first vertical panels) (a); Morphological changes and growth arrest in gametocytes treated with different inhibitors (b); Bars and solid lines graphs represent growth arrest from rings to schizonts stages in the parasites treated with different inhibitors (b and c); and Graph represents the IC_{50} value of Z-FA-FMK for inhibiting 50% parasite growth *in vitro* (d).

MCAs are important enzymes in malaria parasite, which are absent in humans and differing significantly from the orthologous human caspases. Therefore, MCAs offer a new potential drug target for anti-parasitic chemotherapeutics, which needs biochemical characterization to support the discovery of innovative drug candidate.

In order to characterize *Pf*MCA-2, we identified its catalytic domain with conserved cysteine and histidine residues using bioinformatics tool. The expression of MCA-2 has been achieved successfully after trying many host cells and expression vectors. Recombinant MCA-2 activity has been tested using different known fluorogenic substrates, Z-GGR-AMC and Z-GRR-AMC. Enzymatic assay showed that *Pf*MCA-2 efficiently cleaved arginine/lysine specific peptide, but not caspase-specific substrate. Consistently, *Pf*MCA-2 activity was sensitive to effector caspases inhibitor, Z-FA-FMK, and mildly inhibited by aprotinin and E-64. However, general caspase inhibitors such as Z-VAD-FMK and Z-DEVD-FMK had no effect on *Pf*MCA-2 activity. Z-FA-FMKinhibits parasite growth with an IC_{50} value of 2.7 µM along with the notable morphological changes (Fig. 1).

*Pf*MCA-2 specifically expressed in schizonts and gametocyte stages and there was a notable depletion of *Pf*MCA-2 expression in Z-FA-FMK treated schizonts and gametocytes stages of parasite (Fig. 2).

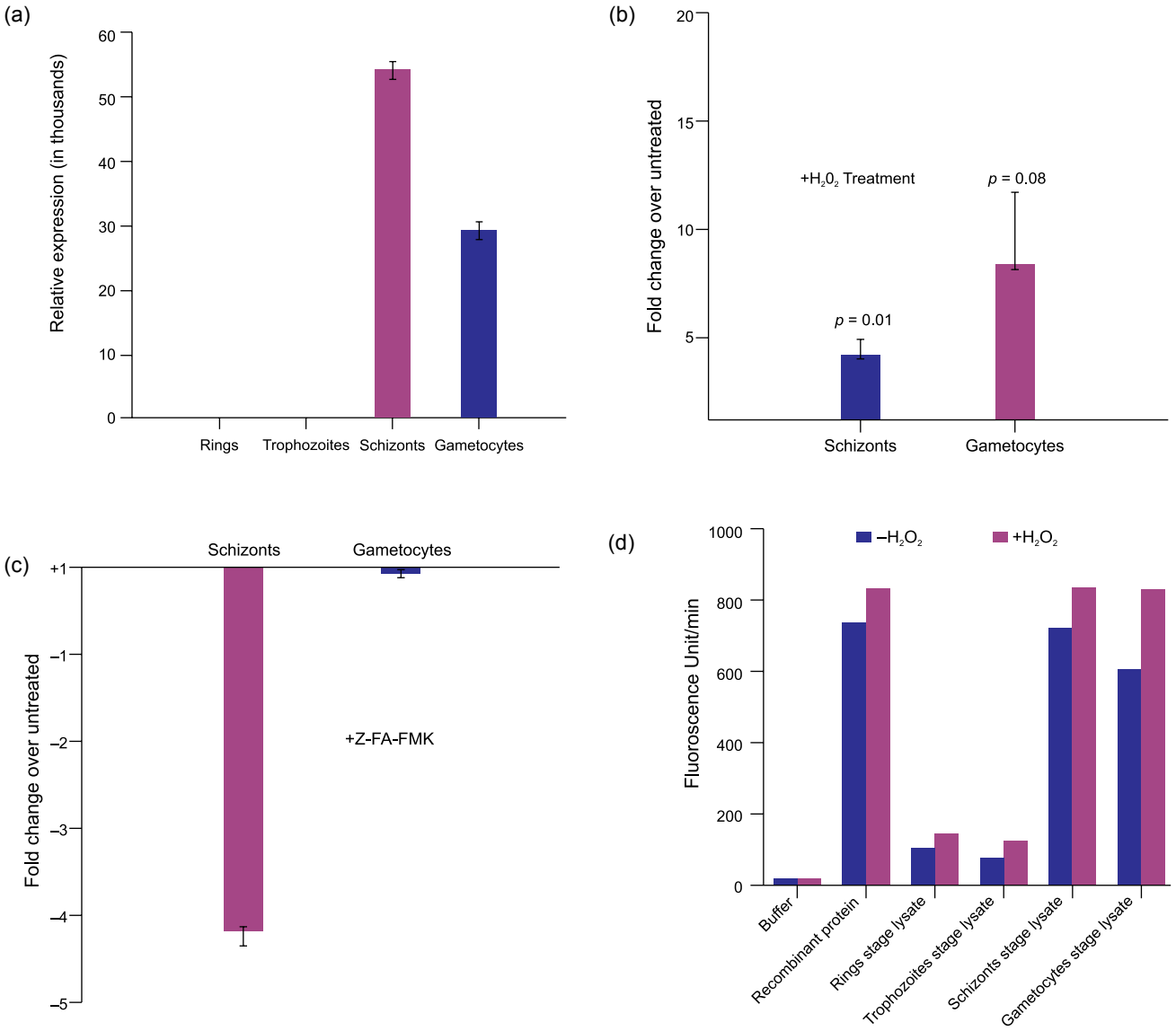


Fig. 2 *(contd...)*

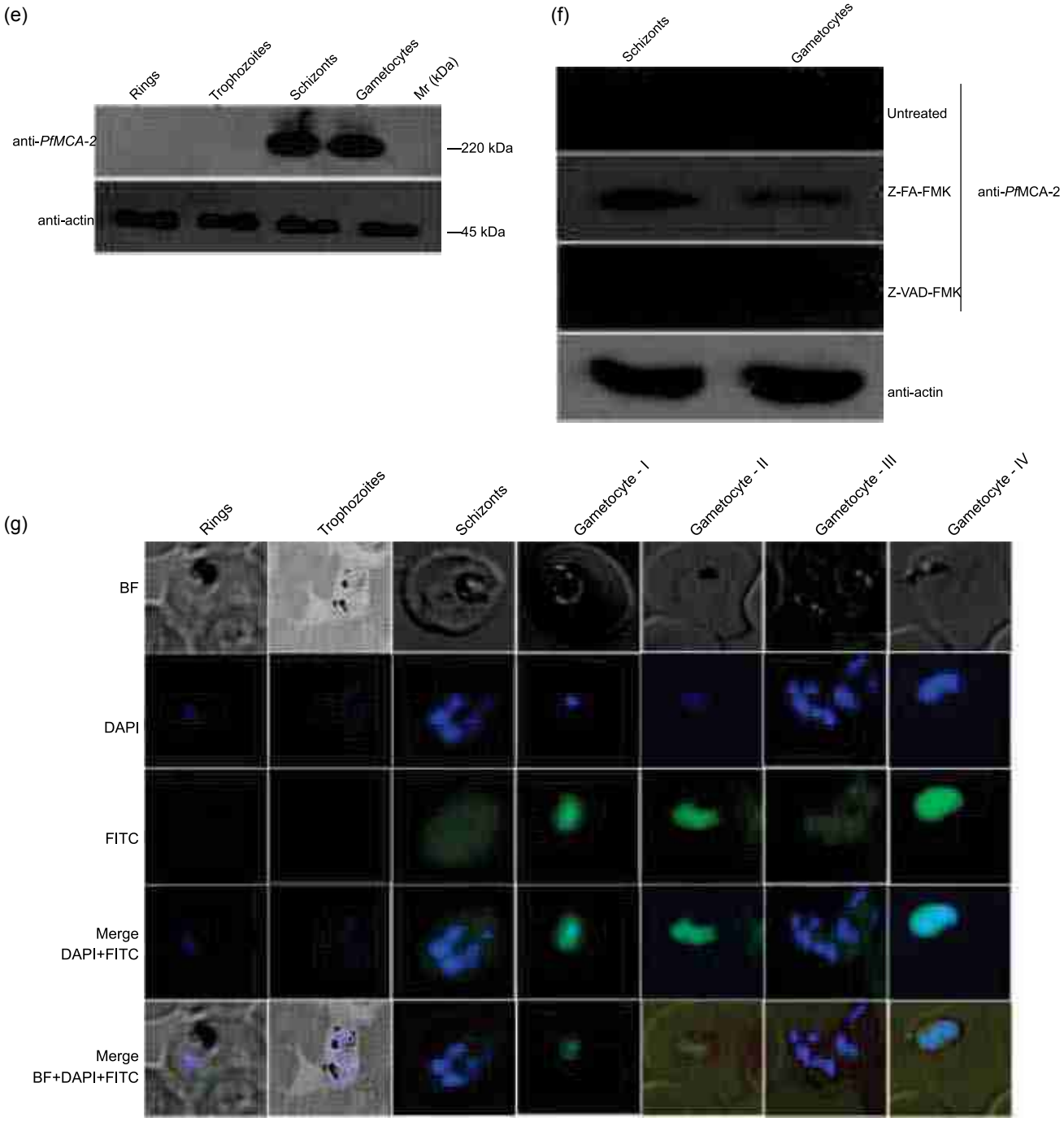


Fig. 2: Expression and localization of *PfMCA-2*: Expression profile of *PfMCA-2* at transcript level in different stages of parasite (a) (Refer gel image in S4 a, b and c); Graphical representation of *PfMCA-2* transcript expression profile in presence of H_2O_2 (b); Graphical representation of *PfMCA-2* transcript expression in Z-FA-FMK treated schizonts and gametocytes (c); Native *PfMCA-2* activity in H_2O_2 treated and untreated different parasite stages (d); Immunoblotting showed native *PfMCA-2* expression in schizonts and gametocyte stages of parasite lysates after probed with *anti-PfMCA-2* antibody (Refer full image in S4 (e); The level of *PfMCA-2* expression in inhibitors treated schizonts and gametocytes (f) (Refer full image in S4 f); and Immunofluorescence assay showed green FITC signal in the schizonts and gametocyte I-IV stages (g).

Notably, *Pf*MCA-2 cleaves a phylogenetically conserved protein, TSN (Tudor staphylococcal nuclease) and the proteolysis of *Pf*TSN did not occur after treatment with the Z-FA-FMK (Fig. 3).

The production of large amount of reactive oxygen species in presence of Z-FA-FMK caused oxidative stress which in turn leads to loss of cell viability. The oxidative stress further generates positive feedback for the occurrence of cell death in term of phosphatidylserine externalization and DNA fragmentation *in vitro* (Fig. 4).

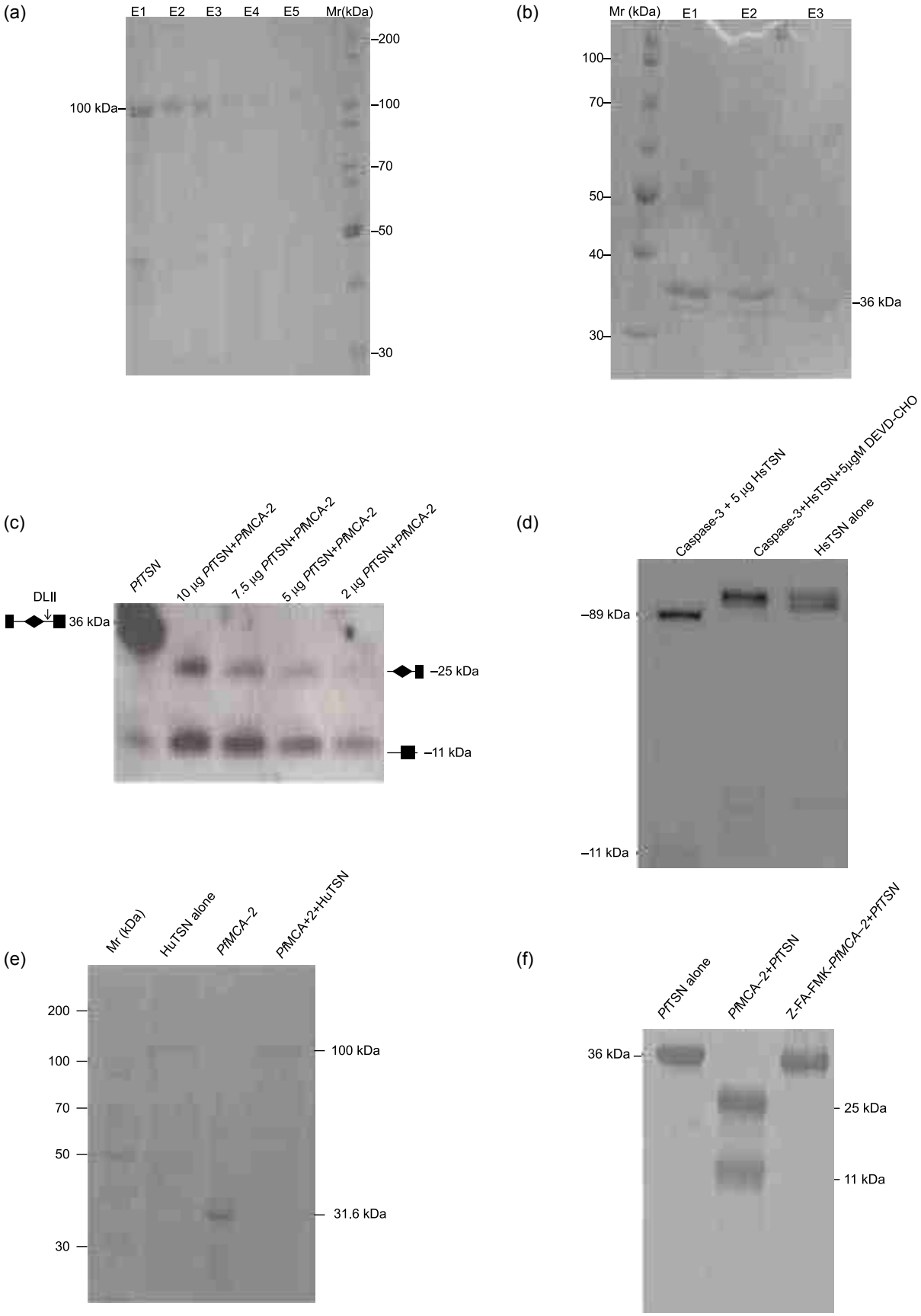


Fig. 3: *PfTSN* is a natural substrate of *PfMCA-2* in *P. falciparum:* SDS-PAGE analysis of recombinant purified HsTSN and *PfTSN* (a and b); *PfTSN* is cleaved by *PfMCA-2 in vitro* in a dose dependant manner (c); Recombinant HsTSN was cleaved by caspase-3 and its fragmentation was blocked by inhibitor (N-Ac-Asp-Glu-Val-Asp-CHO (DEVD-CHO) (d); *PfMCA-2* was not cleaving HsTSN (e); and Z-FA-FMK blocked *PfMCA-2* mediated *PfTSN* cleavage (f).

Parasite Biology

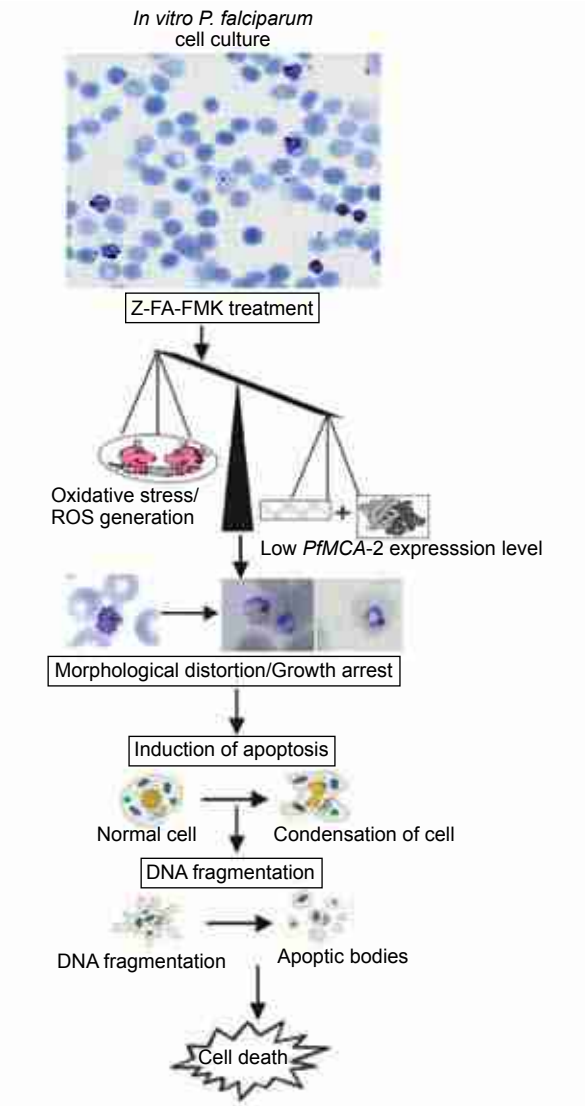


Fig. 4: Schematic proposed model for *Pf*MCA-2 dependent apoptosis-like cell death induced by Z-FA-FMK (a known inhibitor of effector caspases) *in vitro* (Vandana *et al* 2018).

2.2 Designing, synthesis and evaluation of the mechanism of allosteric inhibitor to combat drug resistance problem

Malarial cysteine proteases, falcipains are the major hemoglobinases required for the parasite growth and development. Falcipains consist of pro- and mature domains that interact via 'hot-spot' interactions and maintain the structural integrity of enzyme in zymogen state. Upon sensing the acidic environment, these interactions dissociate and active enzyme is released.

For inhibiting falcipains, several active site inhibitors exist, however compounds that target via allosteric mechanism remain uncharacterized. Therefore, we designed and synthesized six azapeptide compounds, among them, NA-01 and NA-03 (Fig. 5) showed growth arrest by specifically blocking auto-processing (Fig. 6). Inhibitors showed high affinity for enzymes in presence of prodomain without affecting the secondary structure.

Binding of NA-03 at the interface induced rigidity in prodomain preventing structural reorganization. We further reported a histidinedependent activation offalcipain (Fig. 7). Collectively, for the first time we provided a framework for targeting allosteric site of crucial hemoglobinases of malaria parasite. Targeting exosites might provide high selectivity and would be less prone to drug resistance.

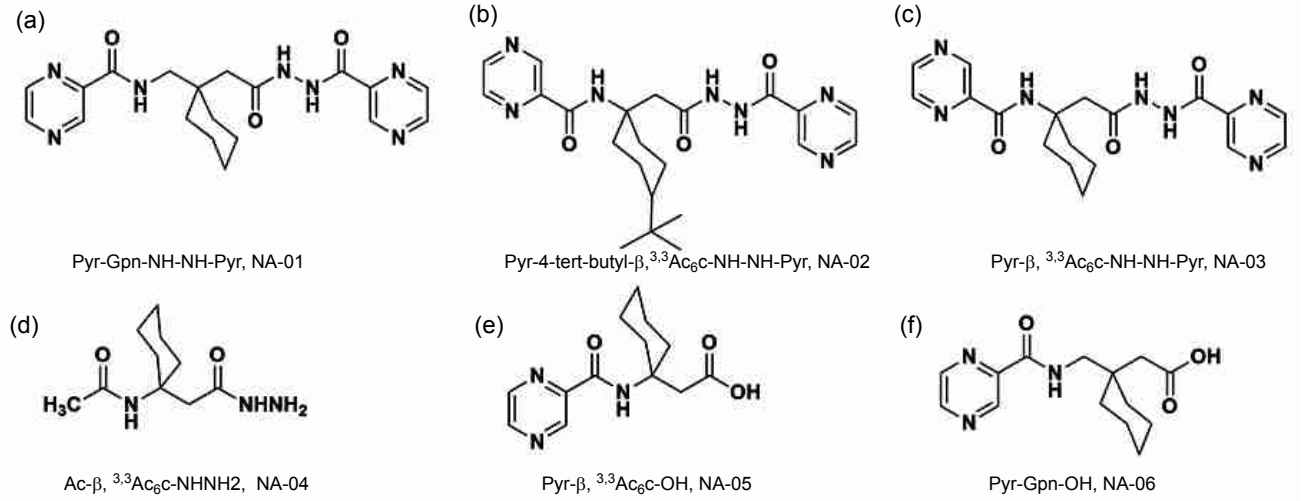


Fig. 5: Chemical structures of compounds—(a) Pyr-Gpn-NH-NH-Pyr, NA-01; (b) Pyr-4-tert-butyl-β,^{3,3}Ac$_6$c-NH-NH-Pyr, NA-02; (c) Pyr-β, ^{3,3}Ac$_6$c-NH-NH-Pyr, NA-03; (d) Ac-β, ^{3,3}Ac$_6$c-NHNH2, NA-04; (e) Pyr-β, ^{3,3}Ac$_6$c-OH, NA-05; and (f) Pyr-Gpn-OH, NA-06.

