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From the Editors' Desk

Dear Colleagues,

We are immensely pleased to present you the Volume 3, Issue 1 of *Journal of Medical Arthropodology & Public Health*, published by the SOCIETY OF MEDICAL ARTHROPODOLOGY (www.soma16.org), dedicated to the spirit of 'serving science and society', now bejewelled with the ISSN: 2583-6455 (Online).

Journal of Medical Arthropodology & Public Health aims to spark the principle of the inextricable triad of 'invention, innovation and discovery', and promote interdisciplinary collaboration by providing a forum for research across all scientific disciplines that tackles important, emerging topics under the umbrella of medical arthropodology, particularly vector-borne diseases, and many of the world's grand challenges. The torrent of *Journal of Medical Arthropodology & Public Health – a vade mecum* - is continuing to cascade its way forward to bring you once again results of the most thoughtful scientific works on the Indian soil, just as in the past, and Volume 3, No. 1 (June 1, 2023) is right there in your hands, on time. It has been our efforts to bring diversity in our research papers drawn from various disciplines of medical arthropodology. Therefore, you find in the current issue a variety of exciting research papers. These papers however represent only a fraction of the vast and unexplored spectrum of disciplines within the unfathomable folds of the integrated science of medical arthropodology and public health which are to come to surface gradually and periodically in the future issues! Thus, we are endeavouring hard to publish on the pages of the *Journal of Medical Arthropodology & Public Health* – a broad-scope, open access-cum-print journal papers on both basic and applied research that has a positive impact on translation

of sophisticated data-based scientific studies into usable products by the end-user – the research papers that truly serve the science and society. We will accomplish this task through consilience. Our aim at the *Journal of Medical Arthropodology & Public Health* is to maximize the global visibility and impact of your published articles.

The Journal of *Medical Arthropodology & Public Health* is for all those men and women who are interested in scientific discovery, and in its industrial, commercial, and social consequences. It will explore, interpret and report the results of human endeavour set in the context of science and society. Through the *Journal of Medical Arthropodology & Public Health* scientists will be motivated to think beyond their discipline and believe that collaborative science and interdisciplinary ideas can advance national policies related to the control of vector-borne diseases, on one hand, and bring other biomedical concerns under thorough scanning and surveillance, on the other. This transformation is essential to inspire new thinking, besides exploring new horizons in the biology of medically important arthropods and paving pathways to consolidate new ideas toward their control through a process ensuring way to new and revolutionary ideas!

Soliciting your continued support and patronage in our comprehensive evolution both as the journal and the authors, we remain as heretofore,

Yours cordially,

Prof. Dr B.K. Tyagi & Dr Rina Tilak

June 1, 2023 Chief Editor Executive Editor

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INTRODUCTION

With the discovery of Sir Dr Ronald Ross about mosquito being the obligate invertebrate host for mediating transmission of the human malaria parasite[1], the quest for a term or a word defining the whole process had also

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begun, although this was certainly not for the first time the needle of suspicion of carrying a disease pathogen had been directed toward the mosquito; first being the hypothesis about the human lymphatic filariasis parasite, *Wuchereria bancrofti*, needing a mosquito, *Culex pipiens*, for nursing a part of its life cycle, though not completely correctly defined[2] and the second was the demonstration, although without a parasitological evidence, the Cuban epidemiologist Carlos Juan Finlay suggested in 1881 that yellow fever was caused by an infectious agent transmitted by a mosquito now known as *Aedes aegypti*, but soon later, in his investigation of Finlay's theory, the U.S. Army pathologist and bacteriologist Major Walter Reed demonstrated in 1900 the transmission of yellow fever from one human to another through the bite of *Ae. aegypti*. None of these epochal discoverers used the term 'vector' to express the role played by the mosquito!

THE PROBLEM

Since the late 19th century four countries notably were in the forefront of advancing gradually and solidly the emerging discipline of mosquito-borne diseases, viz., Britain, France, Italy and United States of America, although Russia (and later U.S.S.R.) was emerging as a strong competitor. By the advent of 20th century London School of Tropical Medicine & Hygiene and Liverpool School of

Table 1. Important arthropod vectors and chronological details of incrimination by disease pathogens they transmit in humans and animals

Human/ animal disease	Pathogen(s) involved	Vector(s) involved	Year of Vector incrimination	Country of Discovery	Authority
Filariasis	*Wuchereria* and *Brugia* spp.	Mosquitoes	1886	Taiwan, China	Manson
Texas cattle fever	*Babesia gemina*	Tick	1891	N. America	Smith & Killbourne
Nagana disease in cattle	*Trypanosoma* spp.	Tsetse flies	1895	Africa	Bruce
Malaria	*Plasmodium* spp.	Anopheline mosquitoes	1897	India	Ross
Avian malaria	*Plasmodium* ?	Mosquitoes	1898	India, UK	Ross

Human/ animal disease	Pathogen(s) involved	Vector(s) involved	Year of Vector incrimination	Country of Discovery	Authority
Plague	Bacterium (*Yersinia pestis*)	Fleas	1898	Karachi, India (Now in Pakistan)	Simond
Human malaria cycle	*Plasmodium* sp.	Anopheline mosquito (*An. sacharovi* and *An. stephensi*)	1898	Italy	Grassi, Bignami and Bastianelli
Yellow fever	Togavirus	Mosquitoes (*Aedes aegypti*)	1990	Cuba	Finlay/Reed, Carroll, Lazear and Agramonte
American Sleeping sickness	*Trypanosoma* spp.	Tritomine bugs	1895 1908	S. America S. America	Bruce Chagas
African sleeping sickness	*Trypanosoma* spp.	Tsetse flies	1903	Africa	Bruce & Nabarrow
Dengue	Flavivirus	Mosquitoes	1906	Africa	Graham
Fowl spirochaetes	Spirochaetes (*Borrelica conserina*)	Tick (*Argus persicus*)	1903		Marchoux & Salimbeni
Relapsing fever	*Borrelia recurrentis*	Lice	1907	India	Mackie
Onchocerciasis	*Onchocerca* spp.	Blackflies	1926	Sierra Leone	Blacklock
Encephalitides	Virus / Bacteria	Mosquitoes Ticks	1930-1990	Various countries	Various scientists
Zika	Zika Virus	*Aedes africanus, Ae. aegypti* and *Ae. albopictus*	1948	Africa	Dick (1952)
Chikungunya	Chikungunya Virus	*Aedes aegypti* and *Aedes albopictus*	1952	Africa	Robinson

Tropical Medicine & Hygiene had already introduced academic courses on insects of medical importance which substantially influenced countries like France. The term medical entomology (entomologie médicale) was used for the first time in France around 1910[3], to include, in addition to mosquitoes, all those insects and non-insectan arthropods as well which mediated transmission of pathogens. It is worth noting that within this very specialized teaching programme, not only had the word entomology, and *a fortiori* the medical entomology, still not occurred, but that not much time was given to disease pathogen carrying insects! What is more, the use of the term 'vector' was still evasive in academics and research programmes.

WHAT IS A VECTOR IN BIOMEDICINE?

Etymologically the word 'vector'(Noun- **vec-ter**; Adj.: **vectorial**; Verb: **vectorize**[5], coined in the 18th century by William Rowan Hamilton (4th August 1805 – 2nd September 1865) as part of a quaternion which is a sum q = s + v of a Real number s (also called scalar) and a 3-dimensional vector, and as defined in The New Pocket Oxford Dictionary, 9th edition[6], is a Latin word '*vehō*', which (i) originally applied in mathematics and physics, is defined as a quantity having direction as well as magnitude, specifically determining the position of one point in space relative to another. It is typically represented by an arrow whose direction is the same as that of the quantity and whose length is proportional to the quantity's magnitude. (ii) Also, much later in biology, the word came to be used as the carrier or transporter of a disease or infection. The expression 'vector' in medical arthropodology has apparently been borrowed from that used in mathematics and physics with a rather arbitrary argumentation or validation, possibly only to justify 'mobility and transportation' of the pathogen in the mosquito and other arthropod carriers. One of the major considerations in reaching out to a useful definition is the phenomenon of 'vector shifts' between insect- and tick-borne transmission occurring with some frequency, and probably facilitated by similar feeding mode and internal environments (from the evolutionary perspective of the pathogens or parasites). Some scientists, therefore, have argued if the term 'vector', with its current definition, is really justifiable in the light of current knowledge, particularly zoonosis, i.e., canonical case of one pathogen, two (or more) host species system.[4] Many important and rapidly emerging pathogens of humans, leave aside livestock and wildlife, are 'vector-borne' (Table 1). However, the term 'vector' has been applied to diverse agents in a broad range of epidemiological systems, by which the

trait of the expression 'vector' pronouncedly transgresses from the bibliographic definition and adds more to the confusion of the usage.

OUR ARGUMENT

The biological vector is a living organism unlike that of mathematics or physics. In biology an organism is vector not by its own choice but commissioned by the parasite's inexorable necessity to complete a part of the life-cycle for its very survival. Thus, the parasite-vector relationship in biology is more of an evolutionary and sustenance continuum rather than mere direction and magnitude. On scrutiny of some common definitions and identification of strengths and weaknesses of each definition, we are convinced that there are the functional differences in the expression of 'vector' amongst mathematical, physical and biological sciences and between vectors and other hosts from a range of ecological, evolutionary and public health perspectives. The biological expression in the science of medical arthropodology alludes toward the epidemiological and evolutionary processes that are not apparent in other disciplines under reference.