Parasite Biology

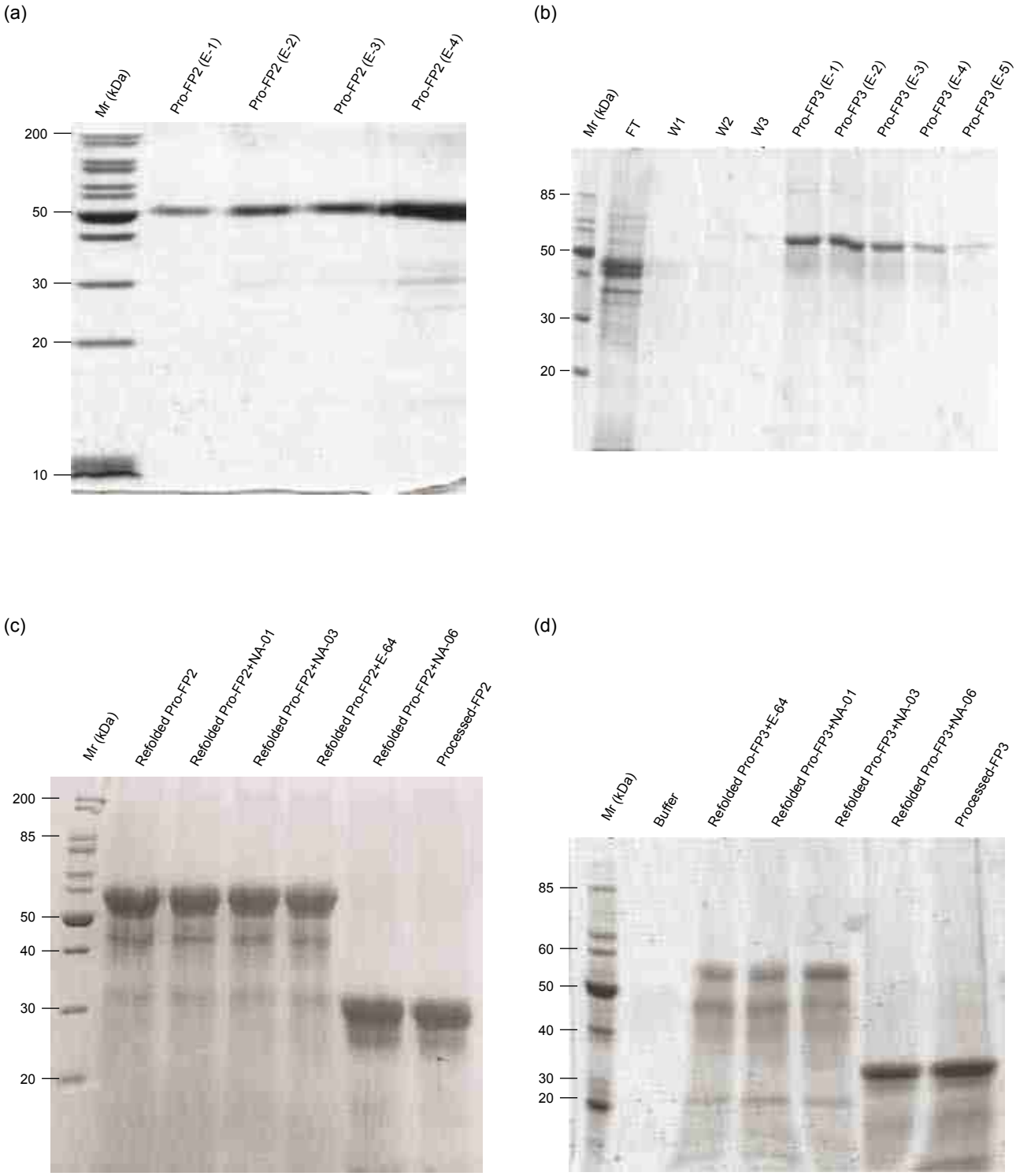


Fig. 6: Compounds inhibit auto-processing—(a and b) Purification profiles of pro-enzymes (whole enzymes) indicated a band size corresponding to 50 kDa for pro-FP2 (a) and 53 kDa for pro-FP3 (b); These enzymes were further refolded (Refolded pro-enzymes) and activated under acidic conditions (pH 5.5); (c) Processed (Active) FP2 indicated cleavage of mature enzyme showing a band of 27kDa (lane 6) while auto-processing of FP2 was blocked in presence of inhibitors NA-01, NA-03 and E-64 indicated by the band of 50kDa; and (d) Similarly for pro-FP3, efficiently activated enzyme indicated by a band of 27kDa (lane 7) whereas no auto-processing was observed in presence of inhibitors NA-01, NA-03 and E-64 indicated by the band of 53kDa. The negative control NA-06 did not have any effect on pro-enzymes processing (c lane 5, d lane 6). All results were analyzed by 12% SDS-PAGE.

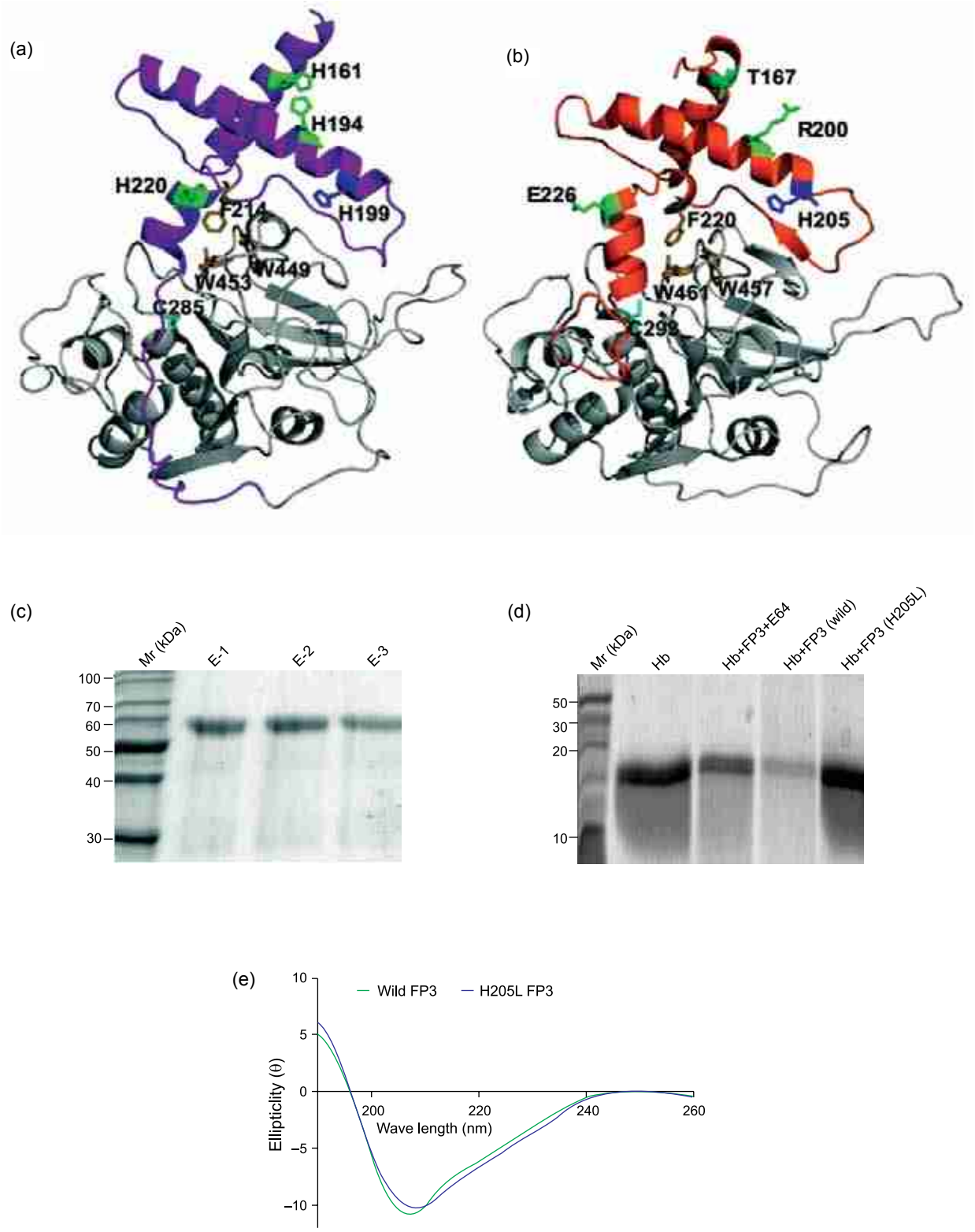


Fig. 7: Role of histidine residue in FP3 processing—(a) FP2 and (b) FP3 prodomain have four histidine residues, among them H205 (blue) in FP2 prodomain (purple) and H199 (blue) in FP3 prodomain (orange) is highly conserved. Rest of three histidine residue positions H161, H194, H220 in FP2 and T167, R200, E226 in FP3 are differentially conserved represented in green sticks. Mature domain containing catalytic cysteine (cyan) C285 in FP2 and C293 in FP3 and hydrophobic interaction residues (brown) F214, W449, W453 in FP2 and F220, W457, W461 in FP3 are also highlighted; (c) Purification of H205L-FP3 mutant indicating band of ~53 kDa; (d) Enzymatic activity assay indicating that wild FP3 effectively hydrolyze Hb unlike H205L-FP3 mutant and inhibitor E-64; and (e) CD spectra exhibiting wild FP3 (green), H205L-FP3 mutant (blue) incubated in 10 mM phosphate buffer, pH 8.0. The absorbance of each spectra was measured between 190 and 260 nm after an average of five best scans.

2.3 Understanding liver biology of *Plasmodium*

Liver is an important organ in human body, over the evolution malaria parasites developed their biological mechanisms to invade and flourish inside the organ until ready to egress from it. To increase daughter cells which are responsible for clinical manifestation in humans, the parasite takes the advantage of immunologically less guarded, nutrient rich and metabolically active hepatocytes and uses them. After rigorous efforts made by malaria researchers, we are not able to detect the parasite during its pre-erythrocytic stage, which may revolutionize the malaria diagnosis and treatment strategies. Here, our research group is working on the entry, persistence and exit of parasite from the hepatocytes (Fig. 8), results may toss a ray of light on new knowledge for novel therapeutics or vaccine candidate development.

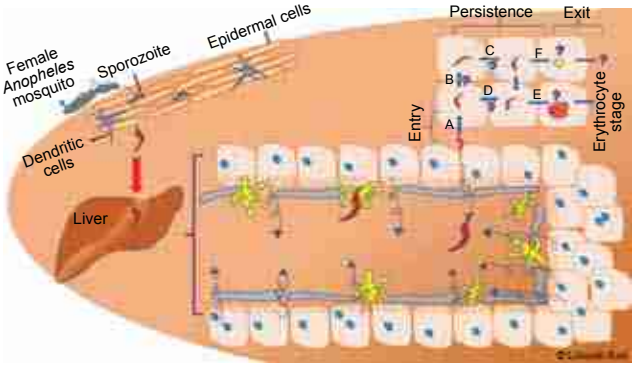


Fig. 8: Hepatic entry, persistence and exit of malaria parasite.

2.4 Molecular characterization of *P. falciparum* phosphoethanolamine methyltransferase (*Pf*pmt) gene: A novel antimalarial drug target

Plasmodium falciparum parasite synthesizes phosphatidylcholine for growth, rapid multiplication at blood stages and for gametes development with the help of enzyme *P. falciparum* phosphoethanolamine methyl transferase (*Pf*pmt) through serine-decarboxylase-phosphoethanolamine-methyl transferase (SDPM) pathway. So, the compounds from ASINEX compound library with Schizonticidal score of $IC_{50} \geq 5$ µM (Primary hits) were tested for cytotoxicity, gametocidal activity and protein specificity and kinetics. Two compounds were found competitive inhibitors of *Pf*pmt non-toxic to HEK-293 cell lines with significant gametocidal activity.

In vitro studies

Primary hits were tested for gametocidal activity and cytotoxicity activity before protein inhibition assay. Primary hits were added in serial dilution to the *RKL-9* gametocytes culture when gametocytes growth started, and IC_{50} was calculated (Figs. 9a and b).

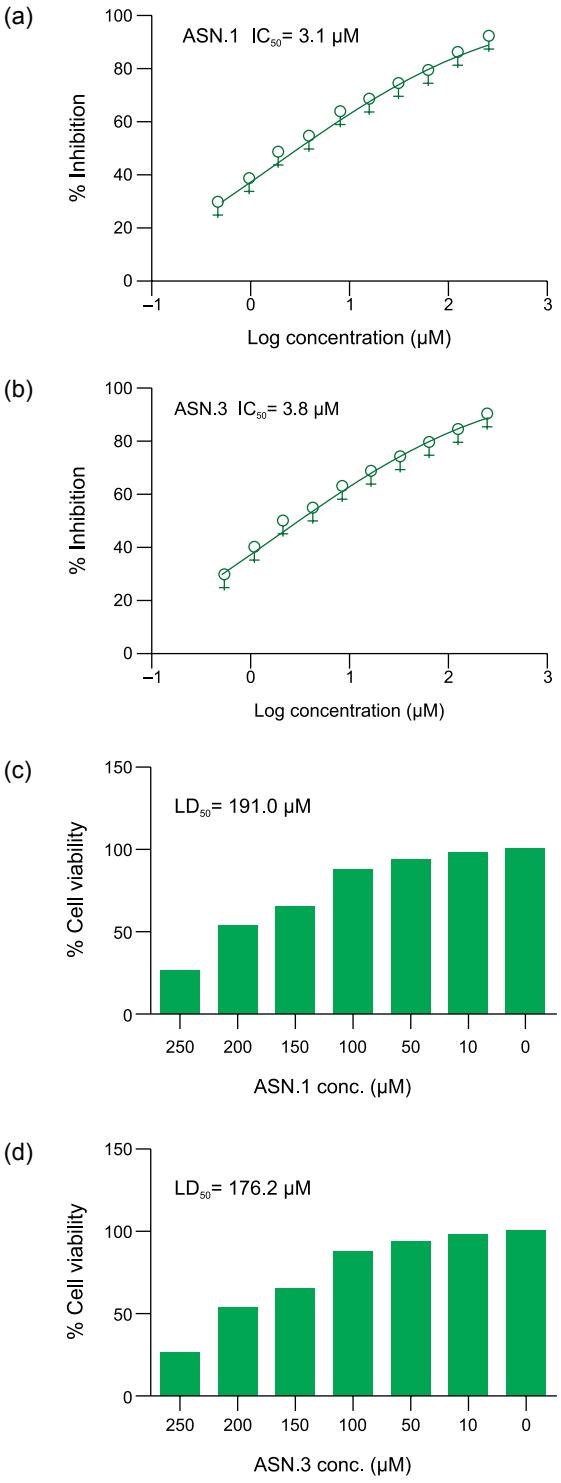


Fig. 9: (a & b) Gametocidal activity of primary hits against *RKL-9* strain in terms of IC_{50}; and (c & d) MTT toxicity of primary hits against HEK-293 cells (p >0.001).

Colorimetric analysis-based toxicity of primary hits was tested for human cell lines using MTT assay against kidney cell line, HEK-293 cell line. Primary hits were tested at different concentrations (10, 50, 100, 150, 200 and 250 μM) (Figs. 9c and d). About 5000 HEK-293 cells were embedded with different conc. of primary hits and fortunately, primary hits ASN.1 and ASN.3 were found non-toxic even at higher concentration with very high LD_{50} concentration, *i.e.* 191 and 176.2 μM, respectively. The primary hits with better gametocidal effect and safety index were taken for further experimental analysis since; high safety index implied the better therapeutic safety of inhibitors.

Primary hits were assayed with established *Pf*pmt assay and showed significant inhibition of *Pf*pmt at 510 nm at very low micromolar (μM) concentration. The Michaelis-Menten kinetic plot was plotted for experimental values to determine the mode of *Pf*pmt inhibition by inhibitors. Inhibitors were having V_{max} equal to the substrate pEthanolamine and these inhibitors were also interacting with the crucial amino acids within the substrate binding cavity in the binding orientation similar to the substrate that signified the competitive mode of inhibition of *Pf*pmt (Fig. 10).

In vivo efficacy

The efficacy in mice in terms of percent growth inhibition of parasitaemia was studied. The mean percent parasitaemia and percent growth inhibition of parasite of *Pf*pmt inhibitors was calculated based on Day-5 of dosing @ 50 mg/kg, 10 mg/kg oral dosage; and 5 mg/kg, 1 mg/kg IV dosage (Table 1). ASN.1 showed good potency both at oral as well IV dosages implying its better drug-likeness but ASN.3 only reduced the growth of parasite with IV dosages which could be due to the pharmacokinetics of ASN.3 (though it can be optimized and improved).

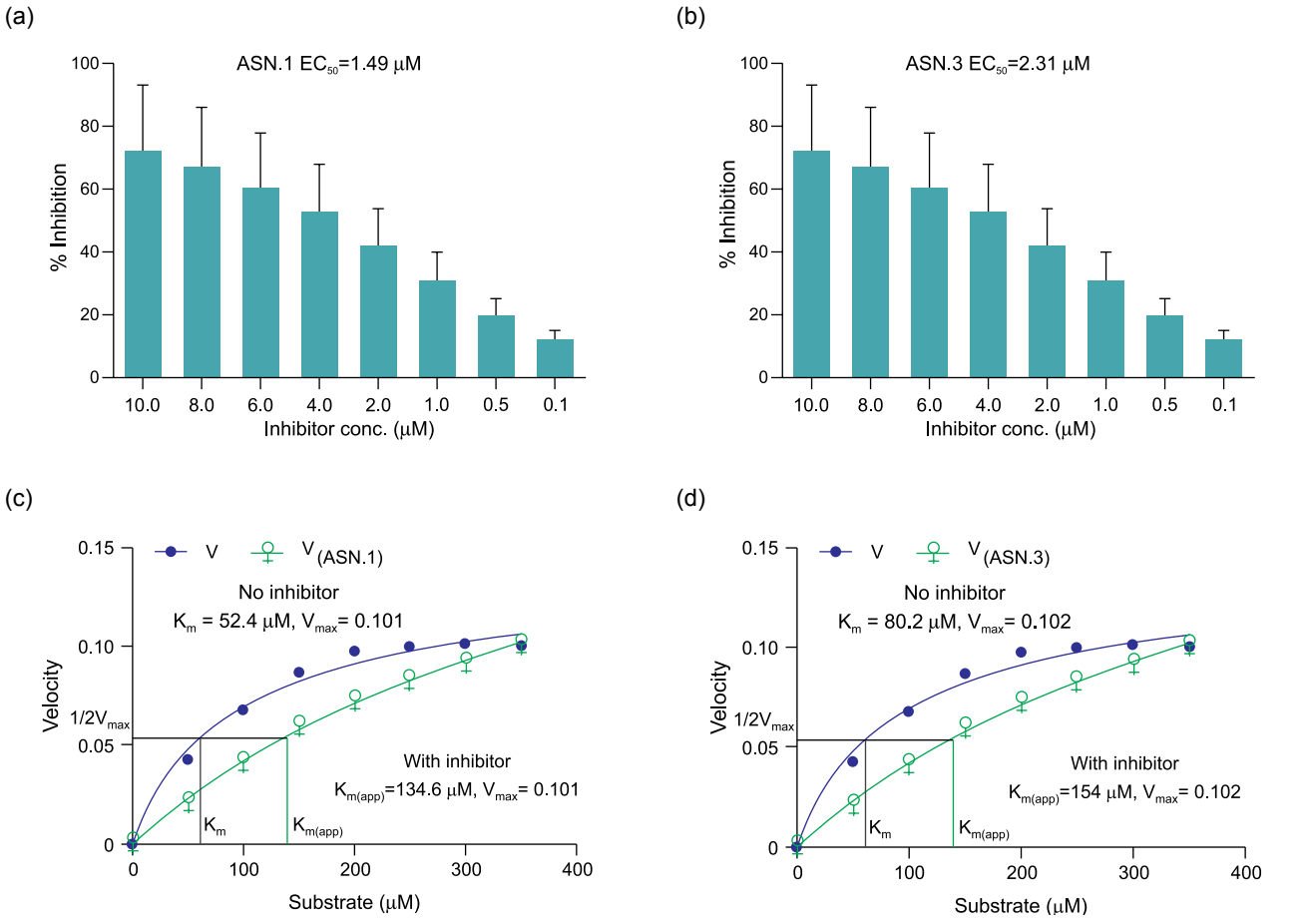


Fig. 10: S-adenosyl methionine (SAM) dependent inhibitor assay and kinetics of *Pf*pmt at 510 nm—(a) EC_{50} of ASN.1 inhibitor against *Pf*pmt with P*; (b) EC_{50} of ASN.3 inhibitor with P*; (c) Inhibitor kinetics of the ASN.1 with 134.6 μM; and (d) Inhibitor kinetics of the ASN.3 with 150 μM. *P = p >0.05.

Table.1. Efficacy of *Pf*pmt inhibitors in *P. berghei*-infected mice in terms of percentage growth inhibition of parasite at Day-5 of infection

Day	Day-5 (Oral)				Day-5 (Intravenous)			
Dosage	50 mg/kg		10 mg/kg		5 mg/kg		1 mg/kg	
	Parasitaemia	Growth inhibition	Parasitaemia	Growth inhibition	Parasitaemia	Growth inhibition	Parasitaemia	Growth inhibition
ASN.1	14.2 ± 1.73	55.06	21.3 ± 1.9	32.5	8.5 ± 0.31	73.1	12.7 ± 1.32	59.8
ASN.3	21.5 ± 0.84	30.36	27.6 ± 1.73	12.6	15.2 ± 1.02	49.4	18.1 ± 0.22	42.05

Parasitaemia and growth inhibition are shown in percentages; Positive control (% parasitaemia) = 0.012 ± 0; Negative control (% parasitaemia) = 31.6 ± 0.48.

Conclusion

Primary hits, ASN.1 and ASN.3 were found non-toxic and showed good gametocidal activity. They also showed competitive inhibition for *Pf*pmt. *In vivo* studies implied that the inhibitors have significant efficacy against *P. berghei*. Hence, these inhibitors have good probability to be a effective antimalarial, and can also be optimized to improve the bioactivity and used as template for structure-based drug designing. ❑

Epidemiology

3

3.1 Comprehensive case management programme (CCMP) for control of malaria in Odisha: A pilot project

The study was carried out in four districts with different transmission intensities. Pairs of intervention and control blocks, matched on malaria incidence were selected. CCMP activities included training and supervision, malaria microscopy at PHC level, ensuring no stock-outs of malaria tests and drugs, stratifying areas based on risk factors, focal screening and treatment in remote areas and appointing alternative providers to underserved areas (Fig. 1). Use of District Health Information System 2 (DHIS2) was used for data management.

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.

Larger differences in pre- and post-changes in API between intervention and control sub-centres were registered in the higher transmission-risk areas compared with the lower risk areas. All the changes were statistically significant.

Fig. 1: CCMP patient-card featured in WHO coverage on malaria control in Odisha.

There was 85% decline between pre- and post-CCMP on average monthly positive cases notified per Sub-centre in the intervention blocks, while the decline was 32% in control blocks (Fig. 2).

NVBDCP Odisha developed and tested strategies within CCMP to inform scaling up. Success of CCMP mass surveys led to the creation of DAMaN (funded by MoH Odisha). CCMP thus developed a viable approach to scale up malaria services in hard-to-reach areas that drive transmission

3.2 Study on estimation of malaria disease burden to support malaria elimination in Punjab

The National Framework for Malaria Elimination in India 2016–30 launched by Hon'ble Minister of Health and Family Welfare in February 2016 has laid out the vision, mission, broad principles and practices to achieve malaria elimination from the country in a phased manner by 2027 and sustaining zero indigenous cases and deaths due to malaria by 2030 and beyond in line with the regional and global targets. The principles and practices will vary according to the epidemiological situation of malaria in different states for which the entire country has been divided into 4 categories: Category 3 (Intensified Control Phase), Category 2 (Pre-elimination Phase), Category 1 (Elimination Phase) and Category 0 (Prevention of Re-introduction phase). With the launch of India's malaria elimination initiative, the states and UTs have a remarkable opportunity to get rid of this disease and contribute to better health and socio-economic development especially among the country's most vulnerable populations.