The fact that, in the broader sense, the conventional term 'vector' is not limited to arthropods only and encompasses within its definition certain rodents that are also considered vectors. From a medical and veterinary perspective, some scientists have attempted to explain that a combination of the 'haematophagous arthropod' and 'mobility' definitions since it offers important insights into contact structure and control, and emphasizes the opportunities for pathogen shifts among taxonomically similar species with similar feeding modes and internal environments.[4] Additionally, from a population dynamics and evolutionary perspective, they have suggested that a combination of the 'micropredator' and 'sequential' definition is most appropriate because it captures the key aspects of transmission biology and fitness consequences for the pathogen and vector itself. The diverse nature of the value of a definition of the term 'vector' in medical arthropodology complicates further due to the fact that the same 'vector species, in different temporal and spatial conditions or under differential climatic vicissitudes, may epidemiologically behave differently.[4]

From the foregoing information, it is inevitably absolutely and essentially certain that the term 'vector' has multiple expressions, and the biological entity (species)-associated vectorial expression particularly stands apart from that of

mathematical or physical science. Thus, the definition(s) or expression(s) of the term 'vector' in vogue are considered inappropriate for medical arthropodology, and. alternatively, considering the disease epidemiological systems of both vector and pathogen, it is strongly advocated to bring in place a new definition of the vector and/or replace appropriately the term with another meaningful word to cover all aspects of host-pathogen-vector biology.

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Commentary

WHERE TO LOOK FOR RESERVOIR(S) OF KFD VIRUS, AND WHAT TO LOOK FOR?

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While looking for a suitable location to intensely start investigations on the zoonotic origin of KFD, it came to my mind Agumbe region in Western Ghats which is full of tree caves, abandoned wells, and old abandoned buildings built by the British and inhabited by bats etc. Elsevier had recently published a brilliant paper "*on how mammalian species richness is associated with Kyasanur Forest disease outbreak risk in deforested landscapes in*

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the Western Ghats". It is a forest disease, and every single monkey death or human case had taken place in the forest environment, particularly the interface.

Western Ghats are formed by a chain of mountains, with a span of around 30-50 km into the West Coast of India. These mountains stretch through the states of Kerala, Tamil Nadu, Karnataka, Goa, Maharashtra and Gujarat, spanning a length around 1,600 km, with an area of around 140,000 km^2. The mountain range is discontinued only at Palghat Pass by a 30 km stretch. Various scientific studies suggest that the Western Ghats were formed due to the existence of a long fault parallel to the coast, extending from the Gulf of Cambay to Cape Comorin. It owes its origin to the faulted edge of a raised plateau. Western Ghats are globally recognized as a region of immense importance in terms of exceptionally high biological diversity, endemism, high geological, cultural and aesthetic values. (Please see the reports by well-known scientists, Dr Kasturirangan and Dr Madhav Gadgil on Western Ghats).

The Ghats act as a key barrier to check the western arm of the South west Monsoon shifting eastward, which in turn brings adequate rainfall to the western margin of the Ghats. Hosting over 400 species, seven different types of vegetation,1,741 species of flowering plants and 403 species of birds, the Western Ghats are recognized as one of the eight 'Hottest Hotspots' of biological diversity.

Bats are an important group found and they undoubtedly harbour a large and diverse array of viruses, some of which have jumped species boundaries to emerge in new hosts and occasionally cause disease outbreaks. Why bats are seemingly such important reservoir hosts for zoonotic viruses, (as reported by many scientists)? The number of viruses carried by bats is significantly greater than other mammalian orders. The social dynamics of bat populations, with very large numbers roosting and species co-habitation, provide the perfect setting for viral transmission. The capacity of bats to travel to different or new geographical regions provides a mechanism for viruses to become established in naïve bat populations. The characteristic flight-adapted physiology of bats also provides an explanation for their high virus burden, while the unique anti-inflammatory and proinflammatory responses in bats, as well as distinctive immunological traits such as the reduced number of interferon genes (such as in the black flying fox) and that the interferon genes are continually expressed in the absence of an initiated immune response, may in part explain why bats are often asymptomatic carriers for a

myriad of viruses. Since incriminating bats as reservoir hosts for many zoonotic viruses this group of animals has acquired an unjustified negative reputation, especially those species that roost in urban habitats, leading to an unsympathetic mindset among many communities. Climate change, urbanization and industrial and agricultural advancements have greatly impacted bat populations globally while encroachment onto bat habitats through urbanization has increased the chance of viral spillover events into humans or companion and production animals.

A critical public health priority in the States along the Western Ghats because of its recent rapid expansion and the high mortality (2% - 10%) associated with its neurological and hematological complications; and a model system for understanding viral spillover because of the extensive wildlife-human interface across the region. KFD virus is transmitted by several tick species, the primary vector to humans and monkeys being *Haemaphysalis spinigera*. This species is found in high relative abundance in the region, has high viral prevalence, and feeds on many taxa of mammalian hosts including humans which are exposed to these ticks in th*e* anthropogenic ecotones of forest fringe.

Outbreaks of KFD have expanded from a single district in the state of Karnataka in the decade following the virus' first identification in 1957 to an extensive region now comprising five states across South India. Recent work has demonstrated a strong direct association between the expansion of KFD outbreaks an*d* the loss of native forest which was further supported by phylogeographic analyses. Earlier studies (1957s) had found forest loss was too high. As such, variation of species' distributions within those ranges was not incorporated into the assessment of species richness, nor was there any assessment of potential interaction between sympatric species. Additionally, the associations between KFD and individual species' abundance and relative abundance were not previously explored. A more detailed investigation of these aspects of mammalian biogeography and community ecology in KFD outbreak hotspots will add considerable insight into the epidemiology of KFD spillover while also providing an ecological evidence-base for developing wildlife surveillance infrastructure across the Western Ghats states. The incorporation of wildlife monitoring and sampling into KFD surveillance is particularly important since the investigation of infection in wildlife hosts has fallen off dramatically in recent decades, prior to which some mammalian susceptibility had been identified via serology but reservoir host competence was not established.

This decline in wildlife surveillance has resulted in a considerable knowledge gap in the fundamental infection ecology of KFD, while also leaving any new efforts at building surveillance to what species should be sampled and where they should be sampled. Given the extensive forest loss in the region, delineating potential host communities across the spectrum of habitat fragmentation will be important in understanding how risk of spillover is modulated by wildlife communities. The extent of viral competence is not known for most mammals of the Western Ghats and therefore identifying key reservoir hosts, or distinguishing between maintenance and amplification hosts, is not currently possible. As such, we are largely ignorant of the importance of generalist species, which typically are more resilient to anthropogenic pressure, frequently dominate fragmented landscapes as biodiversity is lost, and often host zoonotic pathogens. Conversely, the extent to which greater species richness in less fragmented landscapes may buffer against viral transmission (or against tick dispersal and feeding success) is also unknown. Therefore, there is an urgent need for targeted surveillance mechanisms to sample wildlife across heterogeneous landscapes to fill these critical knowledge gaps and thereby ultimately develop a more sound approach to the control and prevention of this rapidly expanding tick-borne arbovirus.

Let us now talk about the soft ticks since KFD virus has been isolated from several Argasid ticks, *Ornithodoros chiropterphila* collected ectoparasitic on, and from the roosting place of the bat (*Rhiolophus rouxi*). KFD virus was also isolated from these bats collected from the same roosting place. (The investigators should have actually looked for many other mammals like Pangolins, turtles and snakes as suggesteed by some, but they could not).

The *Ornithodoros* ticks have a world-wide distribution, with most species being distributed in the tropics and dry regions of the globe. Argasid ticks show diverse adaptation to using their hosts. Most members of the family are characterized by a single, prolonged larval blood feeding and multiple, short blood feeding events of subsequent developmental stages on several host individuals.). By doing so, these ticks are capable of taking up pathogens (viral, bacterial, or protozoan) and transferring them to other hosts, thus they have important vectorial role . Most of soft ticks inhabit holes and crevices and have access to hosts only occasionally, hence they developed extreme adaptations to prolonged fasting and short feeding bouts whenever hosts are available. Their vectorial capacity for

several important zoonotic diseases is well-known, including human relapsing fever (its causative agent transmitted by *Ornithodoros* spp.), tick-borne relapsing fevers (caused by several *Borrelia* spp. transmitted mainly by *Ornithodoros* and *Argas* spp.) or African swine fever (vectored by *Ornithodoros moubata, O. porcinus, O. erraticus*, or *O. savignyi,* and more recently Kyasanur Forest Disease vectored by *O. chiropterphila rhinolophi.*

Soft ticks have a special relationship with bats (Mammalia: Chiroptera). Bats are widely distributed; show high species diversity (being the second largest order of mammals) and several adaptations, which make them ideal host candidates for tick parasitism. Their morphological adaptations for flight hinders the range of their behavioral responses to reduce tick burden (e.g., their highly specialized limbs are inadequate for proper grooming), most species are social, spending their resting periods in dense groups and they are highly attached to their specific roosting sites, of which most are either underground (caves) or crevices in rocks or trees – excellent hiding places for soft ticks. Thus, several soft tick species-groups evolved specific associations with bat hosts. For example, all the known 17 species of the Nearctic soft tick genus Antricola (and Parantricola) are exclusive parasites of bats together with all species belonging to the subgenus Carios, Chiropterargas, Nothoaspis, and Reticulinasus, and several other species from the genera Alectorobius and Ornithodoros . While most of these soft tick species are tropical in their distribution, there are at least five species which regularly occur on bats in the Western Palearctic. These species are *Carios vespertilionis*, *Chiropterargas boueti, C. confusus*, *Reticulinasus salahi*, and *Secretargas transgariepinus*. All these parasitize bats mainly roosting either in abandoned structures or inside cave. Our knowledge on the distribution and ecology of bat-specific soft tick species is scanty, (as most of the literature only lists occurrence records or describe specific case reports, without a systematic review on their range, status and importance (including the work of Rajagopalan in 1968).

What one should do is to start working on bats intensely, all over the western ghat region, particularly micro chiropterans, not the Fruit eating bats hanging on big trees in urban areas. Looking for data on their geographical distribution, host-parasite relationships and vectorial importance and also raising awareness on future challenges posed by these species on human health. Particular attention should be paid to the ticks, the argasids (*Ornithodoros*) which are found in roosting places

like caves, abandoned old wells and dilapidated buildings. In the wake of recent climate change events and urbanization have influenced bats' distribution. We also should look for the abiotic (climate linked) and biotic (host distribution linked) factors regulating the distribution of insectivorous bat and their soft tick ectoparasites.

Unlike *Haemaphysalis* ticks Argasid ticks like *Ornithodoros* have two or more nymphal stages, each stage requiring a blood meal from a host. Unlike the Ixodid ticks, which stay attached to their hosts for up to several days while feeding, and these *Ornithodoros*, are adapted to feeding rapidly (about an hour) and then promptly leaving the host. How do ticks reproduce? Most ticks that transmit disease mate while on a host's body. After feeding on a host animal's blood, the adult female lays eggs — from 1,500 to as many as 5,000. A female soft tick mates with a male finds a host and takes a blood meal five to 10 times her body weight. She then drops off the host and lays a small batch of eggs, repeating this behavior throughout her adult life, which can last several years. A tick passes through several stages before being able to reproduce. A hard tick progresses through four stages: egg, larvae, nymph and sexually mature adult, but a soft tick can remain a nymph through up to seven molts, growing larger each time until the adult stage is reached. All life stages of a tick require a blood meal before molting to the next stage. The mouth structures that attach a tick to its host when feeding prevent the tick's easy removal. No such study was ever done on *Ornithodoros c. rhinolophi*, in India. New attempts to investigate the zoonotic status of KFD, under proposals now with the Researchers, should start from here. This is the only clue we have linking bat, tick and KFD virus. Ornithodoros is a nocturnal tick that hides during days in the cracks and crevices of human and animal habitation, and hunts for blood at night. The lifecycle of Ornithodoros ticks are shown below, and published literature are too many to be quoted here,. There are great variations in different species. Only limited studies about *O. rostratus* have been conducted in South America and several aspects of their life cycle differ among studies or remain unexplored. In order to better elucidate the biology of *O. rostratus*, the investigators fed these ticks on mice under laboratory conditions. To complete their life cycle on mice, *O. rostratus* goes through a larval stage, 3-6 nymphal instars (nymph 1-6) and adult male and female. Adults can be originated from nymph 3-6. Nymphs 4 with higher weight after feeding tend to originate adults. Adults originated from early instars tended to be lighter. Females tended to be heavier than males. Larvae needed on

average 2.7 days to complete their blood meal whereas other instars ranged from 17.3 to 78.3 min. The capacity to ingest blood was higher in larvae and females in comparison to males. The preecdysis period ranged from 5 to 12.5 days. After one blood meal, females remain on average 15.2 ± 5.8 days laying 276.8 ± 137.2.9 eggs. Females originated from nymph 4 had similar oviposition time, egg incubation and conversion ingested blood/number of eggs produced, but presented lower initial weigh and weigh gain, generating fewer eggs. Our results added novel information on *O. rostratus* biology and was discussed considering the variability of Argasid populations and in context with the differences about their life cycle described in many published works. In the case of *O. moubata,* the hexapod larval state hatches from the egg after about a week. It moults a few days later and develops into a nymphal stage without a blood meal. Nymphs are blood suckers, and the blood meal takes less than half an hour. There are several nymphal stages. Those ticks developing to be males go through four nymph stages, and the females go through five. Copulation takes place when the female has received a blood meal. Copulation simulates ovarian development, and the female lays eggs about two weeks after copulation. The female can copulate and lay eggs several times during its lifetime, producing a total of about 500 eggs.

I had erred in giving importance only to the role of bats as zoonotic reservoirs. They are important, but only in the presence of the *Ornithodoros* ticks which now appears to me to play a very important role as Feeder of the Virus. Can we call it the basis for zoonotic cycle? The adult ticks can survive for more than 3-4 years, with the virus in them, as has been established with their African counterparts, *O. moubata* and *O. savignyi.* Then there is the other established cycle of Small mammals-*Ixodes-Haemaphysalis-monkey*-man which I would call the Epidemic chain. From the zoonotic chain to the epidemic chain, how does it connect? This in what we should try to find out.

We should have the vision of Rockefeller Foundation to support the venture and someone like Jorge Boshell Manrique, the forest man with the machete, who led a band of Indians into forest research during the early years in 1957 in Shimoga District. This is what is needed in Western Ghats, and having a cozy field station in a place like Shimoga town, which has some infra structure, including a Virus Diagnostic Laboratory managed by the State Government. But it is an urban area good for living comfortably. But we need a forest area, particularly the interfaces,

where ecological changes take place like Agumbe area (virgin forests) in the Western Ghats, and the gradual exploitation of which has lead to changing host-parasite relations.

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Editor's Note:

The author, *Padmashree* Dr P.K. Rajagopalan, a nonagenarian, is an authority on vector-borne diseases and one of the pioneer researchers on KFD in India. For details about his diverse research interests in VBDs and updated bio-bibliography, readers are advised to read:

Tyagi, B.K., 2022. *Padmashree* Dr P.K. Rajagopalan — A nonagenarian and still going strong medico-Arthropodologically. *J Med Arthropodol & Public Health* 2(2): 67-95.

An electronic copy can be also requested from Prof. Dr B.K. Tyagi (abktyagi@gmal.com)

Original Article

A RATIONAL APPROACH FOR DESIGNING THE MULTITARGETING ANTIMALARIAL COMPOUNDS AGAINST *PLASMODIUM FALCIPARUM* KINASES TO EFFECTIVELY COMBAT THE RAPIDLY EMERGING DRUG RESISTANCE

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ABSTRACT

The development of parasite resistance to primary antimalarial drugs has caused a significant number of fatalities in malaria-affected countries, with drug target mutations being the sole reason. As a potential solution, the development of multitargeting drugs has gained attention. Studies have shown that the probability of multiple target mutations is low because it would significantly impact the parasite's fitness. Furthermore,

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multitargeting drugs have the potential to be effective with reduced dosages, increased efficiency, and improved safety profiles. Among the viable targets for malaria drug development, kinases, a class of enzymes that play a critical role in various stages of the parasite's life cycle, are highly promising. Therefore an integrative approach combining computational methods, biochemical target-specific inhibition assays, and phenotypic screening may be an effective strategy for developing antimalarial compounds targeting multiple kinases.

Keywords: drug discovery, high-throughput virtual screening, molecular dynamics, drug resistance, kinase, multitargeting

Malaria is a life-threatening infectious disease caused by the *Plasmodium* parasite and transmitted through the bites of infected *Anopheles* mosquitoes. *P. falciparum* is responsible for the maximum number of death cases. The disease is a significant public health concern, particularly in tropical and subtropical regions of the world, where the majority of cases and deaths occur. According to the latest malaria report (World Malaria Report, 2022), there were nearly 247 million cases, and 619,000 reported deaths in 2021. This represents a 2 million increase in cases compared to the previous year. The group most susceptible were young children aged five years or below, who accounted for 80% of all malaria-related deaths https://www.who.int/health-topics/malaria. Despite the significant progress in reducing the malaria burden over the last two decades, the disease continues to pose a major global health challenge[1]. The parasite has developed resistance to most of the frontline antimalarial medications, making it increasingly challenging to treat and control the disease[2].

The statistics mentioned above pose the considerable public health challenge of malaria, emphasizing the urgent need for effective strategies to combat the disease.

THE QUEST TO DISCOVER THE MULTITARGETING DRUGS FOR MALARIA THERAPY

Compared to single-target and combination therapy, the multitarget strategy stands out as a novel and promising approach in terms of combatting drug resistance[3].

Multitargeting drugs exhibit polypharmacology by targeting multiple molecular targets[4]. It is commonly observed that biological network systems have robust homeostasis and redundant mechanisms. This suggests that relying on single-target drugs may not be sufficient and may lead to adverse side effects. On the other hand, a coordinated pharmacological approach that simultaneously modulates multiple targets is necessary to achieve the desired therapeutic outcome[5]. There is less potential for drug resistance with multitargeting medications compared to single or combination therapy, and additionally, the drugs are associated with a more effective, safer profile, comparatively less expensive, and require fewer daily doses[6,7].

The statistical and network analysis of the new molecular entities (NMEs) approved by the U.S. FDA between 2000-15 showed that from among the 361 total NMEs, 146 were single-target ones, 66 with two targets, 25 with three, and 16 with four targets, respectively. The remaining 95 NMEs had higher target numbers between 5-31[8]. Among the 101 FDA-approved NMEs from 2015-17, the contribution of multitargeting drugs was nearly 21%[4]. In January 2019, a search of the Journal of Medicinal Chemistry website for papers using the term "multitarget" yielded 265 results. Surprisingly, nearly 88% of them were published in the recent decade, indicating a growing interest in multitarget drug discovery and development in recent years. This trend highlights the increasing recognition among researchers of the potential benefits of developing drugs that can simultaneously target multiple pathways or proteins, rather than just a single target, in treating complex diseases[5].

1. *Plasmodium falciparum* kinases are exploitable drug targets

Kinases are a group of enzymes that catalyze the transfer of γ-phosphate from ATP to target proteins, thereby modulating their activity and function. Malaria kinases exhibit only 35-60% sequence similarity with the corresponding human orthologues[9]. In *P. falciparum*, kinases are involved in critical cellular processes such as cell division, differentiation, invasion, and egress from host cells. The parasite employ diverse range of kinases to phosphorylate proteins, lipids, and carbohydrates for its survival and proliferation. Some of the kinases extensively studied as potential targets for antimalarial drug development include Calcium-Dependent Protein Kinase 4 (*Pf*CDPK4), Calcium-Dependent Protein Kinase

1(*Pf*CDPK1), Cyclin-Dependent-Like Kinase 3 (*Pf*CLK3), Thymidylate Kinase (*Pf*TMK), Mitogen-Activated Protein Kinase 2 (*Pf*MAP2), Phosphatidylinositol 4-Kinase (*Pf*PI4K), cGMP-Dependent Protein Kinase (*Pf*PKG) and Protein Kinase 5 (*Pf*PK5), etc. Inhibiting these kinases can disrupt vital cellular pathways and interfere with the parasite's ability to infect and replicate within the host. The versatile roles of these kinases in *Plasmodium falciparum* make them attractive targets for drug development[10].

Additionally, the availability of crystal structures of the kinases provides valuable insights into their functional mechanisms and enables the rational design of small molecule inhibitors that selectively bind and inhibit their activity. Kinases also represent a highly druggable class of molecules extensively studied in cancer therapeutics[11]. Furthermore, *Pf*PI4K, an exploitable drug target, has gained significant attention, with one of its inhibitors (MMV390048) currently undergoing Phase II clinical trials[12].