Malaria has been a major public health problem in Punjab and whole state was endemic for malaria. The malaria situation in Punjab for the last 25 years is shown in Fig. 3. Malaria incidence was high

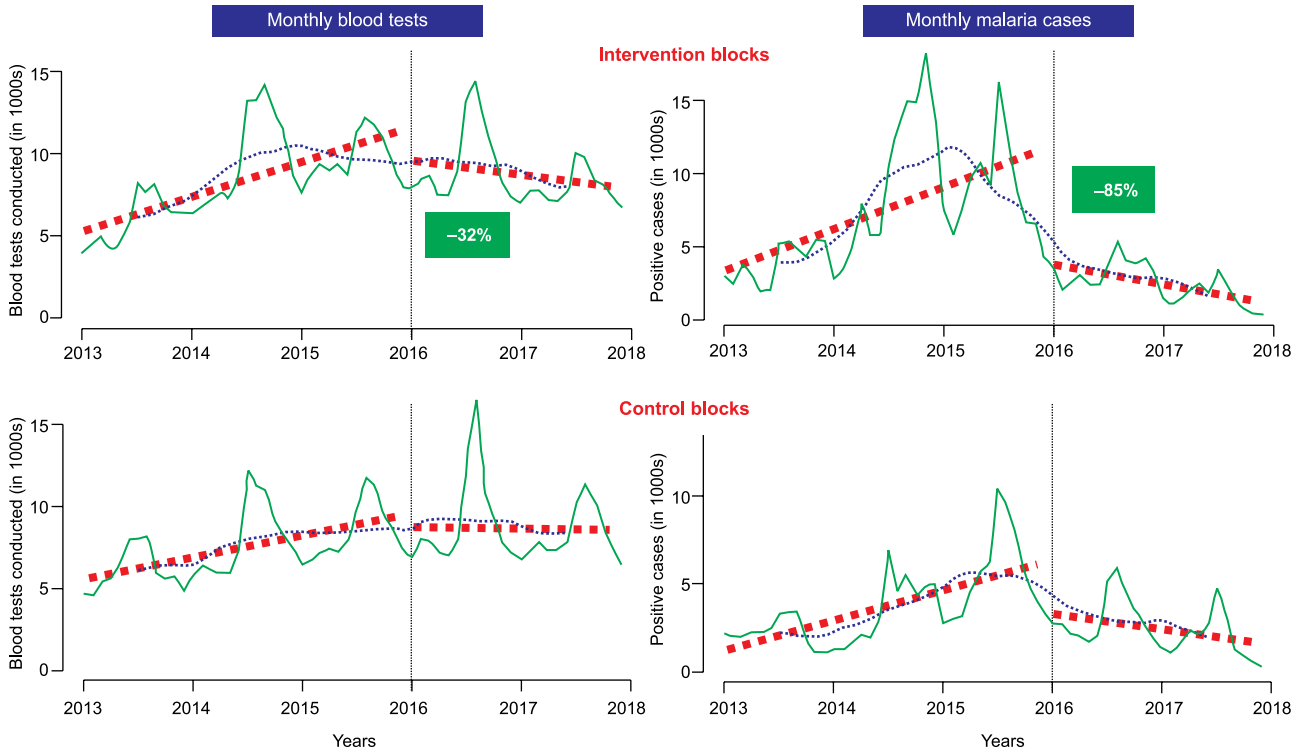


Fig. 2: Impact of CCMP on malaria.

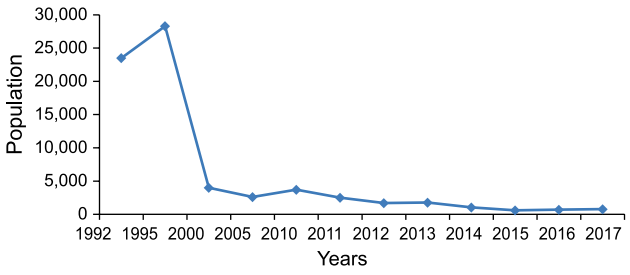


Fig. 3: Malaria trend in Punjab (1992–2017).

in the state during 1990–2000. However, with the constant efforts for malaria control coupled with the high use of pesticides in the agricultural fields, malaria has shown a drastic decline since 2000.

In view of launch of malaria elimination in India, the state of Punjab has qualified for malaria elimination as per National Framework of Malaria Elimination, 2016–30. The Department of Health and Family Welfare, Government of Punjab is collaborating with the National Institute of Malaria Research (ICMR) in order to validate the data of malaria of the state and to provide technical expertise to consolidate the efforts in elimination of malaria. With this joint venture, the goal of malaria elimination in the state is envisaged to be achieved.

Punjab is one of the states which is reporting ≤1 API in all the 22 districts for the last five years and thus qualifies for malaria elimination under Category 1. The epidemiological data of the Punjab state for the last six years is given in Table 1.

There is a gradual decline in malaria cases including *P. falciparum* cases over the years. However, the actual burden of disease has not been estimated to strategize malaria elimination in the state. This as a first step to elimination of malaria, the disease burden study is being carried out in Phase I along with studies on vector bionomics, and transmission dynamics.

Table 1. Malaria situation in Punjab (2012–17)

Year	Population	BSC	ABER	Total(+) *Pf*	SPR	API	Death
2012	28589419	2911780	10.2	1689 (43)	0.06	0.059	0
2013	28645496	2971013	10.4	1761 (31)	0.06	0.061	0
2014	28678576	3092693	10.8	1036 (11)	0.03	0.036	0
2015	29081922	3033940	10.4	596 (13)	0.02	0.020	0
2016	29434188	2691331	9.14	692 (7)	0.02	0.020	0
2017*	29641531	2430999	8.20	805 (12)	0.03	0.027	0

*Malaria cases have been reported only from 106 villages in 14 districts of the state; Total population: 29.6 million; No. of districts: 22; No. of districts reporting >50 cases/year: 5; No. of districts reporting >10–50 cases/year: 9; No. of districts reporting <10 cases/year: 8.

3.2.1 Estimation of malaria disease burden in Punjab

This is one of the important terms of references in the MOU between Punjab and NIMR. Therefore, an elaborate proposal was developed in collaboration with ICMR-NIMS and submitted to ICMR for funding and the same was approved. This study was launched in July 2017 after initial preparation for recruitment and training of staff. The progress made in the study up to March 2018 is presented in this report:

Sample size computation and selection of study area

The recorded API of the state for the last three years is 0.02 per thousand (varying from 0.002 to 0.5 in different districts), the required sample size for estimation of malaria burden is worked out assuming the API 0.2 per thousand with permissible error of 20 and 95% confidence interval. Thus, the required sample size was 9 Lakhs. The overall malaria incidence in the state is very low. However, for stratification, the district wise API reported in 22 districts in the last four years (2012–15) was used for identification of three strata representing high, medium and low API zones. Within each stratum, three districts were selected and sample of three lakhs were drawn from these districts in each stratum with three blocks (with about one lakh population from each block) from these districts amounting to total 9 blocks from 9 districts allocated equal in high, medium and low API stratum. The location of nine study districts is shown in Fig. 4.

Selection of blocks from 9 districts were based on API of last four years. Accordingly, three groups of districts were formed namely high (API > 0.1), medium (API 0.03 < 0.1) and low (API < 0.03). For selection of 3 blocks from 3 different districts from each group, the districts were arranged as per the level of API (in descending order) and then blocks within the districts were arranged in ascending and descending order alternatively. Three Blocks from three districts of each group were selected using PPS sampling from the sampling frame of each three groups. Overall, 9 block PHCs were selected from the sampling frame of Block PHCs of the state. The selected districts and blocks along with study population are given in Table 2.

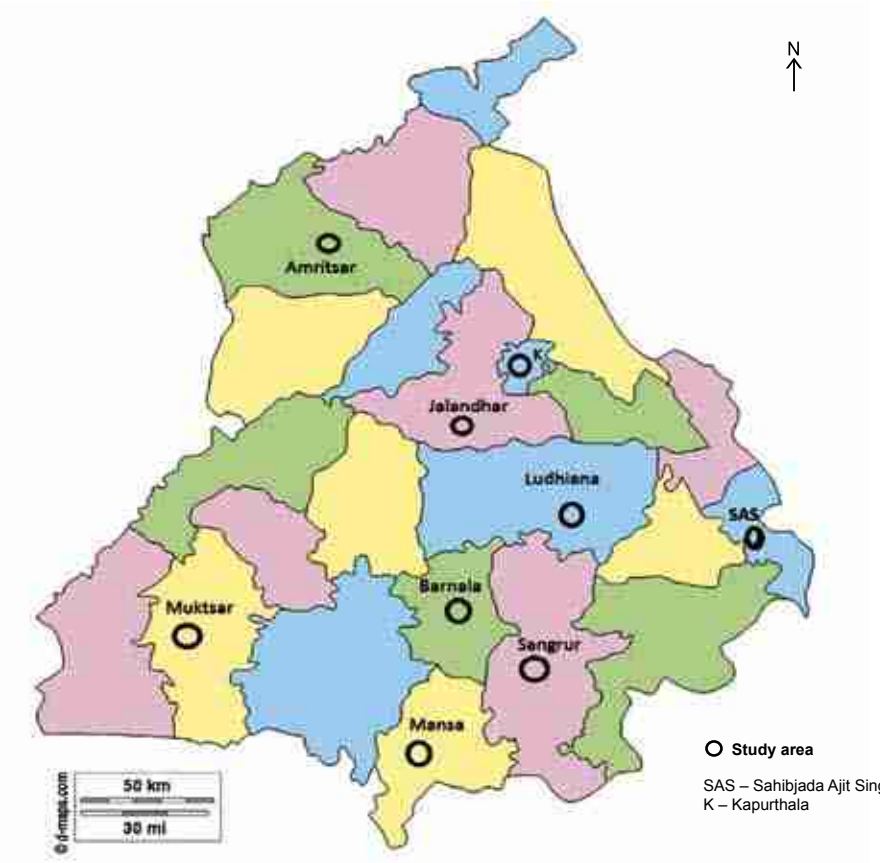


Fig. 4: District map of Punjab showing location of study districts for disease burden estimation.

Table 2. District-wise list of selected blocks and study population for malaria surveillance for estimation of disease burden in Punjab

Endemicity	District	Block	Study population		
			Male	Female	Total
High	Mansa	Khiala-Kalan	53431	47811	101242
	Muktsar	Alamwala	51932	48129	100061
	Mohali	Gharuan	53434	49839	103273
Moderate	Ludhiana	Peri-urban area	50285	46894	97179
	Sangrur	Urban Sangrur	53592	49576	103168
	Barnala	Dhanaula	56314	51366	107680
	Jalandhar	Mehatpur	53210	49693	102903
Low	Amritsar	Peri-urban Amritsar	50509	50950	101459
	Kapurthala	Urban Phagwara	53072	48977	102049
Total			475779	443235	919014

Household listing and population enumeration: Household listing and population enumeration was undertaken to track each and every malaria case from the study area. The household and population data available with Anganwadi/ASHA workers was used after confirming its quality and completeness.

Surveillance: Active surveillance was organized w.e.f., 1 July 2017 with the help of state government for which additional manpower was deputed by the state government in order to effectively cover 9 lakh population every fortnight. Active surveillance is being done by house-to-house visits by MPWs/ASHAs and diagnosis is made by using bivalent RDT so that treatment may be ensured immediately. The format used for case reporting was the same as prescribed by the National Vector Borne Disease Control Programme. The active and passive surveillance was strengthened in the study population. For this purpose, All ASHAs working at village level in each selected blocks were motivated and trained in doing case detection through RDT. This has resulted in obtaining most reliable surveillance data from study sites. Through state govt efforts, we have also introduced test, treat and track strategy foreach malaria case so that complete treatment is ensured and this also helped us to differentiate between local or imported/migratory case. The month wise incidence of malaria cases reported from the study area is shown in Table 3. Three cases of mixed infection (*Pv* + *Pf*) out of 25 RDT positive cases (*Pv*) were detected by PCR and eight cases were found positive (*Pv*) out of 209 RDT negative cases tested by PCR.

Malaria case reporting from health facilities: Line-listing of all existing govt/private health facilities, in the study area was made. All fever cases reported and treated at these facilities were counted for morbidity estimates. A separate case reporting format at the facility was used for this purpose. Private pathology laboratories, testing blood for malaria were enrolled in the project programme for reporting cases. Malaria is a notifiable disease in the state and hence reporting by registered private health service providers was ensured with the active collaboration of local IMA branch and inter personal communication with these practitioners. Project staff is responsible for visiting each health facility to record malaria cases every month. This ensured the complete detection of cases in the study population. The total number of cases tested and found malaria positive through surveillance, govt health facilities and private health facilities are given in Table 4.

Table 3. Total malaria cases reported from study area in Punjab (July 2017 to March 2018)

S. No.	Districts	Jul–Sep 2017		Oct–Dec 2017		Jan–Mar 2018		Total	
		No. tested	Positive (*Pf*)	No. tested	Positive (*Pf*)	No. tested	Positive (*Pf*)	No. tested	Positive (*Pf*)
1.	Mansa	3537	66 (2)	3079	5	3128	2	9744	73 (2)
2.	Muktsar	1689	9 (1)	2719	0	1943	0	6351	9 (1)
3.	Mohali	2669	14	2740	9	3139	0	8548	23
4.	Ludhiana	1305	2	4817	2 (1)	3156	0	9278	4 (1)
5.	Sangrur	10336	1	11062	0	4436	0	25834	1
6.	Barnala	5577	4	4509	0	3402	0	13488	4
7.	Jalandhar	4126	25	3195	9	1749	3	9070	37
8.	Amritsar	6021	1	5557	0	1356	0	12934	1
9.	Kapurthala	4251	1	4349	1	2413	0	11013	2
	Total	39511	123 (3)	42027	26 (1)	24722	5	106260	154 (4)

Table 4. Malaria cases reported through ACD, Govt. facilities and private practitioners from study area (July 2017 to March 2018)

S. No.	Districts	ACD		Govt. facilities		Private practitioners		Total	
		No. tested	Positive (*Pf*)	No. tested	Positive (*Pf*)	No. tested	Positive (*Pf*)	No. tested	Positive (*Pf*)
1.	Mansa	6526	29 (2)	2923	37	295	7	9744	73 (2)
2.	Muktsar	5354	8 (1)	700	0	297	1	6351	9 (1)
3.	Mohali	3261	18	5186	5	101	0	8548	23
4.	Ludhiana	5700	0	2822	0	756	4 (1)	9278	4 (1)
5.	Sangrur	5677	1	8220	0	11937	0	25834	1
6.	Barnala	6480	4	6067	0	941	0	13488	4
7.	Jalandhar	6674	2	1849	0	932	35	9255	37
8.	Amritsar	10593	1	1785	0	556	0	12934	1
9	Kapurthala	4401	1	5210	0	1402	1	11015	2
Total		54666	64 (3)	34762	42	17217	48 (1)	106447	154 (4)

Proactive surveillance was carried out in hot spots such as labour camps and migratory population that constitute the most vulnerable population for malaria infection.Large labour force coming from malaria endemic states are working in Punjab in Agriculture, brick kilns and other small scale industries. Therefore, Malaria cases reported during NIMR surveys as well as CHC/PHC/private practitioners were investigated to know whether the case is indigenous or imported. The study revealed that about 30% of cases were found in migrant labourers with movement history.

Malaria disease burden in the Punjab state shall be worked out based on one year's surveillance data and cases reported at government/private health facilities. We will make direct estimation based on primary data generated out of this study. The incidence of malaria in this study shall be strata specific. Thus the total of all the three strata will be the burden of malaria in the state.

3.2.2 Molecular studies to detect low parasitaemic cases in study area

The occurrence of low parasitaemic cases in low transmission areas such as Punjab is much more common and such cases normally remain undetected through conventional methods of microscopy and rapid diagnostic tests. Such undetected cases may pose a greater risk of flaring up transmission and thus seriously affecting malaria elimination efforts. Therefore, high precision molecular techniques are required to be employed in such settings so as to provide reliable diagnosis and case detection to reduce parasite reservoir in those areas progressing towards malaria elimination. Therefore, besides conventional methods of diagnosis, molecular techniques were also employed to examine doubtful fever cases in the present study to estimate disease burden in Punjab.

Finger-prick blood samples were taken from the patient and two or three drops of blood (approximately 50 µl) of all the fever patients from a finger prick were spotted on Whatman filter paper. These filter papers were allowed to dry and then stored at 4°C for subsequent molecular analysis. DNA was isolated by using Qiagen DNA easy kit with slight modifications in protocol. Nested PCR specific to the two human malaria parasite species (*P. falciparum* and *P. vivax*) was performed using a pair of primers targeted to the 18S rRNA gene. For the primary PCR reaction, 2 µl of genomic DNA were used in a 15 µl reaction. For the nested PCR, 2 µl of 1:10 diluted primary PCR product was used as a template in a 15 µl reaction.

The amplified PCR products were analysed using a 1.5% agarose gel, stained with ethidium bromide and observed under transilluminator. The presence or absence of different *Plasmodium* species was analysed with species-specific amplicon sizes. For this, 100 bp DNA ladder was used to identify the size of molecule run. Bands of 120 base pair and 206 base pairs correspond to presence of *P. vivax* and *P. falciparum;* respectively.

3.2.3 Species-specific nested PCR analysis and comparison with conventional diagnosis with RDT and microscopy

A total of 235 blood samples were analysed for the presence of Plasmodium DNA by species-specific nested PCR. Out of 235 samples, the 26 were malaria RDT positive samples and 209 were malaria RDT negative samples. Out of 26 RDT positive samples, 25 were *P. vivax* and 1 was *P. falciparum*. The PCR results showed that out of 25 vivax cases, 21 were positive for vivax and three

samples (Figs. 5 a and b) were found to have mixed infection, *i.e.* both *P. vivax* and *P. falciparum* (12%) and one sample was found negative for malaria by PCR (4%). From 209 negative RDT samples, eight were found to be positive (3.8%) by PCR indicating low parastaemia (Fig. 6).

Entomological studies: Mosquito collections were carried out every month in SAS Nagar (Mohali) from rural area and labor hutments in the morning hours to know the anopheline fauna, vector density and seasonal prevalence. During entomological surveys, nine anopheline species were recorded from these districts (Table 5).The density of primary malaria vector *An. culicifacies* was very low throughout these months and ranging between 0 to 4.5 per man-hour. The highest density was recorded during monsoon months of July and September. The density of *An. stephensi* was ranging between 0 to 7.5. The density of *An. fluviatilis* was also recorded during post-monsoon months of September to December. The density of *An. annularis* and *An. subpictus* was also found in abundance throughout these months.

Besides longitudinal entomological data from SAS Nagar, random mosquito samplings were also conducted in three districts of Mansa, Rupnagar and Mukatsar and the results are presented in Table 6. During survey, six anopheles species were recorded from these three districts. The density of primary vector *An. culicifacies* was high in Rupnagar district but very low in Mansa and Mukatsar districts. However, the density of *An. stephensi* was quite high in Mansa and Muktsar in comparison to Rupnagar The density of secondary vector *An. annularis* was high in Rupnagar district but it was absent in Muktsar and very low in Mansa district.

Vector species were tested for their susceptibility to DDT, malathion and deltamethrin. *Anopheles*

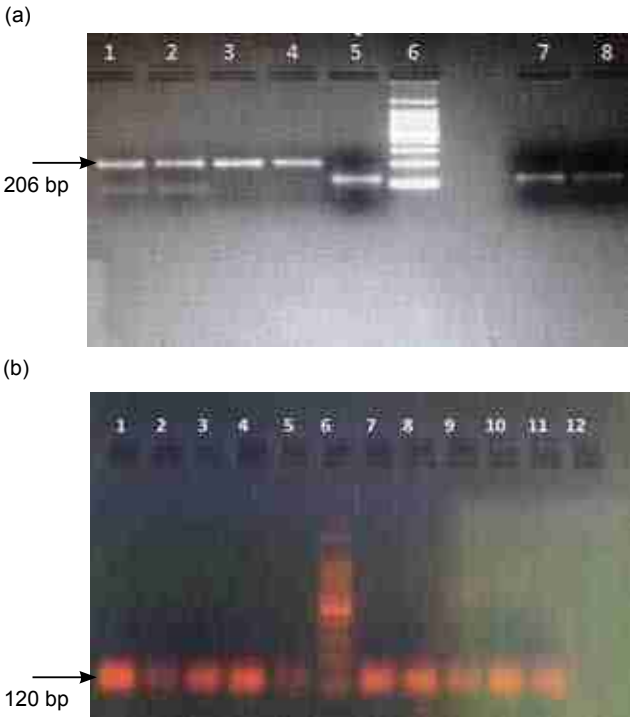


Fig. 5: (a) Gel picture showing three mixed infection (*Pv & Pf*) from *vivax* positive patients. Lane 1: Positive control of *P. falciparum*; Lanes 2–4: Patient sample; Lanes 5, 7 and 8: *P. vivax* positive patient; Lane 6: 100 bp DNA ladder; and (b). Gel picture showing PCR product of *P. vivax* positive patients.

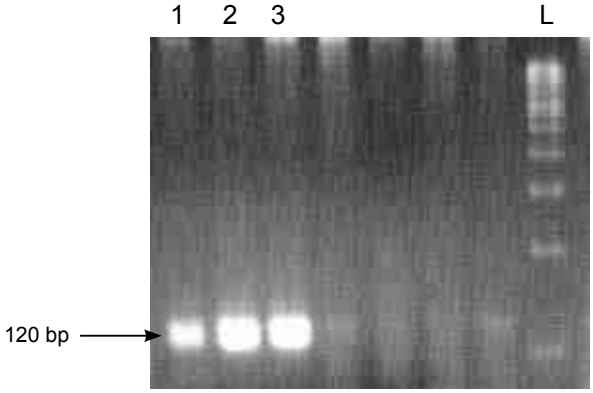


Fig. 6: Gel picture showing two fever patients (negative by slide) positive for *P. vivax*. Lanes 1 and 2: Negative patient sample; Lane 3: *P. vivax* positive patient sample; Lane L: 100 bp DNA ladder.

Table 5. Man-hour density of *Anopheles* mosquitoes in District SAS Nagar, Punjab (April 2017 to March 2018)

S.No.	Species	2017									2018		
		Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar
1.	*An. culicifacies*	0	0.3	0	4.5	4.3	1	0.2	–	0	0	0	0
2.	*An. stephensi*	0	3	0.5	7.5	3	2	0.1	–	0	0	0	0.5
3.	*An. fluviatilis*	0	0	0	0	0	1.9	1.2	0.2	1	0	0	0.2
4.	*An. annularis*	1.7	20.3	0.5	15.8	5.3	8	3	–	5.3	0	0.8	0.8
5.	*An. subpictus*	0	0	0.5	84.5	215.8	14.2	17.9	–	0.1	0	0	0
6.	*An. vagus*	0	0	0	0.3	37.8	0.5	0	–	0	0	0	0
7.	*An. nigerrimus*	0	0	0	0.3	0	3.4	0.3	–	0	0	0	0
8.	*An. pulcherrimus*	0	0	0	0.3	1.8	0.7	0.2	–	0	0	0	0
9.	*An. pallidus*	0	0.3	0	0	0	0	0	–	0	0	0	0

Table 6. Man-hour density of *Anopheles* mosquitoes in Punjab

S.No.	Species	Mansa	Rupnagar	Muktsar
1.	*An. culicifacies*	0.4	5.7	0.5
2.	*An. stephensi*	6.3	0.7	15.7
3.	*An. annularis*	0.1	5.3	0
4.	*An. subpictus*	9.3	10.3	0
5.	*An. vagus*	0.5	0	0
6.	*An. pulcherrimus*	18.6	0.3	0

culicifacies was found susceptible to deltamethrin and malathion, which is currently being used for indoor residual spray (IRS) in Punjab. However it was resistant to DDT.

Molecular entomological studies

The molecular studies were designed to understand the human host preference of malaria vector mosquitoes and to identify the Anopheline species which could have role as malaria vectors. Till March 2018, 154 malaria cases were recorded from the study area and Mansa district one of the selected districts, contributed most of the cases, therefore, the entomological investigations were carried from this district to study the prevalent species of *Anopheles* and to assess their vectorial capacity and host parasite interaction.

Adult mosquitoes were collected manually by the mouth aspirator in the human dwellings and cattlesheds. The collections were kept in cages and the mosquitoes were morphologically identified by using taxonomic keys and adult mosquitoes were then stored at 4°C for molecular analysis.

Molecular identification: DNA was extracted from the legs of each mosquito by following the protocol of Qiagen DNA extraction kit (Blood & Tissue) with slight modifications. The rDNA ITS2 was amplified using primers 5.8 F (50-TGTGAACTGCAGGACACATG-30) and 28R (50-ATGCTTAAATTTAGGGGGTA-30). The samples were heated at 94°C for 5 min before 35 cycles of amplification at 94°C for 1 min, 61°C for 30 sec and 72°C for 30 sec followed by a final extension step of 5 min. The amplified products were analysed on 2% agarose gel. *Anopheles pulcherrimus* was found dominant species in Mansa district and was confirmed by PCR of ITS2 gene and compared with *An. stephensi* and *An. culcifacies*. In Fig. 7, lanes 2 and 4 are the PCR products of *An. pulcherrimus* showing base pair length of 500 bp and lanes 3 and 5 of *An. culicifacies* having base pair

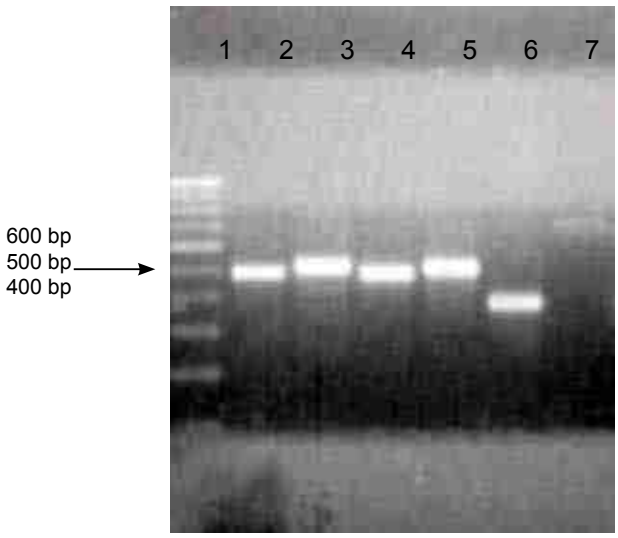


Fig. 7: Gel picture showing ITS2 PCR products of three Anopheline species. Lane 1:100 bp DNA ladder; Lanes 2 and 4: *An. pulcherrimus*; Lanes 3 and 5: *An. culicifacies*; Lane 6: *An. stephensi*; Lane 7: Negative control.

length of approximately 530 while *An. stephensi* around 400 bp. Further, studies on host feeding behaviour and infection rate in malaria vectors are in progress.

3.3 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 further for a period of 5 years (2016–2021) to cover 20 Dams and there components under Phase-III. Under the project two Field Units, one each at Indore (6 Dams and 1238 villages) and Sanawad district (7 Dams and 834 villages) were established. The Bhopal Unit in the earlier phase was retained with mandate to cover 7 Dams and 224 villages. Overall 20 major dam projects are to be covered by these three units (Fig. 8).

The objectives of the study were: (a) To assess the adverse health impact of reservoirs, downstreams, canals and command areas on incidence of malaria and other vector-borne diseases; (b) To assess risk factors related to malaria and other vector-borne diseases and water-borne diseases in resettlement and rehabilitation colonies; (c) To assess the quality of drinking water in terms of toxic minerals in the existing water sources (if any) and microbial contamination in the canal drinking water sources; and (d) To make recommendations of mitigation measures for each component in dam for control

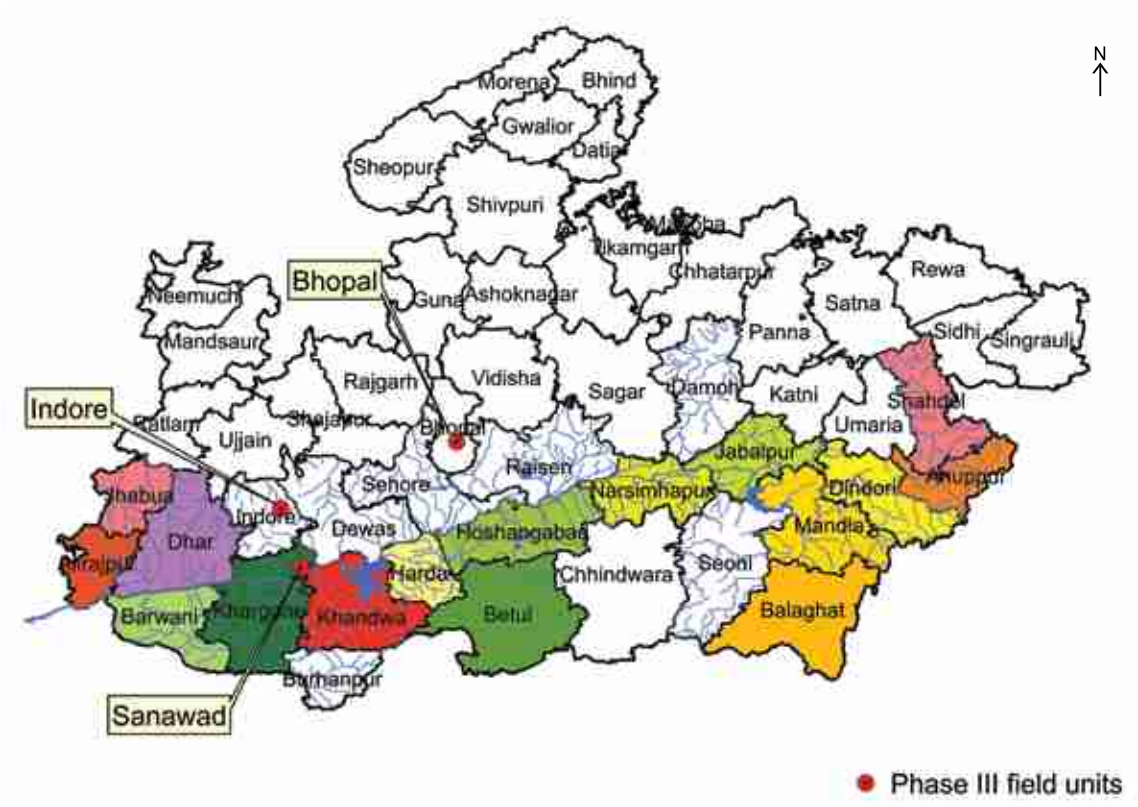


Fig. 8: Study sites in Madhya Pradesh, India.

of malaria and other vector-borne and water-borne diseases.

The study unit at Bhopal surveyed villages in seven project sites covering 11 districts, namely: Dudhi Project (Chhindwada Hoshangabad, Narsinghpur districts); Morand Project (Harda, Hoshangabad districts); Ganjal Project (Hoshangabad, Betul districts); Chinki Project (Narsinghpur district); Bargi Project (Jabalpur, Seoni, Mandla districts); Halon Project (Mandla, Balaghat districts); and Upper Narmada Project (Dindori, Anooppur districts). From January to August 2017, a total of 224 villages were surveyed.

The study unit at Indore surveyed villages in six project sites covering seven districts, namely Omkareshwar Sagar Project (Khandwa, Khargone, Dhar); Sardar Sarovar Project (Barwani, Khargone, Alirajpur, Dhar); Maan Dam Project (Dhar); Narmada Malwa Gambhir Link Project (Indore, Ujjain); Jobat Dam Project (Alirajpur); and Alirajpur Lift Irrigation Project (Alirajpur). From January to August 2017, a total of 254 villages were surveyed.

The study unit at Sanawad surveyed villages in seven project sites covering four districts, namely: Chaingaon Makhan Project (Khandwa district); Upper Beda Project (Khargone district); Balwara Lift Project (Khargone district); Bistan Lift Project (Khargone district); Lower Goi Project (Badwani district); Punasa Lift Irrigation (Khandwa district); ISP Project (Khandwa, Dewas, Khargone and Badwani). From January to August 2017, a total of 293 villages were surveyed.

In all the three units, cross-sectional surveys were done and blood slides were examined. The positive cases were treated and reports were discussed with the concerned Health Centres for follow up. Man hour density (MHD) of the vectors was also recorded. Drinking water samples were tested using HiWater^{TM} Test Kit (HiMedia), and positive samples were recommended for chlorination. ASHA workers and Anganwadi workers were trained about how to prepare blood smears and reporting to concerned PHCs along with awareness regarding vector-borne diseases, symptoms and control measures Figs. 9a and b). 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 (NVDA) and accordingly actions

Fig. 9: (a) Entomological surveillance; and (b) Blood slide preparation.

were taken by the NVDA. The data regarding entomological and epidemiological surveys with the current situation of vector-borne diseases and water testing were communicated to the State Health Department and mitigation measures for identified problems were also suggested to the stake holders. After each survey, detailed recommendations were submitted to NVDA and State Health Department for necessary action for control of vector-borne diseases.

3.4 Urbendemic: How to improve vector-borne diseases control in the urban area of Delhi

Dengue cases in Delhi from 2011 to 2015 were obtained from MCD. All these dengue cases registered were geocoded and mapped with the help of Geographic Information System (GIS), which further give us fair idea about the location of permanent clusters of dengue cases in some parts of the Delhi (Fig. 10). The dengue cases data are also being analyzed in correlation to the surface temperature and environmental characteristic of the localities. Analysis is under progress to understand the local risk factors for disease transmission.

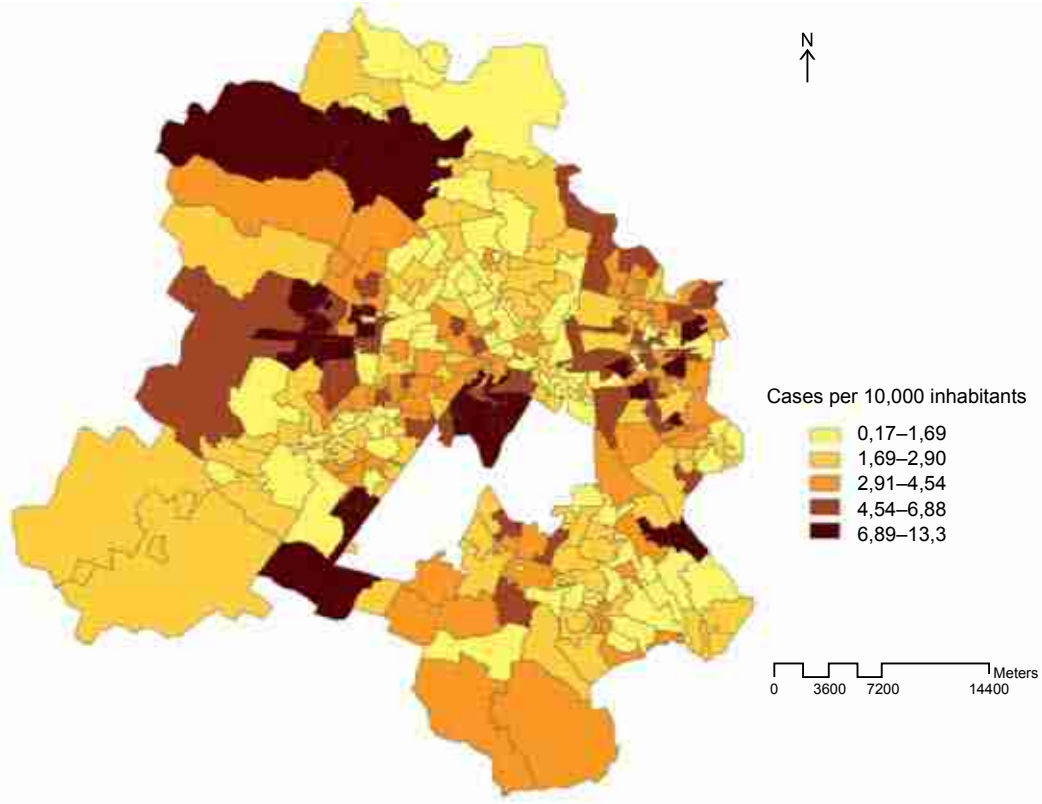


Fig. 10: Mean dengue cases in Delhi (2011–15).

3.5 Studies on Health Impact Assessment of Sardar Sarovar Project (SSP) in Command Areas of Rajasthan

The study was conducted in the command areas of Sanchore and Barmer, Rajasthan.

The recommendations were made to the Health Dept. of State government for taking up interventions like, biological control through introduction of larvivorous fishes in newly constructed diggis and sump wells, minor engineering changes like repairing of canals, de-weeding in canals (Fig. 11).

3.6 DST-ICMR Centre of Excellence for Vector-borne Diseases

A Centre of Excellence for Climate Change and Vector-borne Diseases supported by DST was established in 2017 with the aim of:

1. Determination of thresholds of temperature for survival of vectors of dengue, kala-azar and Japanese encephalitis and respective pathogen for transmission, based on laboratory work and/or disease distribution;
2. Modelling of projected scenario of dengue, chikungunya, Japanese encephalitis, Kyasanur

Minor engineering

De-weeding

Canal before repairing

Canal after repairing

Biological control

Larvivorous fishes

Introduction of larvivorous fishes in diggies

Sump wells

Fig .11: Interventions for mosquito control.

Forest disease and scrub typhus and disease vectors;

3. Determination of climate-driven ecological risk for malaria, dengue, chikungunya, kala-azar, Japanese encephalitis and Kyasanur Forest disease;
4. Setting up a system for seasonal forecast/early warning of outbreaks malaria and dengue for guiding the national programme for preparedness; and
5. Creation of facilities for executing training programmes for capacity building of stakeholders in assessing the impact of climate change on major vector-borne diseases in India.

3.7 Capacity building

1. A total of 200 Laboratory Technicians from 22 districts of Punjab were trained in malaria microscopy in three days refresher training courses for 10 batches of 20 LTs each.
2. About 30 Insect Collectors from all over Punjab were trained in mosquito identification and sampling techniques in a two days workshop jointly organized by the NVBDCP Punjab unit and NIMR at Chandigarh.
3. Entomologist from state was trained in mosquito sampling and identification.
4. Three Research Assistants were trained in molecular diagnosis of malaria parasite.
5. Nine Field Workers were trained in malaria surveillance and treatment work. ❑

Clinical Research 4

4.1 Monitoring the therapeutic efficacy of antimalarial medicines in India

The ICMR-NIMR in collaboration with the National Malaria Control Programme have implemented nation-wide sentinel sites monitoring system in the country for monitoring the therapeutic efficacy of antimalarial drugs since more than a one decade and has provided evidence for updating the national malaria treatment policy being used for the treatment of malaria in the country in the past. Standard protocols developed by WHO on surveillance methods for monitoring the therapeutic efficacy of antimalarial drugs in uncomplicated *P. falciparum* malaria was followed to assess the efficacy of recommended antimalarial drugs in the country. During 2017–18, the uncomplicated *P. falciparum* infection patients were administered six-dose regimen of recommended artemisinin based combination therapy including artemether lumefantrine (AL) and artesunate plus sulphadoxine-pyremethamine (AS + SP) and chloroquine (CQ) to uncomplicated *P. vivax* infected patients over 3 days at sentinel study sites and were followed up to 28 days. Genotyping involving polymorphic markers, namely msp-2, msp-1 and Glurp were employed to differentiate recrudescence and re-infection in cases of treatment failure. To monitor the drug resistance pattern in the samples for AL resistance, mutations in *Pfmdr1* and *Pfcrt* gene were analyzed in the samples obtained at Day-0. Additionally, 100% samples were selected from these sites to monitor SP drug resistance through gene polymorphisms in *dhfr and dhps* in samples obtained on Day-0.

At two sites in northeast India (NE sites; Mizoram and Arunachal Pradesh) where AL is first-line treatment for uncomplicated *P. falciparum*, the PCR corrected efficacy was 100%. A single case of drug failure observed on Day-28 after AL treatment in Mizoram among the enrolled study participants at NE sites showed *P. falciparum* reinfection.

At Madhya Pradesh and Maharashtra sites where AS + SP is first-line treatment for uncomplicated *P. falciparum* cases, the PCR corrected cure rates after 28 days follow-up was 100%. A single case of *P. falciparum* reinfection was also observed on Day-14 at Betul site of Madhya Pradesh.

Pfcrt mutations were observed in 100% samples of NE states with AL treatment and from the other sites with AS + SP treatment. The results are in support to the presently available data on the key chloroquine resistance mutation K76T; where in very few samples carrying the wild-type allele have been reported across different malaria endemic regions. Among *Pfmdr1* gene mutations, 66.7% of the samples carried mutation in the 86 codon whereas wild type was obtained for 184 and 1246 codon among the NE study sites.

At sites where AL has been recommended for treatment of uncomplicated *P. falciparum* malaria, 96.7% samples carried mutation in the *Pfdhfr* gene whereas 100% of the samples were mutated for *Pfdhps* gene. Only 3.3% of the samples carried the wild type allele for the *Pfdhfr* gene with no wild type pattern observed in the *Pfdhps* gene. Similar results were observed at sites with AS + SP treatment for uncomplicated *P. falciparum* malaria with 96.4% samples carrying mutation in the *Pfdhfr* gene whereas 100% of the samples were mutated for *Pfdhps* gene. Additionally, 5.4% of the samples carried the wild type allele for the *Pfdhfr* gene with no wild type for the *Pfdhps* gene.

In conclusion, the study indicates that the efficacy of ACT-AL studied at two study sites, *i.e.* Mizoram and Arunchal Pradesh is high (100% at both the sites). AS + SP is effective in treating *P. falciparum* malaria at sites other than NE states (*i.e.* Madhya Pradesh and Maharashtra) with an

efficacy of 100%, whereas CQ showed an efficacy of 100% in treating *P. vivax* malaria at one site in Uttar Pradesh.

4.2 A survey to assess the infectious reservoir of *Plasmodium* infections and to monitoring the efficacy of antimalarial medicines in East Garo Hills district, Meghalaya and Udalguri district, Assam, northeast India

This study has generated useful data about the efficacy of recommended ACT, *i.e.* AL presently recommended in NE region, which will help to guide the drug policy to avert spread of drug-resistant malaria.

The study also generated the prevalence data on extent and distribution of asymptomatic infectious reservoir in the community that helped to delimit and formulate the interventions required for achieving pre-elimination stage of malaria.

The national drug policy on malaria revolves around the results of such studies which will help in strengthening healthcare facilities for reducing the morbidity as well as mortality from malaria in the highly vulnerable population groups in the country.

4.3 Clinical development of antimalarials

The NIMR is actively involved in clinical development of antimalarials, and following clinical trials are ongoing.

4.3.1 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 multicentre, phase IIIb, single arm trial to assess the safety, tolerability and efficacy of Eurartesim oral film coated tablet formulation (160/20 or 320/40 mg PQP/DHA) in children and adolescent patients with acute uncomplicated *P. falciparum* malaria was carried out at two sites—Ranchi and Mangaluru.

A total of 100 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 PCR-corrected ACPR and finally 96.8% of them were still showing a PCR-corrected ACPR on Day-63.

A total of 33 adverse events were reported. No severe adverse event/deaths were reported, indicating that the combination was safe and effective.

4.3.2 Study on Triple Artemisinin-based combination therapies compared to Artemisinin-based combination therapies

This is a multicentre, open-label randomised trial to assess the efficacy, safety and tolerability of Triple Artemisinin-based combination Therapies (TACTs) compared to Artemisinin-based combination Therapies (ACTs) in uncomplicated falciparum malaria and to map the geographical spread of artemisinin and partner drug resistance. It is coordinated by Mahidol Oxford Research Unit.

In this study, patients were recruited at three sites in India, *i.e.* Ispat General Hospital, Rourkela; Medical College Midnapur; and Agartala Government Medical College. A total of 299 uncomplicated falciparum malaria patients fulfilling screening criteria were enrolled in the study, whereas 112 patients were recruited in Rourkela, 102 in Midnapur and 85 at Agartala site. Result analyses are in progress.

4.4 Establishment of National Malaria Slide Bank (NMSB)

This study aims to establish a Malaria Slide Bank at national level to impart the trainings and assessments for malaria microscopists at regular intervals and quality assurance. A total of 21 samples were collected in 2018. All the samples collected so far have been diagnosed by polymerase chain reaction as well as microscopy.

Out of them, 16 were of *P. vivax (Pv)* positive, four were *P. falciparum (Pf)* positive and one was mixed infection of both *Pf* and *Pv*. The blood smears are stored and maintained by NIMR, New Delhi (Fig. 1).

4.5 Pilot study to validate portable digital microscope for malaria microscopy

NIMR validated a portable digital microscope for malaria microscopy in laboratory (Fig. 2). The

Fig. 1: Slide banking procedure and slides with smears.