2. High Throughput virtual screening is the preferred initial approach for multitarget drug discovery

High Throughput virtual screening (HTVS) and molecular docking-based studies have emerged as effective strategies in identifying potential lead molecules for drug development. This approach encompasses several stages: target identification, homology modeling, ligand preparation, protein preparation, grid generation, molecular docking, MMGBSA calculation, and molecular dynamics simulations (Fig.1). These methods have become a valuable primary step in drug discovery, enabling the identification of novel compounds to treat various diseases. In particular, virtual screening and molecular docking have proven to be powerful tools in the development of antiviral and antibacterial drugs, as well as antiprotozoal agents[13-16]. This approach can efficiently predict the binding affinity of small molecules to target proteins, aiding in identifying potential drug candidates. Several kinase inhibitor libraries accessible in various databases can be used for HTVS against the *P. falciparum* kinase targets.

Overall, this approach holds great promise in the identification of new leads for the development of therapeutic interventions[17-19]. This approach has proven to be an effective strategy for developing multitargeting drugs, extensively utilized against SARS-CoV-2[20,21]. The effectiveness of the structures predicted by HTVS against

Leishmania was demonstrated through *in vitro* testing[22], which validated the efficacy of this approach.

3. Experimental Design for Testing Hypothesis: Key Considerations and Approaches

The multitargeting hits may be further validated through the kinase inhibition assay to check for their multikinase inhibition nature. The kinase assay may be carried out using NADH/ATPase coupled assay, HPLC assay, ELISA-based protein kinase assay, etc.[23-25]. Parasite growth inhibition assay may be carried out to check the antimalarial effect of the hit compounds. Additionally, the standard *in vitro* resistance mutant generation experiment may be conducted using single-targeting drugs as a baseline to assess the likelihood of resistance to the multitargeting hit compounds[26]. The *in vivo* studies may be carried out to check the safety and efficacy of the best multitargeting inhibitors in animal models (Fig.1)[27].

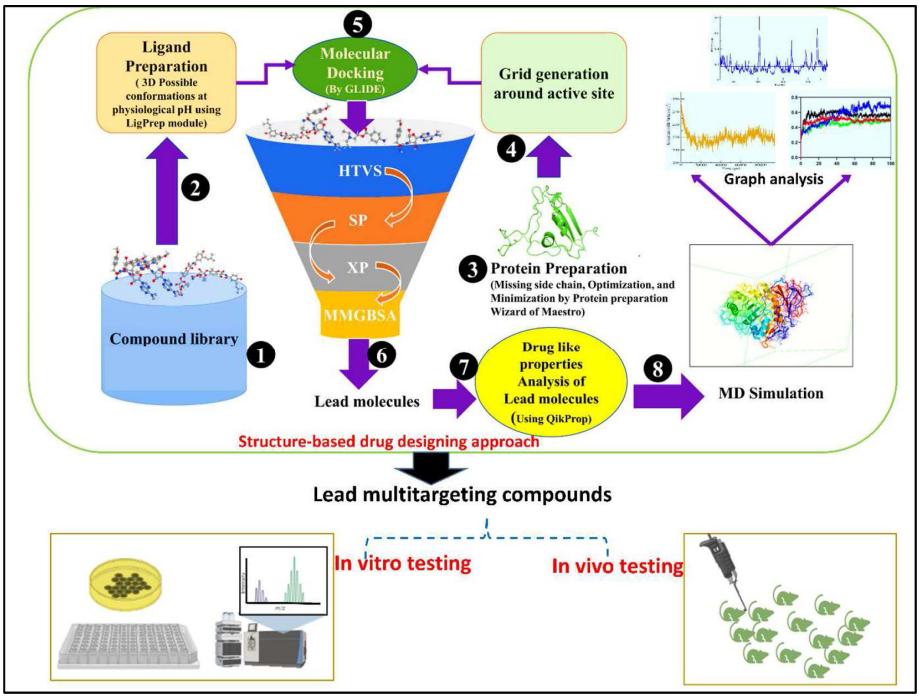

Fig 1. The schematic representation of the *in silico*, *in vitro,* and *in vivo* approaches for multitarget drug discovery against *Plasmodium falciparum* kinases.

CONCLUSION

In conclusion, the above discussed integrative approach combining computational methods, biochemical target-specific studies, and inhibition phenotypic screening has the potential to pave the way for the discovery of antimalarial compounds that target multiple *P. falciparum* kinases and, in doing so, may help address the issue of drug resistance that is becoming increasingly prevalent.

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Conflict of Interest Statement:

The authors declare that there are no conflicts of interest.

Author contributions:

PG carried out work and writing original manuscript, and DP reviewed and edited.

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Original Article

PONGAMIA PINNATA LEAF EXTRACTS EFFICACY AGAINST THE 4TH INSTAR LARVAE OF *AEDES VITTATUS* (INSECTA: DIPTERA: CULICIDAE)

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ABSTRACT

Objective: To explore the larvicidal activity of *Pongamia pinnata* leaf extracts against the *Aedes vittatus*, an emerging threat to public health.

Methods: Secondary metabolites from the leaves of *P. pinnata* were extracted using Water, Methanol, Ethanol, Hexane, and Acetone as solvents. From each extract, 5 different concentrations (50, 100, 150, 200, 250 PPMs) were prepared and tested for their larvicidal

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efficacy against the 4th instars of *Aedes vittatus* under laboratory conditions.

Results: All the extracts collected by using different solvents showed good larvicidal effects after 24 hours of exposure. However, the highest larval mortality was found in the methanolic extract of *P. pinnata* leaves followed by aqueous, ethanolic, hexane, and acetone extracts in the same order. Dose-dependent responses were observed. Mortality percentages of 100%, 98.33%, 83.33, 81.66%, and 76.66% were obtained by methanolic, Aqueous, ethanolic, hexane, and acetone extracts, respectively.

Conclusions: The Methanolic and aqueous extracts of *P. pinnata* leaves were proven to possess efficacy as ideal larvicides against the larvae of *Ae. vittatus*. Hence, the leaf extract of *P. pinnata* may be used to control this emerging threat to human health.

Keywords: Larvicides, Insecticides, Biopesticides, Vector control, Vector-borne diseases

INTRODUCTION

More than 219 million cases and 400,000 deaths occur yearly due to Malaria while 3.9 billion people in over 129 countries are at risk of Dengue, with an estimated 40,000 deaths yearly. Mosquitos also transmit many viral diseases such as chikungunya fever, Zika virus fever, yellow fever, West Nile fever, and Japanese encephalitis[1]. According to a report by WHO[2], there were an estimated 241 million malaria cases and 627 000 malaria deaths worldwide in 2020. From time immemorial, man has been using plant products such as neem leaves and flowers of *Chrysanthemum cinerariaefolium* against many arthropod pests[3]. Pesticides are a major tool in controlling insect pests of agricultural and health importance[4]. Indiscriminative usage of pesticides has negative effects such as environmental pollution, loss of biodiversity, and human health issues ranging from nerve damage to cancers[5].

Aedes vittatus, an important vector and pest mosquito, has a wide distribution in many tropical and subtropical countries worldwide, such as India, the Ashanti

region of Ghana, southern Nigeria, the Jaffna peninsula in northern Sri Lanka, Galicia, Metema and Humera in Ethiopia, southwestern Iran and Khuzistan province, Jarabacoa in the Dominican Republic, and urban Islamabad area of Pakistan[6-13]. In recent years, *Ae. vittatus* has been linked to several viruses with public health implications, including the Zika virus (ZIKV), yellow fever virus (YFV), dengue virus (DENV), and chikungunya virus (CHIKV). The species has also been considered a potential vector for Japanese encephalitis virus (JEV), West Nile virus (WNV), Chandipura virus (CHPV), and Chittoor virus (CHITV)[14]. Studies have also identified *Ae. vittatus* as the vector for chikungunya virus in various regions of Kenya[15] and the species has been found to facilitate the growth of the DEN-2 virus[16]. Additionally, research has indicated that, *Ae. vittatus* is a carrier of *Setaria digitata*[17].

Formulations of natural origin with pesticidal action are called biopesticides[18]. Many plant products are in usage as pesticides for the past 4000 years ago[19]. Several studies have explored the potential of natural products as mosquito control agents. One such study examined different fractions from *Lantana camara* flowers and their repellent properties against Aedes mosquitoes[20]. Another study found that the essential oil of *Kaempferia galan*gal L. and its major chemical constituents exhibited larvicidal activity against *Ae. vittatus*[21]. Additionally, the n-Hexane extract of *Persea americana* seeds demonstrated high potency against *Ae. vittatus* larvae, with the most effective fraction containing dominant fatty acid and fatty acid methyl esters[22].

The current study aimed to investigate the insecticidal activity of *Pongamia pinnata* leaf extracts at various concentrations (50, 100, 150, 200, and 250 ppm) against the 4th instar larvae of *Ae. vittatus*.

MATERIALS & METHODS

(1) Test insect culture: Early-stage larvae of the *Aedes vittatus* were collected from the lake and rockpools located in the Osmania University campus, Hyderabad, Telangana State, India. They were reared in glass troughs by providing yeast and dog biscuits in a 3:1 ratio. Fourth instar larvae were used in larvicidal bioassay.

(2) *Pongamia pinnata* Leaf extracts preparation: Good-quality leaves of the *P. pinnata* were collected from the Osmania University campus, were washed

first with running tap water and then with distilled water and shade dried for 15 days. Later the dried leaves were powdered by an electrical blender. Aqueous, methanolic, Ethanolic, Hexane, and Acetone extracts were collected from the powdered samples using the Soxhlet apparatus and a Rotary evaporator. Aqueous extracts were collected by boiling the powder in distilled water followed by filtration. Five different concentrations (50, 100, 150, 200, and 250 ppm) of extracts by dilution with distilled water and Tween 80.