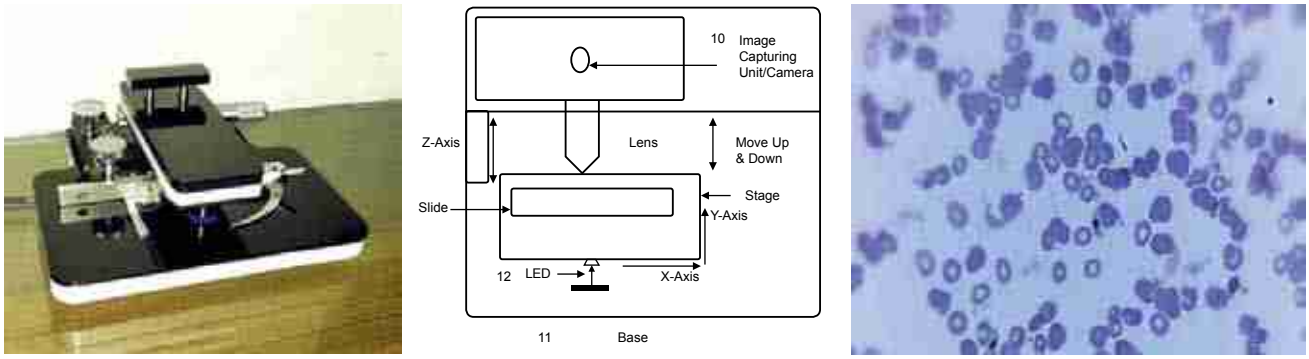


Fig. 2: Digital microscope, its functioning and image of infected RBCs.

morphological distinction, qualitative comparison, determination of species and ability to quantify parasite burden were compared with standard binocular microscope used in the laboratory. The sensitivity and specificity compared to conventional microscopy was 91.2 and 100%, respectively, while compared to polymerase chain reaction method was 84.9 and 100%, respectively. The quantification limit for conventional microscope ranges from 48–280,000 parasite/µl, while digital results ranges from 159–80,000.

4.6 Fever Clinic

At fever clinic, 144 malaria cases were diagnosed from January to December 2017. Out of 144 cases, 140 were *P. vivax* and 4 *P. falciparum*. 67% were males while 33% were females and peak of the malaria cases was obseved in the month of August and September (Fig. 3a). All the confirmed malaria cases were given treatment as per the national treatment guidelines.

NIMR is one of the sentinel surveillance sites for diagnosis of dengue and chikungunya. A total of 1609 dengue cases and 161 chikungunya cases were diagnosed in 2017 (Fig. 3b). Gender-wise distribution was 55% males and 45% females. Maximum number of cases reported in the month

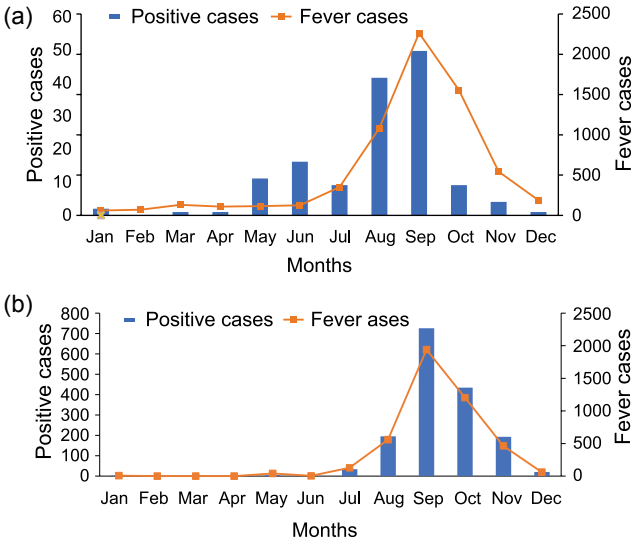


Fig. 3: (a) Malaria cases in 2017; and (b) Dengue cases in 2017.

of September. Dengue serotyping was performed in 24 samples and DEN-3 was found in all the samples.

4.7 Association of delayed haemolysis and intravenous artesunate therapy in severe malaria

The observational study was conducted among admitted severe malaria patients in the Rajendra

Institute of Medical Sciences, Ranchi. The objectives of the study were to study the association of delayed haemolysis with intravenous artesunate in severe malaria patients.

A total of 32 patients were enrolled. All the cases were followed up weekly for four weeks. At each visit clinical examination and laboratory investigations were performed. Haemolysis with significant fall of haemoglobin was observed in 7 patients.

There is need to make clinicians aware of possible delayed haemolysis with injection artesunate and need to monitor it by weekly follow-up.

Highlights of the Research Activities

5

5.1 Bengaluru (Karnataka)

- Phase II and III evaluation of the efficacy and residual activity of SumiShield 50% WG (Clothianidin) for IRS for control of malaria vector was carried out in UKP area of Karnataka. The insecticide was very effective for more than six months from initial applications.
- *Plasmodium vivax* liver stage assays were performed on hepatocytes derived from induced pluripotent stem cells and also on HC-04 cell lines. Infection in liver cells has been observed.
- MozziQuit, a mosquito trapping device captured more mosquitoes than the conventional traps. This may be useful for surveillance of vector mosquitoes.
- A study was initiated in Gulberga district, Karnataka to find out the bionomics of prevalent malaria vectors. *Anopheles culicifacies* and *An. fluviatilis* are the main malaria vectors in this area, breeding mainly in stone quarry pits and streams.
- Parasite panel and reference slides were prepared for quality assurance of RDTs.
- Besides these, technical assistance was provided to the state health department.

5.2 Chennai (Tamil Nadu)

- Intensive surveys were carried out in 5 districts of Kerala, namely Thiruvananthapuram, Wayanad, Ernakulam, Idukki and Pathanamthitta districts during pre-monsoon (March and April 2017) and monsoon (June, August and September 2017) seasons for the collection of *Aedes albopictus* and its subgroup species besides, *Ae. aegypti* for the ICMR funded project on 'Ecology and distribution of *Aedes albopictus* and *Ae. aegypti* with special reference to *albopictus* subgroup species of the subgenus *Stegomyia* in Kerala, India'.
- Extensive field studies on transmission of vector mosquitoes including adult (dawn and dusk) indoor resting collections from human dwellings and cattle sheds; besides, vector incrimination, host blood meal preference, susceptibility status of operational larvicide (Temephos) against immature *An. stephensi* and incubator studies with varied temperatures to find out duration and emergence rate of *An. stephensi* were also carried out as part of the NIH project 'Center for the Study of Complex Malaria in India (CSCMi)'.
- A comparative study on the susceptibility of *An. stephensi* from geographically diverse ecotypes (Coimbatore and Chennai), in Tamil Nadu to *Plasmodium* species, indicated similar infection and infectivity status in both the strains.
- Bottle assay method to monitor insecticide resistance based on knockdown (KD) in *An. stephensi* and *Ae. aegypti* revealed that both are susceptible to the dosage of deltamethrin.
- Monitoring of existing intervention tools/ methods in the programme for scaling down malaria to have a strong impact on reduction of parasite incidence to an extent that would interrupt local transmission in Rameswaram Island was initiated.
- Phase III study on the WHOPES funded project on 'Evaluation of SumiLarv 2MR as a mosquito larvicide for control of *Ae. aegypti* in container habitats in Chennai, India' was carried out and the results showed 100% efficacy of the test compound during the entire observation period of 16 weeks indicating its usefulness in container habitats against *Ae. aegypti*.
- Further, technical support was provided to various institutes/colleges/Government agencies and collaborative research studies were also undertaken with NIMR, Delhi, and other institutes.

- Malaria clinic continued to function catering to the needs of the public by providing early diagnosis and prompt treatment.
- Out of 3 Ph.D. students of the field unit, one is awaiting viva voce, another has submitted the synopsis to the University and the third one is in the final stage of experimental studies.
- During the reporting period, the Field Unit had 3 research publications in peer-reviewed journals.

5.3 Guwahati (Assam)

- A multicentre, open-label randomized trial was initiated at Dhalai district Hospital, Tripura in April 2017 to assess the efficacy, safety and tolerability of Triple Artemisinin-based combination Therapies (TRAC-II) compared to Artemisinin-based combination Therapies (ACTs) in uncomplicated falciparum malaria. A total of 85 patients were enrolled and all the study subjects responded well to the drugs administered.
- Therapeutic efficacy of Artemether plus Lumefantrine (AL) was monitored in malaria endemic blocks along international borders, *viz*. PHC Namsai (Arunachal Pradesh) and Talabung SDH district Lunglei (Mizoram). In total 23 cases were enrolled at Talabung site and 12 cases of malaria were enrolled at PHC Namsai. All the malaria cases were responded well to the recommended antimalarial therapy.
- Surveillance of Dengue vector in Guwahati metropolitan, India was conducted to find the possible breeding habitats of *Aedes* larvae. *Ae. aegypti* found breeding predominantly in discarded tyres, cement tanks and used fish containers.
- Malaria vector susceptibility to insecticides was tested in each identified/selected district/ site of Assam and Meghalaya. The density of *An. minimus* and *An. baimaii* species was found low. Therefore, efforts will be made for searching pockets of the malaria vectors in malaria endemic localities so as to achieve the goal of the project.
- Other activities included providing technical support to the programme, *i.e.* distribution of larvivoroush fishes, health education, training to technical health professionals, *etc.*

5.4 Haridwar (Uttarakhand)

- ***Situation analysis and identification of risk factors of Dengue in District Haridwar:*** A total of 1238 houses were surveyed out of which 346 houses were found positive for *Aedes* breeding. It was observed that major breeding sites in both the areas were coolers and containers and their percent positivity was more than 35%. Prevalence of *Ae. aegypti* was high in Haridwar City (53.7%) as compared to BHEL township (8.7%), whereas percent composition of *Ae. albopictus* was 68.7 in BHEL township and 38.9 in Haridwar City. Overall percent composition of *Ae. aegypti, Ae. albopictus* and *Ae. vittatus* were 21.8, 60 and 18.2%, respectively. A total of 120 dengue cases were recorded in Haridwar district and more than 90% of dengue cases were reported from Bahadarabad CHC.
- ***Stratification of malaria in District Haridwar—A demonstration of elimination in one subcentre:*** During the months of April 2017 to March 2018, a total of 345 blood slides were collected in Chandrapuri subcentre, out of which 8 cases were found positive for *P. vivax,* SPR being 2.3, while 356 blood slides were collected from low malaria sub centre, *viz*. Shivgarh out of which 2 slides were found positive for *P. vivax*, SPR being 0.6. As compared to 2015, 91.5% reduction of malaria cases was observed in Chandrapuri subcentre and 87.5% reduction in Shivgarh subcentre during 2017-18. Overall reduction of 90.9% malaria cases was recorded in both the subcentres. Average man hour density of *An. culicifacies* was 1.5 in Chandrapuri subcentre and 0.7 in Shivgarh subcentre while density of *An. fluviatilis* was high (14.5) in Shivgarh subcentre as compared to Chandrapuri subcentre (0.03).
- ***Stratification of malaria in District Saharanpur with reference to socioeconomic and climatic factors associated with high malaria incidence:*** The objectives of the project are to prepare CHC/Sub-centre/village level stratified map of malaria in District Saharanpur, study breeding ecologies, seasonal abundance, feeding and resting behaviour and susceptibility status to insecticides of malaria vectors, socioeconomic status and climatic variables in relation to malaria transmission, indentify epidemiological risk factors in malaria endemicity in most affected

area in District Saharanpur and formulate control strategy of malaria. Preliminary studies were carried out. PHC-wise epidemiological data of District Saharanpur was collected. Gangoh CHC showed highest API (0.9) followed by Sarsawa (0.53) and Nukur (0.43).

- ***Monitoring of insecticide resistance in malaria vectors in endemic districts of Uttar Pradesh, India:*** The studies were carried out in two districts, namely Saharanpur and Badaun of Uttar Pradesh. In the villages of Maniharan block, Saharanpur district, 49.1% population of *An. culicifacies* was found susceptible to 0.05% deltamethrin, 30% susceptible to 5% malathion and 100% resistance to 4% DDT. Percent corrected mortality of *An. culicifacies* was 10% (range: 6.6–13.3%) against DDT, while 90% (range: 86.7–93.3%) susceptible to malathion and deltamethrin (Range: 86.7–93.3%) in the villages of Gangoh block of Saharanpur district. Insecticide susceptibility test *An. culicifacies* was carried out from the villages of Ujhani, Dataganj and Kadar Chowk blocks of District Badaun. In Ujhani Block, *An. culicifacies* was found 100% resistant to DDT, while percent corrected mortality of *An. culicifacies* was 100% against malathion and 93.3% against deltamethrin. It was observed that there was no mortality of *An. culicifacies* against DDT, while 100% and 93.3% (Range: 86.7–100) mortality was observed against malathion and deltamethrin, respectively in Dataganj block. In Qador Chowk Block, 100% resistance of *An. culicifacies* was recorded against DDT, while 96.7% (93.3–100) and 90% (Range: 86.7–93.3) mortality was observed against malathion and deltamethrin, respectively.
- ***Monitoring of insecticide resistance in malaria vectors in Uttarakhand:*** Four districts, *i.e.* Dehradun, Haridwar, Udhamsingh Nagar and Nainital were selected for the study. Preliminary study was initiated in Bahadarabad block of District Haridwar. Monitoring of insecticide resistance was carried out against DDT, malathion, and deltamethrin. It was observed that *An. culicifacies* population was 100% resistant to DDT, while it was 96 and 100% susceptible to malathion and deltamethrin, respectively.
- ***Industrial malaria control:*** This Field Unit is working on Industrial malaria control since 1986 and successfully controlled malaria in BHEL, Haridwar. From April 2017 to March 2018, a total of 1286 blood slides were collected, out of which the 13 slides were found positive for *P. vivax* SPR was 1.01.

5.5 Jabalpur (Madhya Pradesh)

- After 3 years use of LLIN (LifeNet®, PermaNet 2.0 and NetProtect) by the community 70% nets were found in the households, study was funded by WHO Pesticide Evaluation Scheme (WHOPES), Geneva, Switzerland. In three types of nets, 100% nets up to 24 months, 96.7 in 30 months and 96 in 36 months could meet the criteria of bioassay and tunnel test (as per WHOPES). All the nets effective after 3 years of use had undergone several washes. Loss of insecticide on the nets was between 51 and 76%. Fifty percent of the nets had at least one hole of which 1.5–2% nets had hole of 0.5–10 cm size. Maximum number of holes were found on the lower side of the nets.
- To study the prevalence of asymptomatic malaria cases, in high transmission areas, overall SPR was 8.6%. However, in low transmission areas SPR was 0.4%. SPR was 7.2% among asymptomatic individuals in high and no cases were found in low transmission areas, respectively. In contrast, individuals who presented signs and symptoms of malaria, SPR was 12.1 and 2.7% in high and low transmission areas, respectively. Among asymptomatics, SPR was 10% in children and 6% in adults. However, in symptomatic, SPR was 17% in children and 10% in adults. Further, in asymptomatics, SPR was 27% in post-monsoon and 4% in monsoon seasons. However, in symptomatics, SPR was 15% in monsoon and post-monsoon. Vector density was high in high transmission areas throughout the year.
- For therapeutic efficacy of ACT (AS + SP) study at Betul site, 1741 suspected malaria cases were screened by microscopy, of which, 182 (10.5%) were found parasitaemic. Out of 182, 111 (6.4%) were with *P. falciparum* mono infection and were enrolled in the study. A total of 70 patients with *P. falciparum* mono infection, were enrolled for 30 days follow up study. One patient showed late parasitological failure (LPF) on 14 days of follow up, which was re-infection. The PCR corrected efficacy of ACT (AS + SP) at Betul site was 100%.

- To assess the knowledge and treatment practices it observed that unqualified medical practitioners (UMPs) were providing treatment in rural tribal areas commonly for malaria, typhoid, diarrhoea and skin diseases.
- These UMPs were practicing since 11 ± 8 years. About 80% had received medical training from unauthorized sources. Only 11% of these UMPs were having non-medical graduate degree and 89% were matriculate. Majority of them were using RDTs for diagnosis of malaria. About 70% of *P. falciparum* cases (based on RDT) were treated with mono therapy of Artesunate (E-mal injection). Rest 30% cases were treated with chloroquine (either tablets or injection) inadequate doses. None of them was aware about the national guidelines for diagnosis and treatment of malaria.
- Under capacity building for State Health, a training was conducted on malaria and other vector borne disease for 2 batches of Medical Officers for 3 days each, one batch of Malaria Inspectors for 3 days and 2 batches of Laboratory Technicians for 10 days.

5.6 Nadiad (Gujarat)

- A research study on Fludora-Fusion 562.5 WP-SB (clothianidin 50% + deltamethrin 6.25%) for indoor residual spraying for malaria vector control in Gujarat state, India was carried out. Fludora Fusion, Phase-II study has been completed. Phase-III study is undertaken. A village-scale trial of Fludora-Fusion in comparison with Bendiocarb 80 WP-SB insecticides formulation has been done during May 2017 to February 2018 in Gujarat state, India. Fludora-Fusion 562.5 WP-SB at the dose of 225 mg AI/m^2 and positive control, bendiocarb 80 WP at the dose of 400 mg AI/m^2 were sprayed in 10 villages (each insecticide in 5 villages) in Kheda, Vadoadara and Panchmahal districts of Gujarat. In conclusion, persistence of the Fludora-Fusion 562.5 WP action on most common sprayed surfaces and effects on the elements of vectorial capacity, one round of Fludora-Fusion at 225 mg/m^2 dose may cover the length of the main malaria transmission period and provide effective control of malaria in Gujarat state.
- The main objectives of large-scale (Phase-III) evaluation of efficacy, fabric integrity and community acceptability of PermaNet 3.0 long-lasting insecticidal nets compared with PermaNet 2.0 was to determine and compare the insecticidal activity and fabric integrity of PermaNet 3.0 LNs with PermaNet 2.0 over three years of use by households under field conditions and to assess washing mode and washing habits of LNs by the householders, and to assess the community acceptability of LNs. Cohort nets survey were carried out after 24 months use of nets by house holders. Bioassay, chemical assay and fabric integrity were also carried out.
- Bionomics of malaria vector(s), sibling species composition and to establish their role in malaria transmission in Gujarat study is going on at NIMR, Field Unit, Nadiad. Two districts namely Kheda and Panchmahals (Godhra) with different ecotypes have been selected for the study. Two riverine and two canal irrigated villages in each district, namely Anghadi, Pali, Ravaliya and Muliyad in Kheda and Juni Dhari, Vinzol, Khazoori and Nandisar of Panchamahal were included in the study. Under the study, entomological parameters such as adult mosquito density, parity, human blood index and human landing collection are monitored. Supervision of IRS activity is also done in the study area.
- ***Facility of GLP for insecticide trial:*** Upgradation of insectaries, insecticide testing laboratory and entomology processing laboratory have been completed. The funding of GLP accreditation was sponsored by the World Health Organization Pesticide Evaluation Scheme (WHOPES).
- ***Support to State Health Department:*** To investigate reason of high ABER in Ahmedabad, Anand and Gandhinagar. Our team of scientists, and other supporting staff went to PHCs of various talukas. Scientists had discussions with Medical Officers, Ayush doctors and laboratory technicians present at PHCs. Surveillance records of year 2016 and current year were examined. MF-2 forms and MF-2, 7, 8 and 9 registers were checked.

5.7 Panaji (Goa)

- Proteomic analysis of urine of malaria patients using high resolution mass spectrometry for

identification of candidate biomarkers for *P. falciparum* and *P. vivax* infections was performed. This analysis led to identification of 39 *P. falciparum* peptide antigens belonging to 35 proteins. A subset of 10 peptides from 10 proteins was found to be conserved between *P. vivax* and *P. falciparum* and thus, are of significant importance for diagnosis of either of the species.

- Comparative susceptibility of *P. vivax* infection in wild and colonized *An. stephensi* was done. A total of 27 infected blood feeds with blood of *P. vivax* infected patient, obtained straight from arm, were done in parallel with batches of wild and laboratory reared mosquito females using artificial blood feeders. This study points to many similarities but also some important variation in infection and infection rates in wild *versus* colonized *An. stephensi* population. This study is of great significance for scaling up screens for transmission blocking vaccines, antimalarial compounds and liver stage invasion assays.
- Isolation, characterization and efficacy of naturally occurring mosquito pathogenic bacilli in Goa, India. With culture supernatant (cell free) of the most promising bacterial isolate— Isolate 101 bioassays were performed against III instar larvae of 4 test vectors, *i.e. An. stephensi*, *Ae. aegypti*, *Ae. albopictus* and *Culex quinquefasciatus* and compared with the activity of commercially used mosquito pathogenic bacterial strains, *viz. Bacillus thuringeinsis israelensis* H-14 *(Bti)* and *B. sphaericus* 2362 *(Bs)*.
- A study on the role of gut microbiota in modulation of longevity, fecundity and fitness of *An. stephensi* as a malaria vector was carried out. The cultivable bacteria from the breeding habitat water and the midgut of larvae, pupae, male and female were studied. Based on colony morphological characteristics, total of 90 bacterial isolates were selected for 16S rRNA gene sequencing. All the sequences were blasted with their type species. They were manually curated, edited, analyzed, and aligned using BioEdit software (ver 7.2) and were submitted to the GenBank. The sequences obtained in this study were compared with GenBank database using the BLAST algorithms.
- Field evaluations of mosquitocidal metabolites from *B. subtilis* subsp. *subtilis* (VCRC B471) and *Pseudomonas flourescens* (VCRC B426) were done in phase III trials in Goa. They were found effective for 12–21 days during two cycles of applications.
- Assessment of susceptibility status of *An. stephensi*, *Cx. quinquefasciatus*, *Ae. aegypti* and *Ae. albopictus* populations was done using WHO susceptibility assay kit jointly with NVBDCP Goa entomological team. The tests were performed against DDT (4%), deltamethrin (0.05%), α-cypermethrine (0.05%), lambdacyhalothrin (0.05%), fenitrothion (1%), bendiocarb (0.1%) and permethrin (0.75%) and the report was submitted to NVBDCP HQs.

5.8 Raipur (Chhattisgarh)

- ***Large-scale (Phase III) evaluation of efficacy, fabric integrity and community acceptability of Olyset Plus long-lasting insecticidal nets compared with Olyset Net in India:*** In the baseline chemical analysis, the samples of Olyset Plus and Olyset nets complied with WHO specifications of 20 g/kg (± 25%) target dose of permethrin. Samples of both nets met with the WHO criteria of ≥ 95% knockdown after 1 h and ≥ 80% mortality after 24 h in the baseline cone bioassays against laboratory reared susceptible *An. stephensi*. Nets were distributed in 10 study villages in Kanker (6) and Balod (4) districts in the month of August–September 2014. In a survey of LNs carried out in 100 householders per study arm after one month of net distribution, the HHs reported transient adverse effect. The study was completed after 36 months. Out of 50 Olyset Plus nets withdrawn after 36 months, all nets passed in cone bioassays whereas out of 50 Olyset 30 nets failed. All failed nets when subjected to tunnel tests, met the efficacy criteria of ≥ 80% mortality and ≥ 90% blood-feeding inhibition. After 36 months 50 nets of each type were destructively sampled and 4 samples of 30x30 cm size cut from 4 different sides of each net as per the standard WHO protocol were sent to WHO Collaborating Centre, Gembloux, Belgium for chemical analyses.
- ***Estimating the burden of asymptomatic malaria among the tribal population in malaria endemic area of Chhattisgarh:*** The study was conducted in 3 villages of Keshkal CHC, District Kondagaon. Villages were selected on the basis

of high malaria cases reported by the CHC. A total of 271 persons were screened. Out of which 15 (5.6%) were found positive for malaria (*Pf*–13; mixed (*Pf* + *Pv*–2). Written consent was obtained from the patient or guardian in case of minor. All the 15 asymptomatic cases were given observed treatment with recommended dose of ACT. The cases were followed up to 30 days and all showed adequate clinical and parasitological response (ACPR). Persons reporting with fever (15) at the time of survey were tested with rapid diagnostic kit of which 8 found *Pf* positive were given ACT.