(3) Phytochemical Analysis: Various tests were performed to detect the presence of secondary metabolites in the prepared extracts. Alkaloids were identified using the Mayor's Test, in which the Mayor's reagent was added and the formation of a cream-colored precipitate was observed. The Alkaline Reagent Test was used to identify flavonoids, which produced a yellow color upon adding NaOH. Terpenoids were detected using the Salkowski Test, where the addition of concentrated H_2SO_4 resulted in a red or orange color. The Froth Test was utilized to identify saponins, where the formation of foam occurred with vigorous shaking. The Keller-Killiani Test was conducted to identify glycosides, in which the addition of HCl and $FeCl_3$ produced a red or violet colour. Finally, the NaOH Test was performed to identify polyphenols, and the addition of NaOH resulted in yellow colour.

(4) Test Solutions Preparation: 1 g of the residues from the extraction was added to 985 mL of Distilled water, 5 mL of Tween 80 and 10 mL of respective solvents separately to prepare 1000 ppm stock solutions. By serial dilution, 5 different concentrations (50, 100, 150, 200 and 250 ppm) were prepared using distilled water. Control solutions were prepared using the respective solvents excluding the extracts.

(5) Larvicidal Bioassay: For the larvicidal bioassay test, WHO guidelines[23] were followed. Larvae were taken in three batches of 20 in 100 mL of prepared test solutions separately in 250 mL test cups. The number of dead larvae was counted after 6, 12 and 24 h of exposure, and the percentage mortality was reported from the average of five replicates using the following equation.

%PM = (No of dead larvae / Total larvae population) × 100.

Corrected mortalities were calculated using Abbotts's[24] formula.

$$\text{Corrected Mortality (\%)} = \frac{\%MT - \%MC}{100 - \%MC} \times 100$$

(6) Statistical analysis: Microsoft Excel software was used to subject the results to one-way analysis of variance (ANOVA). The level of significance was set at $p<0.05$. Probit analysis was conducted to calculate LC_{50} & LC_{90} concentrations.

RESULTS & DISCUSSION

(1) Phytochemical Analysis: The results of the phytochemical analysis (Table No.1) show that *P. pinnata* leaf extracts contain a wide range of phytochemicals. The methanol extract showed the presence of the highest number of phytochemicals, including alkaloids, flavonoids, saponins, terpenoids, polyphenols, and glycosides. The ethanol extract also showed the presence of most of these phytochemicals, although in a slightly lower abundance. The water extract showed the presence of alkaloids, flavonoids, saponins, terpenoids, polyphenols, and glycosides, albeit in a lower abundance than the methanol extracts. The hexane and acetone extracts showed the presence of only a few phytochemicals, with the acetone extract containing only flavonoids and terpenoids. The methanol, ethanol and aqueous extracts showed the highest abundance of these phytochemicals, making them potentially useful in the control of pests.

Table 1. Identified secondary metabolites in the *Pongamia pinnata* leaf extracts. Absent: -; Slightly Present: +; Moderately present: ++; Heavily present: +++.

Extracts	Alkaloids	Flavonoids	Saponins	Terpenoids	Polyphenols	Glycosides
Water	+	++	+	+	++	+
Ethanol	++	+	++	+	++	+
Methanol	+++	++	++	++	+++	++
Hexane	-	-	+	+	+	_
Acetone	-	+	-	+	-	-

(2) Larvicidal Bioassay: The results of the larvicidal bioassay (Table 2 and Fig. 1) revealed that the aqueous, methanolic, and ethanolic extracts of *P. pinnata* leaves possessed significant larvicidal activity against *Ae. vittatus* larvae. Among the different solvent extracts, the methanolic extract demonstrated the

highest larvicidal activity, with a mortality percentage of 28.33 ± 0.53 at 50 ppm, 53.33 ± 0.74 at 100 ppm, 73.33 ± 0.35 at 150 ppm, 88.33 ± 0.35 at 200 ppm, and 100 ± 0.52 at 250 ppm. Notably, the 250 ppm concentration of the methanolic extract resulted in the complete mortality of *Ae. vittatus* larvae.

Table 2. *Pongamia pinnata* leaf extracts larval mortality percentages ± Standard Deviations against the 4_{th} Instar larvae of *Aedes vittatus*

Conc. In ppm	Aqueous	Methanolic	Ethanolic	Hexane	Acetone
0	0	0	0	0	0
50	28.33 ± 0.53	33.33 ± 0.46	18.33 ± 0.46	26.66 ± 0.71	16.66 ± 0.64
100	53.33 ± 0.53	53.33 ± 0.74	38.33 ± 0.71	43.33 ± 0.46	33.33 ± 0.46
150	66.66 ± 0.51	73.33 ± 0.35	61.66 ± 0.75	53.33 ± 0.52	41.66 ± 0.46
200	78.33 ± 0.35	88.33 ± 0. 35	71.66 ± 0.74	61.66 ± 0.64	63.33 ± 0.71
250	98.33 ± 1.30	100 ± 0. 52	83.33 ± 0.53	81.66 ± 0.53	76.66 ± 0.53

The ethanolic extract also exhibited significant larvicidal activity against *Ae. vittatus* larvae, with a mortality percentage of 18.33 ± 0.46 at 50 ppm, 38.33 ± 0.71 at 100 ppm, 61.66 ± 0.75 at 150 ppm, 71.66 ± 0.74 at 200 ppm, and 83.33 ± 0.53 at 250 ppm. Similarly, the aqueous extract demonstrated a mortality percentage of 28.33 ± 0.53 at 50 ppm, 53.33 ± 0.74 at 100 ppm, 66.66 ± 0.51 at 150 ppm, 78.33 ± 0.35 at 200 ppm, and 98.33 ± 1.30 at 250 ppm.

On the other hand, the hexane and acetone extracts of *P. pinnata* leaves exhibited relatively low larvicidal activity against *Ae. vittatus* larvae. The hexane extract showed a mortality percentage of 26.66 ± 0.71 at 50 ppm, 43.33 ± 0.46 at 100 ppm, 53.33 ± 0.52 at 150 ppm, 61.66 ± 0.64 at 200 ppm, and 81.66 ± 0.53 at 250 ppm. The acetone extract showed a mortality percentage of 16.66 ± 0.64 at 50 ppm, 33.33 ± 0.46 at 100 ppm, 41.66 ± 0.46 at 150 ppm, 63.33 ± 0.71 at 200 ppm, and 76.66 ± 0.53 at 250 ppm.

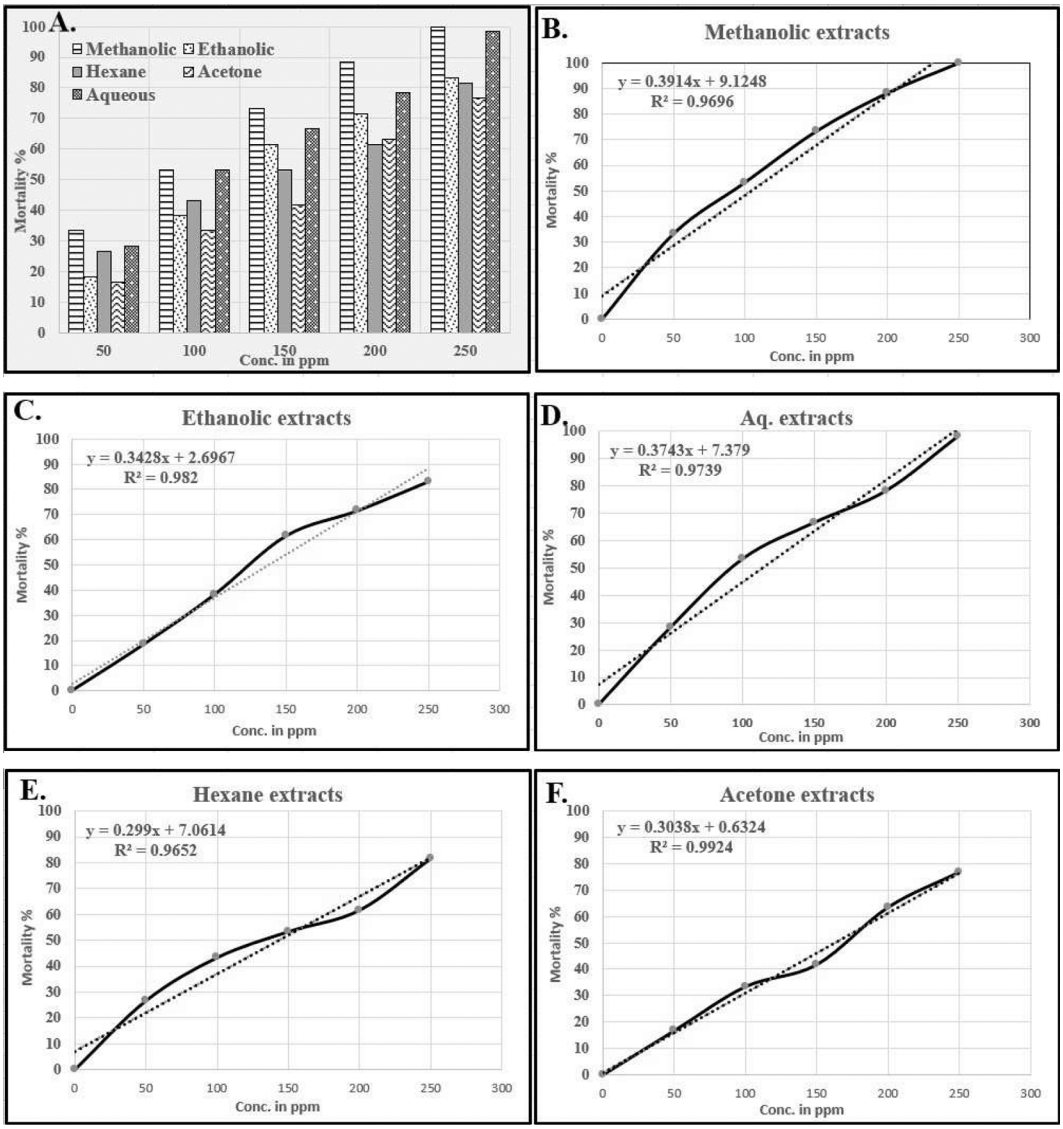

Fig 1. *Pongamia pinnata* leaf extracts larvicidal efficacy against the 4th Instar larvae of *Aedes vittatus.* (A) Bar graph of mortality percentages of different extracts; (B) Line fit plot of Methanolic extracts; (C) Line fit plot of Ethanolic extracts; (D) Line fit plot of Aqueous extracts; (E) Line fit plot of Hexane extracts; and (F) Line fit plot of Acetone extracts

Table 3 and Fig. 2 show the LC50 and LC_{90} values of the different extracts of *P. pinnata* against the 4th instar larvae of *Ae. vittatus* in the present study. Among the extracts tested, the methanolic extract displayed the lowest LC_{50} value of 104.43 ppm, with 95% confidence limits of 104.13 and 104.92, and an LC_{90} value of 206.63 ppm, with 95% confidence limits of 206.33 and 207.12. The aqueous extract showed an LC50 value of 113.86 ppm, with 95% confidence limits of 113.57 and 114.32, and an LC_{90} value of 220.73 ppm, with 95% confidence limits of 220.44 and 221.19. The ethanolic extract exhibited moderate LC_{50} and LC_{90} values with an LC50 value of 137.99 ppm, with 95% confidence limits of 137.77 and 138.42, and an LC_{90} value of 254.68 ppm, with 95% confidence limits of 254.46 and 255.11. The hexane and acetone extracts displayed the highest LC_{50} and LC_{90} values in the present study. The LC_{50} values of the hexane and acetone extracts were found to be 143.17 ppm and 162.5 ppm, respectively, and LC_{90} values were found to be 276.55 ppm and 294.16 ppm, respectively.