- ***Monitoring the therapeutic efficacy of anti-malarial medicines in India:*** Therapeutic efficacy of ACT was monitored in Malewada PHC, Gadchiroli district, Maharashtra where it is being used as a first line of treatment for uncomplicated *P. falciparum* malaria positive cases. In all, 42 cases at Malewada CHC, district Gadchiroli fulfilling the inclusion criteria were enrolled in the study. ACT was given under medical supervision over 3 days as per the National Drug Policy. All the patients enrolled in the study, administered with drug were followed-up to 28 days from Day-0 (Day of enrolment) for parasitological and clinical evaluation. Haemoglobin was checked on Day-0 and 28. The 28-days cure rate with ACT (AS + SP) was 100% and no clinical or parasitological failure was recorded.

5.9 Ranchi (Jharkhand)

- The survey for species composition of anopheline mosquitoes were carried out in the villages of APHC (Additional PHC) Noamundi. 14 species of anopheline mosquitoes were collected from Noamundi area. Among them 5 recognized malaria vectors *An. culicifacies, An. annularis, An. fluviatilis, An. minimus* and *An. varuna* were recorded.
- Entomological survey was carried out in certain forested area of West Singhbum revealed that *An. fluviatilis* species T was predominant, a few specimen of *An. fluviatilis* species S and *An. minimus* were further confirmed by DNA sequencing. Low density of *An. minimus* 2–12 (MHD) was recorded from Noamundi, Badajamda, Purtidiga and Kadajamda villages. The feeding of *An. minimus* was observed in indoors and less number in outdoors.
- Filariasis survey was carried out in the Jamtara district (Kundhit CHC) during the month of September 2017. A total of 1121 individuals (592 males and 529 females) were surveyed for filarial infection. Out of which 160 cases were found positive for microfilariae by microscopy. The microfilaria rate was 14.3%. All the 160 microfilaria positive cases were treated as per the National Drug Policy. The high prevalence of microfilaria cases (14.3%) indicated that the Jamtara district is highly endemic for filariasis.
- Study on Association of delayed haemolysis and intravenous artesunate therapy in severe malaria was carried out in RIMS (Paediatrics and Medicine Departments). A total of 32 patients were enrolled, out of which10 was adult and 22 was paediatric cases. 12 patients have completed the follow up, 4 patients completed only 7 days follow up and 2 day follow up was completed in 3 patients. Data analysis of all the cases is in progress. Preliminary study indicates delayed haemolysis in intravenous artesunate therapy in severe malaria.
- Study on monitoring of insecticide resistance in malaria vectors in Jharkhand state was carried out in four districts of Jharkhand state (Simdega, West Singhbhum, Gumla and Khunti). Four *Anopheles* species (*An. culicifacies, An. fluviatilis, An. annularis and An. minimus)* were tested for susceptibility status against DDT (4%), malathion (5%), deltamethrin (0.05%) and permethrin (0.075%).
- In Simdega district, *An. culicifacies* was resistant to DDT (4%) and susceptible to malathion (5%) and permethrin (0.75%). *An. fluviatilis* was resistant to DDT (4%) at Saraipani and Tukupani villages of Kurdeg CHC and susceptible to malathion (5%) and Permethrin (0.75%). *An. annularis* was resistant to DDT (4%) and susceptible to malathion (5%) and permethrin (0.75%).
- In West Singhbhum district, *An. culicifacies* was resistant to DDT (4%) and susceptible to malathion (5%) and deltamethrin (0.05%) (Chaibasa and Noamundi areas). *Anopheles fluviatilis* was susceptible to DDT (4%), malathion (5%) and deltamethrin (0.05%). *An. annularis* was also resistant to DDT (4%). *Anopheles minimus* was susceptible to DDT (4%).

- In Gumla district *An. culicifacies* was resistant to DDT (4%) and susceptible to malathion (5%), deltamethrin (0.05%) and permethrin (0.75%). *Anopheles fluviatilis* was susceptible to DDT (4%), malathion (5%) and deltamethrin (0.05%). *Anopheles annularis* was also resistant to DDT (4%) and susceptible to malathion (5%), deltamethrin (0.05%) and permethrin (0.75%).
- In Khunti district *An. culicifacies* was resistant to DDT (4%) and susceptible to malathion (5%), deltamethrin (0.05%) and permethrin (0.75%). *Anopheles fluviatilis* was susceptible to DDT (4%), malathion (5%), deltamethrin (0.05%) and permethrin (0.75%).
- Newly opened a Malaria Clinic at the Rajendra Institute of Medical Sciences (RIMS), Ranchi. A total of 413 persons with fever attended the malaria clinic in the research room, where 47 blood smears were found positive for malaria (*Pv*–3, *Pf*–44). The slide positivity rate was 11.4%, slide falciparum rate was 10.4% and *Pf* percent was 93.6.
- Technical support was provided to NVBDCP in the areas of malaria microscopic surveillance and capacity building on entomological aspects.
- Diagnostic and treatment services were provided to malaria and filarial patients attending the field unit clinic.

5.10 Rourkela (Odisha)

- The ICMR funded project entitled, "Comprehensive Vector Mapping in different Ecotypes of Odisha" was undertaken to assess the pattern of disease transmission and distribution of malaria vectors at subcenter levels; to study the bionomics and vectorial attributes of vectors in different ecotypes of Odisha and to develop situation specific comprehensive malaria control strategy in the state. Entomological surveys were undertaken in Deogarh district during post-monsoon and winter seasons. Six villages, two each, in forest, riverine and plain areas were selected for the study which were located in between 21.30 to 21.35° N latitude and 84.37 to 84.48° E longitude. Primary malaria vector *An. fluviatilis* was found only in forest area, the density of which was higher in winter season than in post-monsoon season. *Anopheles culicifacies* was found in all the three areas although the density of the species was higher in riverine and plain areas. Similar results were also obtained in CDC light- trap and spray sheet collection. Blood from the stomach of mosquitoes collected on Whatman filter paper and ovaries pulled from semi gravid females are being analyzed for blood meal preference and sibling species composition. Head and thorax of mosquitoes are also being analyzed for the presence of sporozoites.
- The MMV funded Comprehensive Case Management Programme continued in four districts of Odisha with the primary objective to assess the impact of comprehensive case management system of uncomplicated malaria on its transmission in different transmission settings. Four CHCs, one each in Bolangir, Dhenkanal, Anugul and Kandhamal districts were taken as intervention area and four other CHCs with identical malaria situation of the same districts were taken as control area. The study was undertaken in collaboration with the Government of Odisha after completion of recruitment and training of project staffs as well as orientation training of the Medical Officers and other existing staffs of the Community Health Centres. The malaria indicators, TPR and API decreased gradually in the intervention CHCs of all the four districts in comparison to those of the base year despite increase in the ABER, whereas no particular trend was observed in the control CHCs. *Plasmodium falciparum* and *P. vivax* cases were followed up on Day 5 and 14, respectively for drug compliance and adverse events. The compliance rates of follow-up ranged from 82 to 100% during which no adverse event was noticed. There was no death due to malaria in study area of any of the four districts.
- The multicentric project entitled, "Vulnerability Assessment and Adaptation Measures towards Potential Impacts of Climate Change on Malaria on Hot spots of India" was initiated in Sundergarh district of Odisha during November 2017 to assess the vulnerability of health system and community to climatic changes; to find out the role of stressed protein (heat shock/cold shock proteins) in malaria vector's resistance to survival towards changing climatic conditions and to find out the adaptation measures to combat adverse impacts of climate change. Two villages in each of forest and riverine area in Gurundia and Birkera CHCs under Sundergarh

district were selected for the study. HOBO data loggers were installed in the study villages, both indoor and outdoor, to record hourly data on temperature and relative humidity. Entomological and epidemiological studies are being carried out.

- During August and September 2017 a total of 708 households in the Industrial township of Rourkela were surveyed for the breeding of *Aedes* species. The overall container index (CI) was 36.5 which varied from 18.6 to 45.5 in different types of containers. The house index (HI), breteau index (BI) and pupa index (PI) were 32.3, 33.6 and 58.3, respectively. Desert coolers were found to be the predominant breeding habitats of *Aedes* mosquitoes which accounted for 81.6% of pupae collected during the survey. A total of 599 adults emerged from the larval and pupal samples collected during survey comprising of 61% *Ae. Aegypti,* 30% *Ae. albopictus* and 9% *Ae. vittatus*. Laboratory as well as small-scale field trail on the control of *Aedes* breeding in desert coolers showed promising results.
- During the reported period, 2744 patients with fever reported to the clinic run by NIMR, Field Unit, Rourkela which is the highest among all the Field Units; out of which 42 were found positive for malaria comprising of 23 *P. falciparum* and 18 *P. vivax*. The SPR, SFR and *Pf*% were 1.5, 0.9 and 57.1, respectively. Significant and gradual decline has been observed in both, the number of patients reporting to the malaria clinic and number of malaria cases, since 2010 in comparison to those of the previous years. ❑

Research Support Facilities

6

6.1 Animal House Facility

The animal house is a central facility at NIMR registered with CPCSEA for research and breeding purposes. Majority, it maintains small laboratory animals like balb/c mice and New Zealand rabbits for research activities such as screening the antimalarials, parasite maintenance, insectary maintenance, immunological studies, *etc*. The projects involving the animals are only undertaken after their approval by the Scientific Advisory Committee (SAC) and Institute Animal Ethics Committee (IAEC) of the Institute. The animal facility has dedicated technical staff for its smooth functioning. The new animal house is under construction and to be completed soon.

6.2 Repository of Biological Materials

6.2.1 Establishment of repository

With an aim to develop and maintain a national level repository of biological materials, continued efforts were made to collect and archive different biological materials from various sources including NIMR Field Units at a central place, *i.e.* NIMR, HQs. The development of the repository was initiated with a collection of all biological samples tested positive for malaria parasites. The extent of the repository is not limited to malaria but it also includes samples from other vector-borne diseases falling within the mandate of NIMR. The purpose of developing a national repository broadly include:

- To preserve and maintain diverse *Plasmodium* isolates and strains over long time.
- To characterize parasites based on their genotypes and phenotypes.
- To make the biological materials available for future research purposes to a wider research community.

The repository is aimed to archive the samples prospectively and retrospectively:

- *Prospectively:* All malaria positive biological materials (blood smears/slides, dried blood filter paper spots, whole blood) collected during routine investigations are being transported from the Field Units to the central repository.
- *Retrospectively:* All biological materials from malaria positive cases collected in the past by independent PIs of NIMR are being "decentralized" to the central repository.

The following types of samples are currently being collected in the repository:

Blood smears/slides stored at room temperature; dried blood filter paper spots stored at –80°C; whole blood cryopreserved in liquid nitrogen; and rapid diagnostic kits/tests (RDTs). Records with the details of the samples and originating PI are being maintained apart from several other details of the samples, so that the due credit of the PI who actually collected the samples is safeguarded.

As on 31 December 2017, the repository includes 999 dried blood spots and 24 peripheral blood smears in addition to the samples already archived within the Malaria Parasite Bank (cryopreserved samples only) (Table 1).

6.2.2 Malaria Parasite Bank

The Malaria Parasite Bank (MPB), established in the year 1992, is functioning as a National Resource facility and is involved in the collection of *Plasmodium* isolates from various field/clinic areas across India. The Bank has a variety of human and non-human plasmodia species collected over a period of last 25 years. The routine activities include *in vitro* cultivation of *P. falciparum* to expand the isolates, adaptation of filed isolates to the laboratory conditions, cryopreservation and revival of adapted and non-adapted cultures. Parasite isolates of all five human malaria parasite species, malaria positive

Table 1. Current status of samples archived in the Repository

Sample	Number	Project	Site	PI
Dried blood spots	95	Malaria in pregnancy (prevention)	Ranchi (Jharkahnd)	Dr Anup Anvikar
	29		Jamshedpur (Jharkahnd)	
	6		Rourkela (Odisha)	
	95	Malaria in pregnancy (treatment)	Ranchi (Jharkahnd)	
	29		Jamshedpur (Jharkahnd)	
	6		Rourkela (Odisha)	
	116	Pyramax trial	Mangaluru (Karnataka)	
	374	Therapeutic study of AS+SP	Various	Dr Neelima Mishra
	118	Fever Clinic	NIMR, New Delhi	Dr Deepali Anvikar
	13	Field Unit Chennai	Chennai (Tamil Nadu)	Dr Alex Eapen
	25	Field Unit Nadiad	Nadiad (Gujarat)	Dr Jaspreet Kaur
	35	Field	Tripura	Dr Kuldeep Singh
	40	Field	Mizoram	Dr Kuldeep Singh
	18	Field Unit Rourkela	Rourkela (Odisha)	
Total	999			
Total slides	24	Malaria Clinic	NIMR, New Delhi	Dr Deepali Anvikar

and negative sera; and non-human malaria parasites in cryopreserved status and in their respective animal hosts, wherever possible, are currently being maintained in the MPB.

Collection and preservation of malaria parasites

The MPB successfully preserves, a total of 1457 malaria parasite isolates from different regions across India with 1019 *P. falciparum*, 433 *P. vivax* and only 5 *P. malariae* parasites. The Bank in 2017 received and cryopreserved a total of 11 isolates from NIMR fever clinic, all from Delhi, out of which 10 were of *P. vivax*. The total year-wise break up of the number of *Plasmodium* isolates cryopreserved in MPB since last 10 years is shown in Fig. 1, whereas their state-wise representation is depicted in Fig. 2.

Screening of drug sensitivity status

Since 1993, a total of 287 *P. falciparum* samples from different regions were tested for the sensitivity to chloroquine (CQ) and 187 (65%) were found to be resistant to CQ.

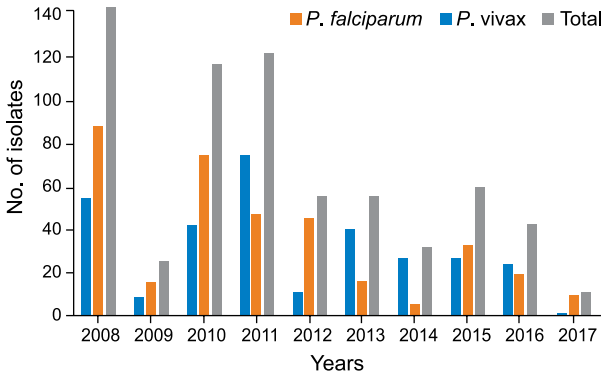


Fig. 1: Number of *Plasmodium* isolates preserved in MPB since last 10 years.

Cultivation of pre-erythrocytic stage of *P. vivax in vitro*

For the first time in India, *P. vivax* pre-erythrocytic schizonts (liver stage) were initially developed in hepatoma cell line using the facilities of parasite bank. However, subsequently the bank was unable to replicate similar studies. In the current year 2017–18, efforts were again initiated to start the liver stage culture of *P. vivax* in hepatic cell lines

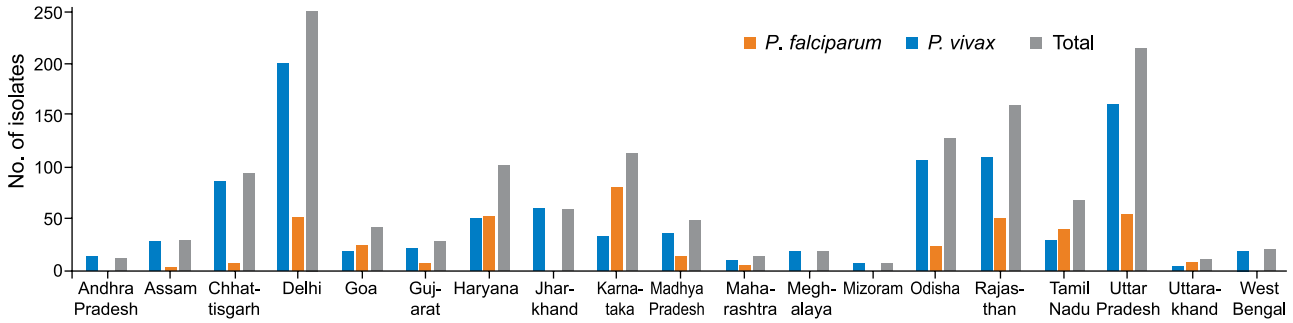


Fig. 2: State-wise distribution of collected *Plasmodium* isolates preserved in MPB since last 10 years.

(HC-04 and HepG2 lines) and/or fresh or cryo-preserved primary hepatocytes. Collaboration is being sought from the Institute of Liver and Biliary Sciences (ILBS), New Delhi on the supply of such primary hepatocytes from liver donors or liver resection surgery patients. Potential collaborative research areas have been identified through a brain storming meeting between ILBS and ICMR-NIMR scientists in February 2018. The following areas were identified: In-depth epidemiological studies to answer the association between malaria and hepatopathies, Primary human hepatocytes, hepatic cell lines, organoids and humanized mice, use of 'Omics' platform in understanding the liver stage biology of *Plasmodium,* and miscellaneous studies including the role of extracellular vesicles in sporozoite-liver interactions.

Cultivation of erythrocytic stage of *P. vivax in vitro*

Repeated efforts have been made to cultivate and adapt erythrocytic stages of *P. vivax in vitro*, like *P. falciparum,* in different combination of media and culture conditions, with little success. For obtaining the reticulocyte-enriched cord blood, a collaboration has been sought from the Obstetrics and Gynaecology Department of the Safdarjung Hospital, New Delhi which is under ethical committee review process.

Supply of biological materials

Providing malaria parasites to the scientific community (various institutes, universities and other research organizations) has been one of the major activities of the parasite bank. The biological materials can be requested from any researcher against an online payment of nominal charges.

The details of various isolates available and corresponding charges are mentioned in Table 2. A total of 69 samples were supplied by the MPB to various users within NIMR (25) and outside NIMR (44). During 2017, a total of Rs. 91,500/- have been collected on this account by supplying parasites to different Universities and Research Institutions of the country. Non-NIMR users included scientists from the National College, Truchirapalli (Tamil Nadu), Institute of Science, Nirma University, Ahmedabad, Punjab University and Indian Institute of Science Education & Research, Pune (Maharashtra). The number of *Plasmodium* isolates supplied by MPB and the resource generated thereof since last 10 years is shown in Fig. 3.

Table 2. Isolates available in the Parasite Bank and their corresponding charges (₹)

Biological materials	Charges (₹)
P. falciparum adapted and characterized for chloroquine sensitivity	₹ 2000/1 ml vial (cryopreserved or running culture)
P. falciparum characterized for erythrocyte invasion phenotype and cytoadherence	₹ 2000/1 ml (cryopreserved or running culture)
P. falciparum cultivated and adapted *in vitro*	₹ 1500/1 ml (cryopreserved or running culture)
P. falciparum cultivated *in vitro* (short-term cultivation/ non-adapted	₹ 1500/1 ml (cryopreserved or running culture)
P. falciparum (original stock)	₹ 1500/1 ml (cryopreserved)
P. vivax (original stock)	₹ 1500/1 ml (cryopreserved)
P. falciparum culture supernatant (spent media)	₹ 750/250 ml (frozen)
Serum/Plasma from *P. falciparum* or *P. vivax* infected blood	₹ 500/1 ml vial (cryopreserved)
Non-human plasmodia	₹ 750/1 ml vial (cryopreserved)
Sera/Plasma from non-human Plasmodia-infected animal	₹ 100/1 ml vial (cryopreserved)

Note: (1) The charges exclude packaging and transportation charges which are to be arranged and borne by the person requesting; (2) The biological materials listed above will be supplied on first-come first-served basis; and (3) The payment has to be made online to Canara Bank, CCRT, Sector 7, Dwarka, New Delhi (RTGS: 2948201010111; IFSC: CNRB0002948).

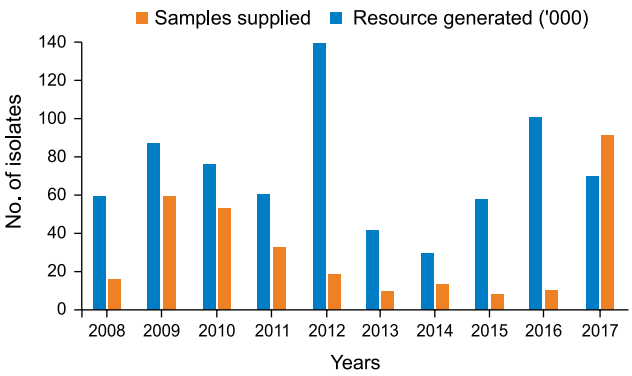


Fig. 3: Number of *Plasmodium* isolates supplied and resource generated (in x1000) by Malaria Parasite Bank during last 10 years.

Human resource development

Imparting training is one of the mandates of NIMR. Expertise are available for providing training in different techniques. Several scientist/research scholars were given training in parasite bank for one week to four months in different techniques.

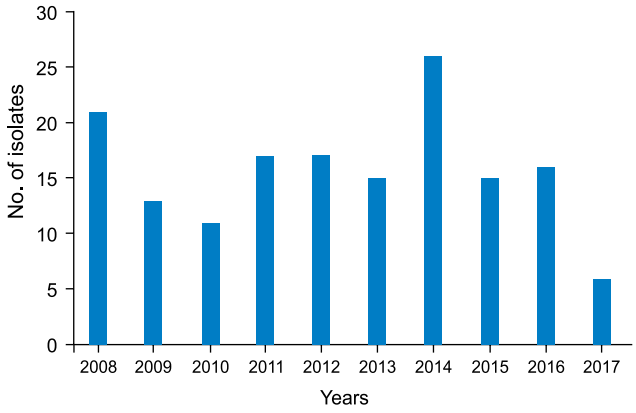


Fig. 4: Number of individuals trained by Malaria Parasite Bank for last 10 years.

The following trainings are available at Malaria Parasite Bank:

- Collection, cryopreservation, and revival of malaria parasite isolates/strains.
- *In vitro* cultivation of erythrocytic stages of *P. falciparum*.
- *In vitro* testing for sensitivity of *P. falciparum* isolates to antimalarials.