Table 3. LC_{50} and LC_{90} values (ppm) of *Pongamia pinnata* leaf extracts against the 4th Instar larvae of *Aedes vittatus*

Extract	LC_{50}	LC_{50} 95% Confidence limits		LC_{90}	LC_{90} 95% Confidence limits	
		LCL	UCL		LCL	UCL
Aqueous	113.86	113.57	114.32	220.73	220.44	221.19
Methanolic	104.43	104.13	104.92	206.63	206.33	207.12
Ethanolic	137.99	137.77	138.42	254.68	254.46	255.11
Hexane	143.17	142.98	143.50	276.55	276.36	276.88
Acetone	162.5	162.26	162.86	294.16	293.92	294.52

In summary, the methanolic extract of *P. pinnata* leaves demonstrated the highest larvicidal activity, followed by Aqueous and ethanolic extracts against *Ae. vittatus* larvae, whereas the Hexane and Acetone extracts exhibited the lowest activity.

Similar results were obtained in a previous study[25]. In that study, the methanolic extracts of *P. pinnata* showed better larvicidal efficacy than hydroalcoholic extracts against the larvae of *Culex quinquefasciatus* and *Ae. aegyptii* with LC_{50} values of 84.8 ppm and 118.2 ppm respectively and with LC_{90}

values of 184.7 ppm and 227.0 ppm, respectively. These findings indicate that the methanolic extract may have the potential to serve as a natural larvicide for controlling Aedes vittatus populations. Future studies should focus on isolating and identifying the bioactive compounds responsible for the observed larvicidal activity.

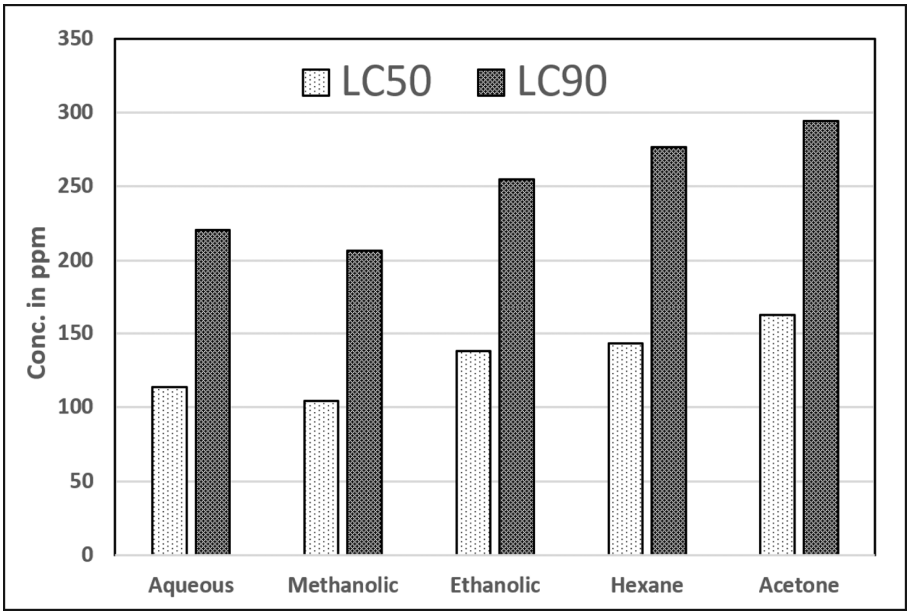

Figure 2. LC_{50} and LC_{90} concentrations of the tested *Pongamia pinnata* leaf extracts against the 4th Instar larvae of *Aedes vittatus.*

CONCLUSION

In conclusion, the phytochemical analysis of *P. pinnata* leaves revealed the presence of a diverse range of phytochemicals, with the methanol extract showing the highest abundance of phytochemicals. The larvicidal bioassay demonstrated significant larvicidal activity of the aqueous, methanolic, and ethanolic extracts of *P. pinnata* leaves against *Ae. vittatus* larvae, with the methanolic extract exhibiting the highest activity. The hexane and acetone extracts showed relatively low activity against the larvae. The methanolic extract displayed the lowest LC_{50} and LC_{90} values, while the hexane and acetone extracts had the highest values. These findings suggest that the methanolic extract of *P. pinnata* leaves has the potential as

a natural pesticide against *Ae. vittatus* larvae. The results of this study are consistent with those of previous studies on the larvicidal activity of *P. pinnata.*

***Conflict of Interest*:**

The authors don't have any sort of financial or non-financial conflicts with any person or firm that can affect the results of this research.

***Author Contributions*:**

MM conceptualized, investigated, curated and analysed data, drafted manuscript and edited.

LM visualized, investigated and wrote the original draft.

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Case Study

TECHNOLOGY TRANSFER, ENTREPRENEURSHIP, AND COMMERCIALIZATION EXPERIENCES OF THE U.S. LAND GRANT UNIVERSITIES: CASE STUDY OF MICHIGAN STATE UNIVERSITY

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ABSTRACT

Technology transfer is a hallmark of U.S. land grant universities. For more than 165 years, Michigan State University, a premier land grant university in USA has been actively engaged in technology transfer, serving communities in Michigan and globally. As a comprehensive university, MSU faculty, staff, and students are generating new technologies related to food, agriculture, health, engineering, and natural sciences, among other areas. Technology transfer is implemented through the traditional

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extension system via MSU Extension and through the recently established intellectual property-led (IP-Led) system via the MSU Innovation Center. This paper describes the rich experience of Michigan State University in IP-led technology transfer. The Innovation Center includes MSU Technologies (MSU-T), serving as the intellectual property protection and licensing arm; MSU Business-CONNECT, serving as the front door to MSU for private companies; and Spartan Innovations, serving as a platform for startup companies based on MSU-generated technologies and innovations. The ultimate goal of the MSU Innovation Center is to transfer and commercialize technologies so that society can benefit from innovations generated by the university and to foster economic growth. Entrepreneurship education and training is an integral part of MSU for building the next generation of leaders and promoting a culture of innovation.

Keywords: technology transfer, intellectual property rights, innovation, commercialization, Entrepreneurship

INTRODUCTION AND BACKGROUND – IMPORTANCE OF NEW TECHNOLOGIES IN THE UNITED STATES OF AMERICA (U.S.)

Science, technology, and innovations have played a significant role in improving the quality of life for people around the world in all sectors of the economy for centuries. Louis Pasteur saved millions of lives through vaccines for rabies and anthrax and his development of pasteurization; countless lives have been saved through penicillin; Thomas Edison made significant contributions to energy and communication through his inventions such as the phonograph, the motion picture camera, and the lightbulb; Norman Borlaug, the "Father of the Green Revolution," is credited with saving over a billion people from starvation; Philip Nelson has reduced losses to spoilage and provided millions of people around the world access to fresh, nutritious food through bulk sterile processing for fresh fruit juices and vegetables; Alexander Graham Bell is credited with patenting the first practical telephone; and scientists at Michigan State University discovered cisplatin's highly effective use as a cancer treatment in 1965, which has become the gold standard. Recently, novel vaccines against the devastating COVID-19 virus and other human

health related technologies and innovations have saved millions of lives globally during the pandemic[1]. Countless other examples of innovators and inventions abound in all areas of food and agriculture, health, engineering, communication, transportation, and other industries. These innovations have come from both public and private sectors, often with the heavy involvement of the government, to address pressing problems of diseases, food security, etc.

HISTORICAL PERSPECTIVE ON TECHNOLOGY TRANSFER IN THE UNITED STATES – BACKGROUND ON MICHIGAN STATE UNIVERSITY

Michigan State University (MSU; http://www.msu.edu) was founded in 1855 as Michigan Agricultural College, the nation's first land-grant college (https://en.wikipedia.org/wiki/Land-grant_university). Through the Morrill Act, the Federal government granted free land to states to establish colleges of agriculture to serve the state's citizens and help them improve their farming practices and livelihoods. This land-grant heritage is captured in MSU's three-fold mission: research, education, and outreach/extension. Historically, the research generated by faculty was focused on finding solutions to problems faced by the state's citizens, and these solutions were disseminated via a robust technology transfer system: Extension.

1. Traditional System (MSU Extension)

As a public land grant university, MSU is dedicated to technology transfer so that communities and society can benefit from the research results and innovations resulting from MSU. Historically, technology transfer at MSU and other land grant universities has occurred through the well-established Extension Service. The main MSU Extension Office is located on the campus of MSU, and extension specialists housed at field offices in all the counties of the state of Michigan serve as conduits for disseminating evidence-based information and technologies to farmers and local communities in rural and urban areas[2].

Over the years, MSU has evolved from a single college of agriculture to a comprehensive public university with more than 17 colleges and units. Today, the outreach mission of MSU goes beyond the boundary of Michigan to all over the world. To reach the goals of speeding up the delivery of technologies through scaling up innovations so society can benefit, and also generating revenue for both

inventors and for the university to reinvest in more research, more recently (in the last 4-5 decades), MSU has engaged in Intellectual Property Rights (IPR)-led technology transfer through licensing and agreements.

2. History of Intellectual Property Rights and Technology Transfer in the U.S.

The first U.S. Patent was granted to Samuel Hopkins in 1790 for a process of making potash, an ingredient used in fertilizer. The U.S. government passed the Plant Patent Act in 1930 and the Plant Variety Protection Act in 1970. The U.S. is also a member of the World Trade Organization (WTO; since 1995) and has also signed the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). The year 1980 is considered a landmark year for IPR ‐ led technology transfer in the U.S.: the U.S. Congress passed both the Bayh ‐ Dole Act, which allows universities and public research institutions to retain ownership of inventions generated through federal government support and the Stevenson ‐ Wydler Technology Innovation Act, which was the first major technology transfer law, and requires federal laboratories to actively participate in and budget for technology transfer activities. Concurrently, the U.S. Supreme Court determined that modified living organisms are patentable subject matter (Diamond vs. Chakrabarty litigation), which gave a significant boost to private sector investments in biotechnology[3,4].

The passage of the Bayh-Dole Act and the Supreme Court decision of Diamond vs. Chakrabarty created an enabling environment for public institutions in the U.S. to establish intellectual property (IP) management and technology transfer/management/licensing offices/programs (generally referred to as TTOs, TMOs or TLOs). With this enabling environment for technology transfer, MSU created an intellectual property rights (IPR) office in 1991, which provides support and services to MSU faculty and staff for protection, licensing, and access to proprietary technologies[5]. Numerous U.S. universities have set up similar offices and programs with the broader goal of transferring new technologies for public use and benefit and providing additional sources of income to support and enhance research and education.

The Society of University Patent Administrators was founded in 1974 to address the concern that inventions funded by the U.S. government were not being

commercialized effectively. This society evolved into AUTM (formerly called the Association of University Technology Managers; https://autm.net/), which fosters networking and provides continuing educational opportunities for the managers and staff members of technology transfer offices (TTOs) and does policy advocacy on IP and technology management issues. These TTOs are broadly categorized as having a service, business, or economic development model, depending on the goal and mission of the institution. The service model emphasizes transfer of technologies that benefit society, with less emphasis on revenue and income generation for the institution. The business model focuses on generating profit for the institution. The economic development model broadly looks at job creation and economic development of the local area or a specific region. Though MSU's office engages in all of these activities to some extent, it would generally fall into the service model category.

Some universities, local governments, and other stakeholders have also established technology parks and incubator facilities to stimulate scaling up, de-risking, demonstration, and commercialization of technologies.

3. The Current Emphasis on Technology Transfer and Commercialization

The majority of public institutions in the U.S. now have their own IP management and technology transfer policies and systems. Thus, there is an enabling environment at public institutions for IPR-led technology transfer and commercialization systems. Public institutions are embracing formal agreements, licensing, and commercia-lization of technologies through public - private partnerships (PPPs). During the past three decades, government funding for public universities and research institutions has steadily declined, necessitating new ways of supporting research programs and generating revenues to support basic and applied research programs.

4. Innovation Ecosystem at MSU

The TTO at Michigan State University started with two staff members, but as the invention disclosures, patenting, and licensing activities grew, the size and role of the office expanded to 35 staff members and three units (MSU Technologies (MSU-T), Business-CONNECT, and Spartan Innovations) under the umbrella of the MSU Innovation Center (https://innovationcenter.msu.edu/).

The three units of MSU's innovation ecosystem handle the different stages of the innovation pipeline described below:

(i) MSU Business Connect: The Front Door to MSU

MSU Business-CONNECT (https://innovationcenter.msu.edu/business-connect/) was created in 2009 as MSU's portal for engagement with the business community and industry.

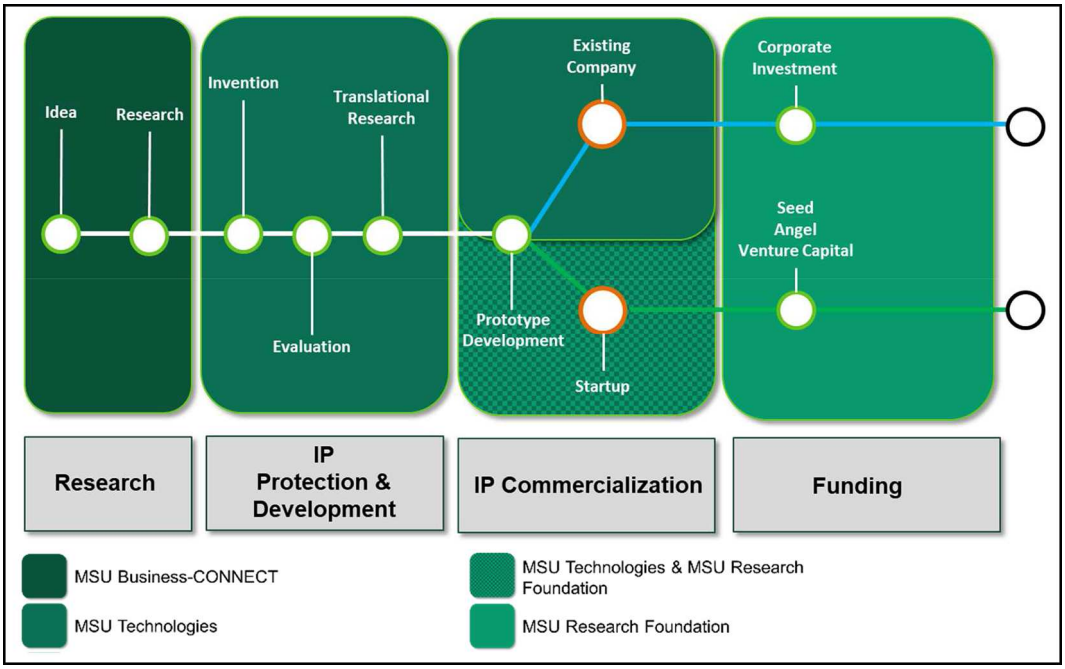

Fig. 1. Michigan State University's Innovation Pipeline. (*Source*: MSU Innovation Center, 2023)

It establishes research partnerships between MSU faculty and industry, provides entrepreneurship support, and promotes businesses that stimulate regional development. It serves as MSU's front door for corporations, directing businesses to the right MSU resources, from recruiting students to finding a researcher for a specific project to enabling strategic communications and planning for business customers. Their goal is to ensure the alignment of customer business goals and needs with MSU's intellectual ability and capacity (Fig. 1).

(ii) MSU Technologies

MSU Technologies (MSU-T; https://innovationcenter.msu.edu/tech-transfer-commercialization/) office was established in 1992 and re-organized in 2007. As the IPR/Technology Licensing Office of the university, it manages MSU's IP and technology transfer and provides many services to the university, including acquiring, protecting, and licensing IP.

The goal of any technology transfer program should be to preserve free sharing of knowledge, but to also ensure adequate compensation and create win-win situations for the mutual benefits of all parties involved. In the changing landscape of technology transfer, having an appropriate intellectual property (IP) management policy in place is therefore necessary to both promote research and protect the interests of all parties.

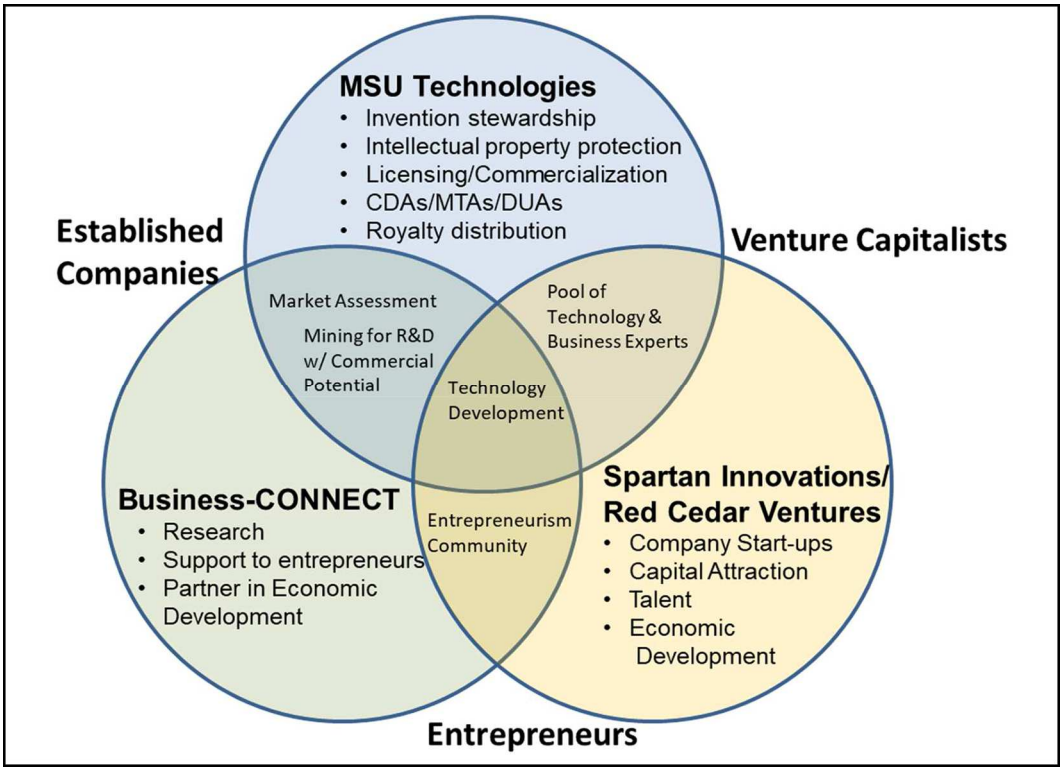

Fig. 2. MSU Innovation Center (*Source*: MSU Innovation Center, 2023)

The policy and practices of patenting and IP protection and licensing have evolved from an initial culture of patenting everything at a high cost, to now being more selective and evaluating technologies for their commercial value and market potential. Also, instead of the university bearing all or most of the costs of patenting and other forms of protections, increasingly, the costs of the patenting/protection are borne by the licensee. There is also more encouragement to work with businesses to scale up and transfer technologies for the public's benefit, and at the same time, where appropriate, generate revenues for public research institutions (Fig.2).