The total number of individuals trained by MPB in last 10 years is shown in Fig. 4.

Centralized parasite culture facility

A completely refurbished centralized parasite culture facility has been created within the purview of the malaria parasite bank to develop a centralized parasite culture facility by providing space and facilities required for parasite culture within a specific area. This would discourage culturing of parasites in various labs across the institute. The aim of the centralized facility is to provide an acceptable and uniform standard of quality to all the users with easy procurement procedures for biological materials, specially the blood and serum needed for the culture. In a centralized facility, it would be easy to ensure that good laboratory practices are followed at all levels. The facility currently has two BioSafety cabinets with a potential to accommodate three cabinets. The newly developed facility is currently under pilot testing for the success of parasite culture experiments and prevention of contamination and will be open to users in a couple of months.

6.3 Library and Information Centre

The Library and Information Centre at NIMR is a resource centre which provides an access to literature and documentation in the field of malaria and other vector-borne diseases. It serves as a bank of information.

The Library and Information Centre of NIMR endeavors to acquire process, organize and disseminate global information to fulfill the information needs of the administrators, policy makers, scientists, research scholars, outside visitors and foreign delegates. This Centre uses *e-granthalaya* software package, which consists of modules on acquisition, cataloguing, circulation, serial, web OPAC, membership and article indexing. All the collections of this resource centre are completely computerized and indexed.

Library timings

Monday to Friday–0900 to 1730 hrs

Library collections

Books	8958
Bound journals	5106
Journals (Online)	25
Newspapers	13
Magazines	17
CDs/DVDs	128
Theses	42
Reports (National and International)	140

Special collections

- Census of India Publications
- WHO Publications
- National Survey Reports on Malaria and other Vector-Borne Diseases
- NIMR Publications

Library services

- Circulation of Books
- Inter Library Loan
- Document Delivery
- Reference and Information Services
- Citation Analysis
- Wi-Fi Internet Access Facility
- Reading Hall
- Photo Copying
- Scanning

e-Resources (Online Journals) services

- ERMED Consortium
- JCCC@ICMR Consortia
- ICMR e-Consortia Journals
- NIMR Subscribed online journals

Documentation services

- New arrivals/List of Addition of books
- Conference Alert
- Abstract on Malaria & other Vector-borne Diseases
- Health Bulletin
- Malaria & Other Vector-borne Diseases Alert
- Annotated Bibliography of NIMR (Research Publications)

Apprentice training

The NIMR Library and Information Centre trains and empowers students of library and information discipline by recruiting apprentices for one year. In the year 2017, three apprentice trainees were recruited and trained successfully.

Resource sharing

Library and Information Centre is an active member of Developing Library Network (DELNET) and shares its resources with 5535 member libraries and information centre across the Globe.

Inter-Institutional Collaboration

7

The Institute collaborated with different national and international centres/agencies through different **projects** for wide coverage, protection and effective control of malaria and other vector-borne diseases:

1. Ecology and distribution of *Aedes albopictus* and *Ae. aegypti* with special reference to *albopictus* subgroup species of the subgenus *stegomyia* in Kerala, India.
2. Center for the Study of Complex Malaria in India.
3. A comparative study on the susceptibility of *Anopheles stephensi* from geographically diverse ecotypes in Tamil Nadu to *Plasmodium* species.
4. Evaluation of SumiLarv 2 MR as a mosquito larvicide for control of *Aedes aegypti* in container habitats in Chennai, India.
5. Bottle assay to monitor insecticide resistance in vector mosquitoes.
6. Monitoring of existing intervention tools/ methods in the programme for scaling down malaria in Rameswaram Island, Tamil Nadu, India.
7. Effect of microclimate changes on vector density and its consequence to malaria transmission in Chennai, India.
8. Comparative forecasting efficacy/accuracy of different statistical methods for malaria.
9. Study on estimation of malaria disease burden to support malaria elimination in Punjab.
10. A multicentric study to estimate the seroprevalence of dengue virus infection in India.
11. Assessment of knowledge, attitude and practices of Mitanin's with respect to malaria control in Chhattisgarh.
12 Determining discriminating concentrations in bottle assays for insecticide compounds that are unstable on filter papers, and for some selected compounds suitable for filter paper impregnation.
13. *Plasmodium vivax* liver stage assays.
14. Bionomics of malaria vectors, sibling species composition and to establish their role in malaria transmission in Karnataka, India.
15. Decoding molecular codes of host seeking behaviour in Indian malarial vectors.
16. Genomic epidemiology of Indian *Plasmodium falciprum* during artemisinin.
17. Rapid identification of specioes, host preference and *Plasmodium* sporozoite in *Anopheles culicifacies* using MALDI-TOFMS.
18. RNAseq transcriptomic analysis of Olfactory system in the male mosquito *Anopheles culicifacies*.
19. Reactive *vs* active cases detection for *Plasmodium vivax* in a vivax malaria focus in southwest Delhi: Search for indigenous transmission.
20. Molecular and functional prediction analysis of newly discovered plant like transcripts (PLTs) in the mosquito *Anopheles culicifacies*.
21. Establishing *Plasmodium berghei* reverse genetic platform at NIMR, New Delhi.
22. Understanding the liver stage biology of *Plasmodium vivax*.
23. Molecular basis of insecticide (pyrethroid) resistance in *Aedes aegypti*.

24. Malaria and hypertension: Inter-relationship in context of malaria.
25. Molecuar diagnosis of the five human malaria parasite species in a single step polymerase chain reaction using single common primer pair.
26. Development of point-of-care, microfluidic device for detection of dengue virus, based on Nucleic acid aptamers.
27. Specific bionomics of characters of malaria vector(s) and their sibling species in Haryana, India.
28. Establishing a country-wide database of important malaria related parameters from dried blood spots collected.
29. Monitoring the therapeutic efficacy of chloroquine in vivax malaria at Fever Clinic, NIMR, New Delhi. ❑

Human Resource Development

8

8.1 Ph.D. Programme

NIMR provides facilities for pursuing Ph.D. degrees to the students. The Institute is affiliated to the Goa University, Goa; Kumaun University, Nainital; Maharshi Dayanand University, Rohtak; IGNOU, New Delhi; Amity University, Noida; University of Calcutta, West Bengal; HNB Garhwal Universtiy, Sri Nagar; University of Delhi, Jamia Millia Islamia, New Delhi; NIRMA University, Ahmedabad; Guru Jambheshwar University, Hisar; Dr APJ Abdul Kalam Technical University, Lucknow; Indraprastha University, New Delhi; Chaudhary Devi Lal University, Sirsa; Magadh University, Bodh-Gaya; and Delhi Technological University, New Delhi.

8.2 Post-Doctoral and Ph.D. Students

Following students are registered and completing their Ph.D./Post-Doctoral degree under the supervision of NIMR scientists: Mr Reva S Thakur, Mr Vikky Awasthi, Mr Bijendra Kumar, Mr Jagbir, Ms Kavita Kadian, Ms Ritu Rawal, Ms Nisha Sogan, Ms Alka Rani, Ms N Elamathi, Mr Rahul Pasupreddy, Ms Bhumika Kumar, Mr Ram Suresh Bharti, Mr Baljinder Kaur Sandhu, Mr Amit Kumar, Ms Shweta Chaudhary, Ms Supriya, Mr Kapil Vashisht, Ms Tanwee Das De, Ms Shelly Goomber, Ms Taruna Katyal Arora, Ms Madhvi Chahar, Mr Mritunjay Saxena, Ms Punita Sharma, Mr Yash Gupta, Ms Priya Gupta, Ms Sonam Vijay, and Mr Brajesh Prajapati.

Dr Pravin Kumar Atul, Scientist 'E', ICMR-NIMR was awarded the Degree of Ph.D. in the subject—Veterinary Pharmacology and Toxicology in the year 2017 from the Narendra Dev University of Agriculture and Technology, Faizabad, Uttar Pradesh, India.

8.3 M.Sc./B.Tech Projects/Dissertations

The Institute also provides facilities for fulfilment of Master's degree in Life Sciences/Biotechnology/Bioinformatics/Biomedical, *etc.*

Several M.Sc. students, namely Ms Drishti Verma, Mr Aditya Sharma, Mr Deepak Saini, Ms Shivani Sharma, Ms Meghna Chatterjee and Ms Hena Fatemah successfully completed their projects/dissertations under the supervision of NIMR scientists.

8.4 Seminars/Conferences/Workshops/Training Courses/Meetings organized

Dr Anup Anvikar

- Organized "Bi-regional training course of facilitators for the WHO external competency assessment of malaria microscopists" at NIMR, New Delhi from 5–8 December 2017.

Dr Alex Eapen

- Three health education/training/summer internship programmes were conducted and 12 students, six each from King Institute of Preventive Medicine & Research Centre, Guindy, Chennai and Department of Community Medicine, Government Medical College, Thiruvananthapuram, Kerala participated. The students were trained on blood smear preparation, staining techniques identification of malaria parasites and differential diagnostic methods of malaria. Lectures on epidemiology and control of malaria were delivered to them.
- Live exhibits and postal displays were arranged at the India International Science Festival, 2017 (Mega Science & Industry Expo) from 13-16 October 2017 at Anna University, Chennai, organized by Ministry of Science and Technology, Govt. of India.

Dr SK Ghosh

- Organized "Regional Entomology Workshop for Sustainable Vector Control and Management" in collaboration with WHO-SEARO from 29 January–3 February 2018.

Dr K Raghavendra

- Organized "10th FAO/WHO Joint Meeting on Pesticide Management (JMPM)", and visits to the GLP Laboratories at IARI and Sri Ram Institute, Delhi from 10–13 April 2017.
- Organized dissemination meeting of the results of "Implications of the Insecticide Resistance Project in Chhattisgarh", attended by Health Secretary, Chhattisgarh WHO, LSTM, LSTHM, NVBDCP at Raipur, Chhattisgarh on 5 June 2017.

- Organized WHO-GLP follow up meeting for "Quality Management Systems for Vector Control Advanced Workshop" for 34 participants from different countries (Malaysia:17, ICMR Institute:10, China: 1) and 3 consultants from WHO. Organized workshop, lectures, demonstrations, hands on training in laboratories and field at the National Institute of Malaria Research, New Delhi from 23–27 October 2017.

Dr Neena Valecha

- Organized "Research Needs for Malaria Eradication with Specific Reference to India and the SEARO Region" in collaboration with Medicines for Malaria Venture on 2 December 2017.

Research Papers Published
(January–December 2017)

9

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insecticide resistance in vectors of arboviruses, December 2016, Rio de Janeiro, Brazil. *Parasit Vectors* 2017; *10*(1): 391.

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Other Activities 10

10.1 Information Education and Communication (IEC)

For creating awareness about vector-borne diseases (VBDs) in school children, a lecture-cum-discussion session was organized at Sarvodaya Bal Vidhyalaya No. 2, Raj Nagar-II, New Delhi in July 2017. Information regarding vector-borne diseases and prevention, and means of personal protection methods were provided to them. Students were informed about sites/places of mosquito breeding. Being July the month of rainy season in north India, students were made aware about the preference of vector mosquitoes (malaria and dengue) that breeds in fresh water/rain water in discarded pots, tyres, drums, coconut shells, *etc.*

Awareness programme about vector-borne diseases (VBDs) in school children through a lecture-cum-discussion session.

Disseminating information about dengue and chikungunya to patients attending OPD of NIMR.

10.1.1 Documentation Cell

The following activities/services provided by the Documentation Cell:

- Various informations were updated regarding the Research Projects (Intramural and Extramural) such as their status, *i.e.* ongoing or completed and, extension period (if any) granted, collaboration detail for projects undertaken by the Institute. These were carried out on the basis of information provided by individual Principal Investigator (PI), Co-PI as well as minutes received from SAC meeting for the year 2017.
- Compiled and enlisted projects approved by the 37th SAC meeting.
- Allotted project IDs to new approved Intramural/Extramural Projects.
- Updated the record of students database of NIMR, including the number of students who registered/submitted and/or completed their Ph.D. degrees, and details of their University affiliation.
- Also updated the information and database about students applying for Trainings/Dissertations/Ph.D./Post-Doctoral studies, *etc.*

10.1.2 Photography and Videography

Several still photography as well as videography were carried out on various occasions/meetings/trainings/workshops/field surveys/functions held at NIMR and ICMR.

Still Photography

Following photography works were carried out during various meetings/workshops/functions/ scientific visits, *etc:*

- Month-wise photography of *Swachh Bharat Abhiyan*.
- Photography of different scientific works undertaken in various laboratories of NIMR.
- Induction training for VBD consultants held at NIMR during 20 March to 28 April 2017.
- India-Africa health sciences collaboration working group meeting held at INSA, New Delhi from 6 to 7 April 2017.
- Birth Anniversary of Dr BR Ambedkar held at ICMR on 18 April 2017.
- Yoga Divas at NIMR and ICMR on 21 June 2017.
- Lecture of Prof. MS Swaminathan held at ICMR on 3 July 2017.
- ICMR workshop on Writing effective policy briefs from 24–25 July 2017 at NIMR, New Delhi.
- Training programme on Web of science organised by NIMR Library on 28 July 2017.
- Independence Day Flag Hosting ceremony held at NIMR on 15 August 2017.
- Meeting to COMBAT dengue organized by NIMR on 16 August 2017.
- Celebration of Hindi *Pakhwada* at NIMR from 14–26 September 2017.
- RAC meeting at NIMR from 1–2 November 2017.
- Annual Day function held at NIMR on 20 November 2017.
- WHO Bi-regional training course of facilitators for the WHO external competency assessment of Malaria microscopists from 5–8 December 2017.
- SAC meeting held at NIMR on 21 December 2017.
- Group photographs of WHO visitors at NIMR.
- A consultative workshop on stakeholders on managing disabilities role held at *Pravasi Bhartiya Kendra,* Chanakya Puri, New Delhi from 14–15 December 2017.
- Indo-German workshop held at ICMR from 18–19 January 2018.
- Celebration of Sports Day at NIMR on 25 January 2018.
- Workshop on Protocol for *P. vivax* epidemiology study in India held at NIMR from 20–21 March 2018.
- International symposium on Health analytics and disease modeling held at NIMS, New Delhi from 5–9 March 2018.

Video Recording

Following video recordings along with editing and adding special effects were carried out on the occasions of various meetings /workshops/ functions and field work activities, *etc.* held at NIMR or other places:

1. National Disaster Programme.
2. Annual Day celebration of ICMR–National Institute of Malaria Research, New Delhi.
3. WHO recognized malaria RDT Lot Testing.
4. National Institute of Malaria Research—A journey through time.
5. Center of Excellence for Climate Change and Vector-borne Diseases.

Distribution of Video DVDs

Video DVDs on malaria, dengue, mosquitoes, bednets and other related subjects produced at NIMR were distributed to participants of different training programmes organized by NIMR, NVBDCP and supported by WHO. The DVDs were also sent to states and given to interested visitors.

10.1.3 *Swachh Bharat Abhiyan*

Swachh Bharat Abhiyan or *Swachh Bharat Mission* is a constitutional vision and execution of the Indian Union Government. Under this mission, primary objective was construction and development of toilets and arrangement of drinking water especially for people living in rural areas in the country. The programme was started as mass campaign on 2 October 2014 and decided to achieve its primary objectives as well as advancement of standards of cleanliness and hygiene in the country up to April 2019 through the mass motivation and participation of everybody.

The *Swachh Bharat Abhiyan* in NIMR was executed by organizing various activities regarding cleanliness and hygiene throughout the year in its campus as well as in the surrounding localities such as:

- Voluntary *Shramdaan* was organized by officers and staff jointly every month at identified spots in the campus.
- Activities were also performed to clean the surroundings of the Institute during the period.
- Communication was made with MCD and District health authorities to ensure cleanliness around the Institute.
- Lectures and demonstrations were organized time-to-time for the trainees in the Institute; attendants along with the patients came for dengue/malaria check up as well as in surrounding colonies such Raj Nagar and Bagdola village.
- Schools, colonies and even other institutions were approached for developing awareness about cleanliness, hygiene and its importance for our health in order to prevent and control vector-borne diseases.
- Printed materials such as poster, pamphlets on cleanliness and hygiene and prevention of vector borne diseases were distributed among the people in Gali No. 4, Raj Nagar, Part II, Palam, New Delhi and students of schools from Govt. Boys Sr. Sec. School, DDA Flats, East of Loni Road, Shahdara; RS Bal Vidyalaya, Jheel, Khurenza, Delhi.
- Besides above, regular monitoring of cleanliness and hygiene as routine activities in the research block, lawns and each corner of the campus were carried out to ensure the standards of cleanliness and hygiene.

10.1.4 International *Yoga Day*

'Yoga' is an invaluable gift to the world by our country India. International *Yoga Day* is celebrated with all enthusiasm throughout the world on 21 June 2017. Behind this wonderful concept seems to lying our Hon'ble Prime Minister Narendra Modi's intense feelings to bring recognition to the respect and trust to the Indian culture. After his request only celebrating on 21 June as a *Yoga Day* was declared in UN Assembly. Following this tradition, even this year 21 June is celebrated as '*Yoga Day*' in our Institute. On this occasion, different *Yoga Aasans* were conducted in the Plaza Hall of the Institute at 1600 to 1700 hrs; and all the scientists, officers and staff participated in the concerned programme with great zeal.

Public lecture on cleanliness

Director addressing on *Yoga Day*

Shramdaan activities by officers and staff of NIMR

Officers and staff doing *Yoga Aasans*

On this day, famous yoga trainer Shri Suraj Kumar and his assistant were invited. This programme was presided over by the Director of the Institute. She first of all drew attention towards the growing stress in every field of life in present times and then emphasized on the importance of *Yoga* in living life without stress and tension. And many beneficial *Yoga Aasans* and *Kriyas*/postures were conducted which was a unique experience in itself and everybody admired this whole heartedly and resolved to adopt in their lives.

10.2 Publication and Information Division

For dissemination of novel scientific information and new knowledge generated on malaria and other vector-borne diseases to the scientific as well as general community, the P&I Division of the NIMR continued its diverse activities in the field of publication and information by regularly publishing different periodicals, books, newsletters, *etc.*

Journal of Vector Borne Diseases

The *Journal of Vector Borne Diseases* is a peers reviewed, open access, quarterly published biomedical journal dedicated to the publication of original research contributions in the field of vector-borne diseases such as malaria, filaria, Japanese encephalitis, dengue, chikungunya, Crimean-Congo haemorrhagic fever (CCHF), leishmaniasis, trypanosomiasis, *etc.* with the aim of their control and prevention. This journal superceded the *Indian Journal of Malariology* in 2003 which was started long back in the year 1947. The journal is included by the major indexing agencies like Science Citation Index Expanded, MEDLINE/PubMed, Scopus, SCimago Journal Ranking, DOAJ, *etc.*

The issues (four issues a year) of the journal were published regularly and timely, during the reporting period. The full articles of the journal can be accessed online through Journal's website (*www.jvbd.org/*) as well as PubMed, DOAJ and other resources. At present, archives from the year 2003 are available on the website. The print version is available on subscription basis with discount to the scientific community and agencies. There is regular improvement in the standard and quality of journal as evidenced by the SCImago Journal Ranking, 2017.

Malaria Patrika

Malaria Patrika is a popular *Hindi* magazine launched in 1993 with four issues in a year. The Division publishes the issues of *Malaria Patrika*, for educating the local as well as scientific community on malaria and spreading awareness on vector-borne diseases and their control. The issues published in 2017 were primarily focused on different ways of malaria prevention, intervention strategies and problems of insecticide resistance in malaria vectors, *etc.*

Plasmodium Newsletter

Plasmodium Newsletter of the Institute, published biannually, highlighted the recent research investigations and advancements in the field of malaria, focusing primarily on the news related to malaria drugs, diagnostic tools and techniques, and reported major activities of the Institute and its Field Units during the reporting period.

Annual Reports

In addition to above, the Division published Annual Report of the Institute (NIMR) for the financial year 2017–18. The Annual Report included all the research activities of the Institute, publications of scientists and researchers, details of inter-institutional collaborations, intramural/extramural funded projects, and other activities of the Institute. The IDVC Annual Report 2017–18 was also compiled and published by the Division incorporating various activities carried out by the Field Units of NIMR.

10.3 Workshops/Seminars/Conferences/Meetings/Training courses attended

Ajeet Kumar

- Attended and invited as a lead speaker to deliver lecture at the plenary session of the National Conference of Young Researchers (*NCYR 2017*) entitled, "New Frontiers in Life Science and Environment" held at Goa University, Goa, India from 16–17 March 2017. Also delivered lecture on "Mosquitocidal activity of *Bacillus subtilis* sub sp. *spizizenii* against three major mosquito vectors prevalent in India".

Anup Anvikar

- Participated in the "VI International Conference on *Plasmodium vivax* Research", at Manaus, Brazil from 11 to 14 June 2017.
- Participated in the 2017 International Centers of Excellence for Malaria Research (ICEMR) Kickoff meeting and South Asia ICEMR pre-meeting at Gaithersburg, Maryland, USA from 18 to 23 August 2017.
- Participated in WHO/ITM training workshop "Dossier Assessment of Malaria Rapid Diagnostic" at Antwerp, Belgium from 4–6 September 2017.
- Participated in XI Central Review Mission of National Health Mission at Chhattisgarh from 4–12 November 2017.
- Participated in South-East Asia Regional Technical meeting on Progress with malaria elimination in the region at New Delhi from 27–28 November 2017.
- Participated in the 'High-level meeting on malaria elimination in the South-East Asia region', at New Delhi from 27–29 November 2017.
- Participated in Ministerial Round table on Accelerating elimination of malaria in the South-East Asia region at New Delhi on 29 November 2017.
- Participated in the "1st meeting of the VIII Working Group on Health for Sharing Information & Cooperation in Pandemic Management" between India and Mekong Ganga Countries', at New Delhi, India from 29–30 November 2017.
- Participated in the third meeting of the Strategic Advisory Group on malaria eradication (SAGme), at New Delhi, India from 30 November–1 December 2017.
- Participated in the review meeting on "Comprehensive case management of malaria", in Hotel Imperial at New Delhi on 1 December 2017.
- Organised the meeting 'Research Needs for Malaria Eradication with specific reference to India and the SEARO Region', at New Delhi, India on 2 December 2017.
- Delivered a talk at the "Sub-National training of trainers on Malaria elimination in India" at Gurgaon from 4–8 December 2017.
- Participated in Media training workshop at Mumbai, Maharashtra on 14 December 2017.
- Participated in the Stakeholder meeting on 'Controlled human infection model' studies at Mumbai, Maharashtra from 7– 8 January 2018.

Ashwani Kumar

- Attended State Taskforce meeting on Vector-borne Diseases Control in the Secretariat Goa on 25 May 2017.
- Attended XII Joint Conference of ISMOCD and IAE and presented a plenary lecture on 'An India without Malaria' at AFMC Pune from 1–3 September 2017.
- Attended 7th International Congress of Society for Vector Ecology, at Palma of Mallorca, Spain from 1–7 October 2017.

Eapen Alex

- EMBO Global Exchange Lecture Course on Malaria Genomics and Public Health, at Madurai, India from 29 January to 11 February 2017.
- 13th Conference on Vectors and Vector-borne Diseases at Chennai, India from 27 February to 1 March 2017.
- National Conference on Drug Development and Research in Mosquito-borne Diseases organized by Ahalia School of Pharmacy, Palakkad, Kerala on 22 September 2017.
- Short course on 'Environmental Health' organized by Harvard T.H. Chan School of Public Health and Indian Institute of Public Health at Gandhinagar, Gujarat from 25–29 September 2017.
- Attended and presented a Research/Scientific paper on 'Inaugural meeting of the Malaria Eradication Group (MEG 2.0)' at Santa Cruz, California, USA from 24–27 October 2017.
- Strategic Advisory Group on Malaria Eradication (SAGME) Research Needs for Malaria Eradication with specific reference to India and the SEARO region at New Delhi, India on 2 December 2017.
- Attended and presented a Research/Scientific paper in the annual 'Joint International Tropical Medicine Meeting (JITMM)' at Bangkok, Thailand from 6–8 December 2017.

Joleen Almeida

- Attended National Conference of Young Researchers 2017 on "New Frontiers in Life Sciences and Environment" held at Goa University, Goa from 16–17 March 2017.

KC Pandey

- Attended as Keynote speaker and session chair at 14th International Congress of Parasitology (ICOPA-2018) in Daegu, South Korea from 19–24 August 2018.
- Attended as Keynote speaker at Indo-US Colloquium on Recent Development in Interdisciplinary Research organised by Delhi University on 2 July 2018.
- Attended and invited as Guest speaker at 11th Symposium on Frontiers in Biomedical Research: Challenges in Human Health, Diagnosis, Prevention and Care organised by Delhi University from 19–21 February 2018.
- Attended and presented a talk on XIII Molecular Parasitology meeting at Marine Biological Laboratory, Woods Hole, MA, USA in the month of September 2017.

K Raghavendra

- Attended Technical Committee (GoI) meeting for "Drafting specifications of Bacterial and Chemical Pesticide and Interventions—*Bti*-5% WP" at MoH & FW, New Delhi on 4 May 2017.
- Attended ICMR Review Group meeting for Evaluation of Public Health Pesticides as Expert, at ICMR, New Delhi on 12 May 2017.
- Attended the NVBDCP Expert Group meeting on Adulticide and larvicide at NVBDCP, Delhi on 20 July 2017.
- Attended "Discussion meeting on Introduction of LLINS in the open market" under the chairmanship of DG, ICMR, and presented case studies on commercialization of LLINs in African countries at ICMR, New Delhi on 26 July 2017.
- Attended the ICMR Review Group meeting for Evaluation of Public Health Pesticides as Expert member at ICMR, New Delhi on 3 November 2017.
- Attended 21st Mandate Group meeting on Use of DDT, under the chairmanship of Secretary Health, MoH & FW, GoI, New Delhi on 13 December 2017.
- Attended "WHO Consultation on Development of test protocols for inter-laboratory validation of discriminatory concentrations of insecticides for monitoring insecticide resistance", held at Geneva, Switzerland from 13–14 February 2017.
- Attended an Open meeting "WHO Consultation on revision of the guidelines on laboratory and field-testing of long-lasting insecticidal nets and insecticides for indoor residual spraying", at Geneva, Switzerland from 27–28 February 2017.
- Attended Strategic meeting of "The Worldwide Insecticide resistance Network (WIN)", to Prepare framework on way forward for resistance management in Arbovirus vector at Rio de Janerio, Brazil from 4–5 May 2017.
- Attended WHO Coordinating office meeting to Apprise WHO SEARO, NVBDCP and WR office on the outcomes of the "Implications of the Insecticide Resistance Project", held at New Delhi on 9 June 2017.
- Attended "International Cross-Border Meeting on Malaria Elimination" in SEAR countries and presented Perspectives of vector control in these countries at New Delhi from 24–25 November 2017.
- Attended WHO Coordinating office meeting on development of "Framework for entomological surveillance for kala-azar elimination in India", held at New Delhi from 27–28 November 2017.

Minisha H Pereira

Attended the National Conference of Young Researchers 2017 on "New Frontiers in Life Sciences and Environment" held at Goa University, Goa from 16–17 March 2017 and received Certificate and Trophy for winning III position at the Poster Competition, organized by Faculty of Life Sciences and Environment, Goa University, Goa.

Neena Valecha

- Attended Technical meeting of experts for Antibody-based diagnostics in malaria under the chairmanship of DGHS at Nirman Bhawan, New Delhi on 5 April 2017.
- Attended FAO/WHO Joint meeting on Pesticide Management at Park Hotel, New Delhi, India from 10–13 April 2017.

- Attended World Malaria Day 2017 at Le Meridian, Janpath, New Delhi on 25 April 2017.
- Attended the group discussion on Generating data on safety of antimalarials at NIRTH, Mumbai on 25 May 2017.
- Attended 11th Meeting of the Executive Council at ICMR HQs, New Delhi on 30 May 2017.
- Attended Data Safety Monitoring Board (DSMB) meeting at ICMR HQs, New Delhi on 30 May 2017.
- Attended GBD India–VBNTD Expert Group meeting at ICMR HQs, New Delhi on 31 May 2017.
- Attended Ethics Committee meeting of BL Kapur Memorial Hospital at BLK Hospital, New Delhi on 23 May and 21 June 2016.
- Attended meeting of Directors and Division Heads of ICMR Institutes at ICMR HQs, New Delhi on 18 July 2017.
- Attended ICMR Workshop on "Writing effective policy briefs" at NIMR, Dwarka, New Delhi on 24 July 2017.
- Attended meeting on Long-lasting Insecticidal Nets (LLINs) at ICMR HQs, New Delhi on 26 July 2017.
- Attended group discussion on National Family Health Survey 2015–16 (NFHS-4) at ICMR HQs, New Delhi on 31 July 2017.
- Attended Group discussion on Diseases Burden Study at NVBDCP, New Delhi on 30 August 2017.
- Attended Technical review meeting of CRS ongoing project by ICGEB at ICGEB, New Delhi on 7 September 2017.
- Attended Data Safety Monitoring Board–India meeting to Review the revised Report and the results from other countries at ICMR HQs, New Delhi on 22 September 2017.
- Attended NIN centenary year celebrations at NIN, Hyderabad on 26 September 2017.
- Attended ICMR Annual Awards Presentation Ceremony at National Academy of Medical Sciences, New Delhi on 11 October 2017.
- Attended Ethics Committee meeting of BL Kapur Memorial Hospital at BLK Hospital, New Delhi on 23 October 2017.
- Attended meeting with Principal Health Secretary, Punjab and Director Health Services, Punjab at Chandigarh on 27 October 2017.
- Attended Expert Group Review meeting of Public Health Pesticides at ICMR HQs, New Delhi on 3 November 2017.
- Attended Initial Screening Committee (ISC) meeting on project "Development of a Point-of-care visual screening test for identification of Glucose-6-Phosphate Dehydrogenise (G6PD) deficiency in malaria endemic population" at TDB Office, Vishwakarma Bhawan, Shaheed Jeet Singh Marg, New Delhi on 7 November 2017.
- Attended Review meeting on "Comprehensive case management of Malaria" at Hotel Imperial, New Delhi on 1 December 2017.
- Attended and Chaired "7th meeting of Biological and Clinical Evaluation of Medical Devices and Immuno-Biological Diagnostic Kits Sectional Committee, MHD 19" at Bureau of Indian Standards, Manak Bhawan, New Delhi on 15 December 2017.
- Attended Informal expert consultation for LLINs at ICMR HQs, New Delhi on 16 December 2017.
- Attended Ethics Committee meeting of BL Kapur Memorial Hospital at BLK Hospital New Delhi on 19 December 2017.
- Attended meeting with Addl. DG for NFHS-4 and NFHS-5 studies at ICMR HQs, New Delhi on 3 January 2018.
- Attended meeting with Addl. DG for NFHS-4 DBS sample transportation from different laboratories by Zoom on 12 January 2018.
- Attended NLEM-2015–Antifungal Medicine Classification and Pricing thereof–Implementation of order dated 17 July 2017 of High Court of Delhi at the Department of Pharmacology, AIIMS, New Delhi on 25 January 2018.
- Attended 11th meeting of Medical Equipment and Hospital Planning Department, MHDC at the Bureau of Indian Standards, New Delhi on 30 January 2018.
- Attended meeting on Material Transfer in Clinical Trials at ICMR HQs, New Delhi on 8 February 2018.

- Attended Clinical Trial of Biocurcumax as adjunct therapy for malaria at AIIMS, New Delhi on 8 February 2018.
- Attended Media Policy-Internal Committee meeting at NIMS, New Delhi on 12 February 2018 .
- Attended meeting of National Malaria Elimination Taskforce under the chairmanship of Secretary, Health and Family Welfare at Nirman Bhawan, New Delhi on 21 February 2018.
- Attended workshop on Strategies on Vector Control at India Habitat Centre, New Delhi on 28 February 2018.
- Attended meeting with NIE Director, OIC and Staff of Chennai Field Unit at NIMR Field Unit, Chennai on 5 March 2018.
- Attended Ethics Committee meeting of BL Kapur Memorial Hospital at BLK Hospital, New Delhi on 6 March 2018.
- Attended Technical Advisory Committee (TAC) on VBDs-cum-TWG under the chairmanship of DGHS at Nirman Bhawan, New Delhi on 14 March 2018.
- Attended meeting with Director NIN for collaboration in conducting vitamin B-12 deficiency mapping study in the state of Assam at NIN, Hyderabad on 23 March 2018.
- Attended Symposium on "Biomedical Communication and Menace of Predatory Journals: Lesson for Scientists" at ICMR HQs, New Delhi on 27 March 2018.
- Attended and presented on "Emerging hurdels in malaria elimination: Expecting the unexpected" at Launch of National Strategic Plan for Malaria Elimination in India (2017–22) in India at Le Méridien, New Delhi on 12 July 2017.
- Attended and presented on "Malaria" in 24th Scientific Advisory Group (SAG) meeting of ECD at ICMR HQs, New Delhi on 29 July 2017.
- Attended and presented on "CCMP: Impact and lessions learnt" meeting with Health Secretary Odhisa on 7 April 2017.
- Attended Technical Expert Group on Drug Efficacy and Response (TEG DER) WHO HQs, Geneva, Switzerland from 1–2 June 2017.
- Attended International Centers of Excellence for Malaria Research (ICEMR), Kickoff meeting and leadership team of the South Asia ICEMR pre-meeting at Gaithersburg, Maryland, USA from 18–23 August 2017.
- Attended Malaria Policy Advisory Committee (MPAC), World Health Organization at Geneva, Switzerland from 17–19 October 2017.
- Attended South-East Asia Regional technical meeting on Progress with Malaria Elimination in the Region at New Delhi from 27–28 November 2017.
- Attended Ministerial Round table on Accelerating Elimination of Malaria in the South-East Asia Region at New Delhi on 29 November 2017.
- Attended World Malaria Report 2017 Launch at New Delhi on 29 November 2017.
- Attended Strategic Advisory Group on Malaria Eradication (SAGme) Research Needs for Malaria Elimination with specific reference to India and the SEARO region at Hotel Imperial, New Delhi on 2 December 2017.
- Attended Technical Expert Group (TEG) on Malaria Chemotherapy: Technical Consultation meeting on updates of the III edition of the Guidelines for the treatment of malaria" at WHO HQs, Geneva, Switzerland from 11–13 December 2017.

Yadav CP

- Attended training on 'Introduction to EpiTM 7' organized by the National Institute of Virology (NIV), Pune from 16–19 January 2017.
- Attended workshop on 'Economic evaluation: introduction, concept and application' organised by the National Institute of Medical Statistics (NIMS), New Delhi from 3–4 March 2017.
- Attended training on 'Advance Techniques in Surveillance and Control of Vector-borne Diseases' organised by the National Institute of Malaria Research (NIMR), New Delhi from 6–31 March 2017.

10. 4 Awards/Honours/Nominations

- Awarded 'National Academy of Vector-borne Diseases (NAVBD) for significant contributions on Environmental Aspects of Vector-Borne Diseases' at the 13th Conference on Vectors and Vector-borne Diseases at Chennai, India from 27 February to 1 March 2017.

- Awarded 'Travel award' by the Joint International Tropical Medicine Meeting (JITMM) to attend the annual meeting of JITMM at Bangkok, Thailand from 6–8 December 2017.
- Dr Ajit Kumar Mohanty, Scientist 'B' of the Institute was awarded 'Best Oral Presentation Award' during XII Joint Annual Conference of the Indian Society for Malaria and other Communicable Diseases (ISMOCD) and the Indian Association of Epidemiologists held at Armed Forces Medical College (AFMC), Pune, India from 1–3 September 2017.

Dr Ajit Kumar Mohanty receiving award at Armed Forces Medical College (AFMC), Pune, India

Awards received by Dr M.K. Das, Scientist 'E'

Dr MOT Iyengar Memorial Award 2015

Awarded by Smt. Anupriya Patel, Hon'ble Minister of State, MoHFW, Govt. of India and Dr Soumya Swaminathan, Secretary DHR, MoHFW, Govt. of India & DG, ICMR, New Delhi in 2017

Mahatma Gandhi Excellence Award 2017

By Sh. Shivraj Vishwanth Patil, former Indian Politician, Legislator, Governor, Administrator, Spokesperson, Writer and Author

Bharat Gaurav Award 2017

By Dr Bhisma Narain Singh, Ex-Governor of Assam and Tamil Nadu

Eminent Scientist of the year Award 2017

By NESA Barkatullah University, Bhopal

10.5 Vigilance cases, Audit objections and RTI matters during the year 2017–18

Vigilance cases

- No. of vigilance cases disposed off = Nil.
- Pending and nature of such cases = Temporary Status Worker is pending, FIR No. 694/2017 dated 8 December 2017 in criminal case.

Audit objections

- No. of replies of audit objections = No audit took place during the financial year 2017–18.
- No. of pending audit paras = Since, no audit took place during the year 2017–18, no paras are pending with reference to the financial year 2017–18.

RTI matters

- No. of RTIs disposed off = 64
- No. of RTIs pending = 0 ❑

संस्थान में राजभाषा संबंधी गतिविधियां

11

संस्थान में वर्ष 2017-18 के दौरान राजभाषा अधिनियम के अनुपालन के उद्देश्य से राजभाषा हिन्दी के प्रगामी प्रयोग को बढ़ावा देने हेतु कई कदम उठाए गए जिसके अंतर्गत तिमाही बैठकों का नियमित रूप से आयोजन किए जाने के साथ ही, *मलेरिया पत्रिका* (हिन्दी) का प्रकाशन किया गया एवं राजभाषा विभाग द्वारा लागू प्रोत्साहन योजनाएं कार्यान्वित की गईं जिनके अंतर्गत निदेशक महोदया द्वारा लागू की गई अधिक शब्द सीमा की प्रोत्साहन योजनाएं जारी रही एवं संस्थान के प्रवेश-स्थल पर एक नवीन हिन्दी-अंग्रेजी शब्द एवं सुविचार लिखने की गतिविधि इस वर्ष भी जारी रही जो कि राजभाषा के प्रति रूचि जागृत करने का प्रयास था।

इसके साथ ही, सरकारी कामकाज में हिन्दी के प्रगामी प्रयोग को बढ़ावा देने के उद्देश्य से प्रतिवर्ष की भाँति इस वर्ष भी हिन्दी पखवाड़ा दिनांक 14 से 25 सितम्बर 2017 तक पूर्ण उत्साह के साथ मनाया गया जिसमें एक ओर दिनांक 15 सितम्बर 2017 को पूर्वान्ह 10:30 बजे एवं अपरान्ह 3:00 बजे दो कार्यशालाओं का आयोजन किया गया। प्रथम कार्यशाला संस्थान के तकनीकी वर्ग के कर्मचारियों एवं अधिकारियों के लिए आयोजित की गई थी, जिसमें व्याख्याता के रुप में श्री प्रेम सिंह, सेवा-निवृत्त संयुक्त निदेशक, विज्ञान एवं प्रौद्योगिक मंत्रालय, नई दिल्ली को आमंत्रित किया गया था और कार्यशाला का द्वितीय सत्र प्रशासनिक वर्ग के अधिकारियों एवं कर्मचारियों के लिए आयोजित किया गया, जिसमें श्री अशोक सचदेवा, पूर्व संयुक्त निदेशक, इस्पात मंत्रालय, नई दिल्ली को आमंत्रित किया गया था। कार्यशाला का उद्घाटन संस्थान की निदेशक डॉ. नीना वलेचा एवं संचालन श्री सुनील कुमार गुप्ता, प्रशासनिक अधिकारी द्वारा किया गया।

वहीं अन्य महत्वपूर्ण गतिविधियों, पुरस्कार वितरण समारोह के अतिरिक्त निबंध प्रतियोगिता, टिप्पण-प्रारूपण प्रतियोगिता एवं कर्मचारियों और अधिकारियों के लिए पृथक-पृथक वाद-विवाद प्रतियोगिताओं का आयोजन किया गया।

हिन्दी पखवाड़े के दौरान उल्लेखित गतिविधियों के अलावा दिनांक 25 सितम्बर 2017 को एक और गतिविधि पुरस्कार वितरण समारोह एवं काव्य (हास्य) पाठ का आयोजन किया गया, जिसका संचालन डॉ. वंदना शर्मा, सहायक निदेशक (राजभाषा) द्वारा किया गया। संबंधित समारोह में मुख्य अतिथि के रूप में डॉ. लल्लन वर्मा, सहायक मुख्य रजिस्ट्रार/ओआईवीएस, ब्युरो ऑफ हैल्थ इंटेलिजैंस, साउथ डीएमसी एवं श्री सतेन्द्र सिंह, संयुक्त निदेशक, संसदीय राजभाषा समिति को सम्मानित अतिथि के रुप में आमंत्रित किया गया। इसके साथ ही संबंधित समारोह को रोचक बनाने के उद्देश्य से राष्ट्रीय-स्तर के हास्य कवि श्री अनिल अग्रवंशी को आमंत्रित किया गया था।

इस समारोह का शुभारंभ मुख्य अतिथि, सम्मानित अतिथि, कवि एवं संस्थान के प्रभारी निदेशक महोदय को पुष्प भेंट कर किया गया। स्वागत समारोह के पश्चात प्रभारी निदेशक डॉ. रमेश चन्द्र धीमान ने अपने संबोधन में सर्वप्रथम हिन्दी पखवाड़े के दौरान होने वाली प्रतियोगिताओं के विजेताओं को बधाई दी और कहा कि राजभाषा की प्रेरणा एवं प्रोत्साहन नीति के अंतर्गत प्रत्येक वर्ष हिन्दी दिवस का आयोजन किया जाता है, जिसका उद्देश्य होता है राजभाषा हिन्दी में कार्य करने के लिए प्रोत्साहित करना और इस आयोजन की सार्थकता तभी है जब हम सभी अपना सरकारी कामकाज अधिक से अधिक हिन्दी में करें।

निदेशक प्रभारी के संबोधन के पश्चात् पुरस्कारों का वितरण किया गया। तत्पश्चात् सम्मानित अतिथि श्री सतेन्द्र सिंह ने सभा को संबोधित करते हुए हिन्दी भाषा की विश्व में उपयोगिता का अनेक उदाहरणों एवं प्रमाणों से हिन्दी भाषा की गरिमा का गुणगान करके अत्यन्त लाभप्रद जानकारी दी। तत्पश्चात आमंत्रित हास्य कवि श्री अनिल अग्रवंशी ने विभिन्न समसामयिक विषयों पर अपनी हास्य एवं व्यंग्यपूर्ण कविताओं से आनन्द विभोर कर दिया।

इसके पश्चात् कार्यक्रम के अंत में मुख्य अतिथि डॉ. लल्लन वर्मा ने सभा को संबोधित किया और अपने संबोधन में सर्वप्रथम पुरस्कार विजेताओं को बधाई दी और संस्थान में राजभाषा के प्रति अत्यंत प्रेम एवं उत्साह पर अपना हर्ष जाहिर किया। इसके साथ ही उन्होंने आने वाले वर्षों में संस्थान में राजभाषा हिन्दी के शत-प्रतिशत कार्यान्वयन की आशा जताई।

अन्ततः कार्यक्रम का विधिवत समापन करने हेतु संस्थान के वैज्ञानिक डॉ. प्रवीण कुमार अतुल, वैज्ञानिक 'ई' ने हिन्दी पखवाड़े के दौरान आयोजित गतिविधियों का सफलतापूर्वक संचालन करने हेतु सभी संचालकों को धन्यवाद करने के साथ ही समग्र कार्यक्रम के आयोजन में संस्थान के हिन्दी अनुभाग के योगदान की सराहना करते हुए हार्दिक धन्यवाद ज्ञापित किया।

यहां यह भी बताना उल्लेखनीय होगा कि संस्थान ही नहीं वरन् संस्थान की क्षेत्रीय ईकाइयों में भी राजभाषा कार्यान्वयन के प्रति जागृत करने के उद्देश्य से हिन्दी दिवस के उपलक्ष में विभिन्न प्रतियोगिताओं का आयोजन किया गया, जिसमें नडियाड, गुवाहाटी, बंगलुरू, जबलपुर एवं गोवा मुख्य हैं। इस प्रकार यह कहने में कोई अतिशयोक्ति नहीं होगी कि वर्ष 2017-18 के दौरान संस्थान एवं क्षेत्रीय ईकाइयों में राजभाषा के प्रयोग को बढ़ावा देने हेतु सृजनात्मक, रचनात्मक एवं व्यावहारिक कार्य एवं कार्यक्रमों के माध्यम से हर संभव प्रयास किया गया। संस्थान एक विज्ञानीय अनुसंधान संस्थान होने के साथ ही राजभाषा नियम अधिनियमों का अनुपालन करते हुए राजभाषा के प्रयोग को बढ़ावा देने में प्रयासरत है और इसका साक्षात् प्रमाण राजभाषा संबंधी गतिविधियों का उल्लेखित सारांश है जो इसके बहुमुखी विकास का प्रतिरूप है। ❑

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12

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12.6 Animal Ethics Committee

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Dr BN Nagpal (On deputation to WHO)
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Dr OP Singh

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