According to the MSU IP Policy (https://innovationcenter.msu.edu/tech-transfer-commercialization/faculty-researchers/msu-patent-policy/), any new inventions developed using MSU funds and facilities are the property of Michigan State University. Also according to the MSU IP policy, royalties generated through licensing of technologies are shared with the inventors(s) Table 1).

Table 1. Royalty Distribution Rates at Michigan State University

Net Licensing Proceeds on a Particular University Invention	Inventor(s)	College	University
First $100,000	50%	25%	25%
Next $900,000	30%	30%	40%
Over $1,000,000	30%	10%	60%

(iii) Spartan Innovations

Spartan Innovations (https://innovationcenter.msu.edu/departments/spartan-innovations/) was established in 2012 to convert MSU innovations into successful Michigan businesses. It is an incubator and provides business development services, university-wide entrepreneurship education, internships for student entrepreneurs, mentoring to help manage new business startup projects, access to venture capital support, funding for scale-up of early-stage technologies. Its resources include commercial/market assessment, commercial development planning, start-up advising, business documentation and support services, mentoring programs, business accelerator programs, venture fellows, entrepreneurs-in-residence, internship programs, business plan development, gap funds and grant funding.

MSU RESEARCH FOUNDATION

The MSU Research Foundation is a non-profit research foundation founded in 1973 to enhance research, encourage innovation, and facilitate all relevant aspects of economic development through modern commercialization practices, venture creation activity and innovation partnerships. The Foundation manages an endowment built from decades of licensing revenue, which provides over $10 million in research funding to MSU annually through a grants program. In addition, the Foundation serves as a Trust for non-traditional gifts to MSU. It has several subsidiary organizations that also each play important roles in the MSU innovation ecosystem: Spartan Innovations (SI) works closely MSU-T on tech transfer and venture development; Red Cedar Ventures (RCV) and Michigan Rise Pre-Seed Fund III (MR) provide early-stage investments to new companies; and Michigan Biotechnology Institute (MBI) focuses on de-risking and scale-up of bio-based technologies.

MSU INNOVATION CENTER PORTFOLIO

Each year, MSU faculty disclose an average of 160 new inventions, and of those, MSU files an average of 67 patent applications based on the assessment of their market potential. About 50 U.S. patents are issued each year for MSU inventions, and the university earns between $2-4 million per year in royalty income from licenses, including patents and copyrights (https://innovationcenter.msu.edu/about/; see MSU IC Annual Reports) (Fig.3).

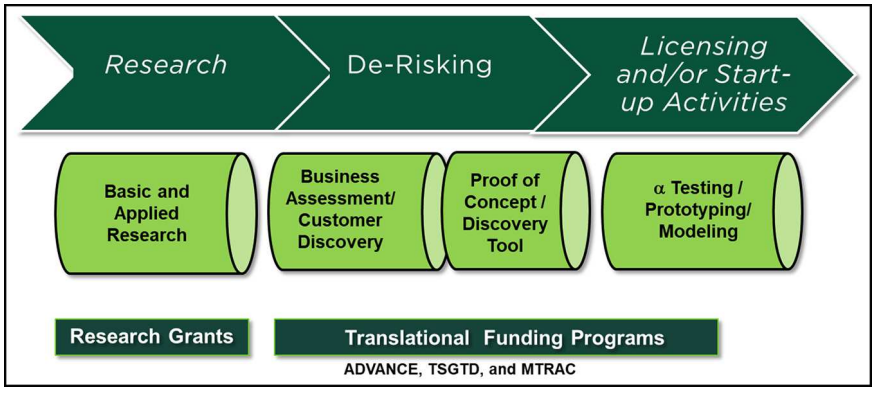

Fig. 3. Translational Funds for MSU Researchers (*Source*: MSU Innovation Center, 2023)

In addition, each year 3-5 new startup companies are formed based on MSU-generated technologies. One example is Neogen, a biotech company formed in 1981 through an investment by the MSU Foundation, and which merged in 2022 with 3M's food-safety industry with an enterprise value of about $5.3 billion. There are many other examples of successful companies being formed through public-private partnerships and commercializing technologies in many countries, including India.

HUMAN HEALTH RELATED TECHNOLOGIES DEVELOPED AND COMMERCIALIZED BY MSU

MSU researchers make innovations in all fields; below are just a few examples of technologies related to human health.

(i) Cisplatin:

Cisplatin and carboplatin were discovered to be highly effective cancer treatment drugs by MSU researchers, and subsequently patented and licensed. The $325 million in royalties earned from 1979-2004 have built a strong foundation and a vast pool of resources to support, enhance, and sustain cutting-edge research, innovations, and technology transfer. Typically, royalties generated from technologies alone are not sufficient to sustain TTOs and reinvest in research unless an institution owns a highly successful innovation. MSU has been fortunate in that the revenues generated from these technologies have allowed the Foundation to foster an ambitious research environment and stimulate a robust entrepreneurial culture at MSU, and the Foundation has awarded more than $350 million to the university through grant programs and other initiatives designed to strengthen research, assist in the development of technologies and bolster MSU's scholarly infrastructure (https://alumni.msu.edu/stay-informed/alumni-stories/one-lab-one-discovery-the-continuous-ripple-effect).

(ii) Wolbachia/malaria:

Researchers at MSU have developed a novel natural mosquito biocontrol strategy, where natural disease-susceptible mosquito populations are replaced with malaria resistant mosquito populations by using the endosymbiotic bacterium *Wolbachia*, which resides naturally in 28% of mosquito species, although not in *A. stephensi*. In 2012, MSU researchers successfully introduced *Wolbachia* into *A. stephensi*, and the bacterium has been maintained in the laboratory mosquito population to the

present. Subsequent laboratory research and controlled field trials in China have shown that *Wolbachia* is rapidly assimilated into the general mosquito population and it can make *A. stephensi* inhospitable to the malaria parasites[6,7,8]. The bacterium can also spread into a wild type laboratory population, such that after seven reproductive cycles (generations), 100% of the *A. stephensi* population carries the bacterium and the malaria transmission potential is significantly diminished.

(iii) Rapid Point of Care Detection of Tuberculosis:

MSU researchers have developed a highly sensitive nanotechnology to detect even low levels of the tuberculosis (TB) pathogen in samples (https://msut.technologypublisher.com/technology/48777). This technology is easy (uses nanoparticles, magnets, and a microscope), quick (less than an hour), and inexpensive compared to traditional methods of chest radiography, sputum smear microscopy, nucleic acid amplification, and cultivation of Mycobacterium tuberculosis (Mtb). It can be used as a rapid point-of-care test for humans or animals. Its patent application is pending and it also has copyright protection.

(iv) Naturally Derived Inhibitors of Fungal Toxin Production:

The aflatoxin produced by fungi, such as Aspergillus parasiticus, is dangerous to consume and can be fatal, especially for children and pets. Contamination is an ongoing problem in animal feed and for the brewing and baking industries. MSU researchers have identified several natural products from lichens and black pepper that greatly reduce toxin production by Aspergillus (aflatoxin) and/or Fusarium (DON, deoxynivalenol; https://msut.technologypublisher.com/technology/45618)[9,10]. These products have been structurally identified and the compounds have been isolated. Their chemical synthesis is simple and easily scalable. They can be added to current fungicides to enhance crop protection and can be used to extend crop storage longevity. The patent is pending.

(v) A Potential E. coli Vaccine to Prevent Travelers' Diarrhea:

Enterotoxic *E. coli* strains (ETEC) produce heat-stable enterotoxin (STa), which causes diarrhea (travelers' diarrhea in humans) and animals (scours). No component vaccines against STa have been developed because the toxin is nonimmunogenic and does not stimulate antibody production in infected subjects. MSU researchers have developed an STa-carrier protein conjugate that is highly immunogenic and

could be used to produce very high titers of neutralizing antibodies for therapeutic treatment of traveler's diarrhea and scours (https://msut.technologypublisher.com /technology/7064).

(vi) Mite Zapper:

A mite parasite, Varroa destructor, causes tremendous damage to honeybees in the U.S. and globally. The Varroa mites can kill honeybee colonies within 1-2 years if left untreated. A new and effective method for Varroa mite control was invented at MSU, referred to as Mite Zapper. The "mite zapper" combines mite biology and a heating element inside the comb to kill mites[11]. The technologies such as mite zapper can be effective tools in integrated pest management (IPM) programs which combine all the possible and available methods and tools of pest control[12].

ENTREPRENEURSHIP AT MSU

MSU has programs designed to benefit students, faculty, staff, and the community with entrepreneurship.

(i) Students:

For students, the **Burgess Institute for Entrepreneurship & Innovation** (https://entrepreneurship.msu.edu/) empowers students to learn through action by providing programs, courses, and resources to foster an entrepreneurial mindset, develop empathy, and create new ventures. **MSU Hatch** is a co-working incubator space for MSU students. Its mission is to generate and advance the culture of entrepreneurship in the community and to expand the knowledge-based economy in the market, focusing on student entrepreneurs. The **MSU Broad College of Business** (https://broad.msu.edu/) has programs in accounting, finance, general management, human resource management, marketing, supply chain management and hospitality business.

(ii) Faculty

In addition to **Spartan Innovations** and **Red Cedar Ventures** (described above), MSU faculty have access to the Conquer Accelerator and the University Corporate Research Park. The **Conquer Accelerator** (https://www.msufoundation.org /conquer-accelerator) is a business accelerator program that provides selected teams with ten weeks of intensive programming

on topics like fundraising, technology and longevity, focusing on completing tailored, goal-driven benchmarks. The **University Corporate Research Park** provides spaces that cultivate and enable startup success through its incubator spaces, and also accelerates corporate innovation and research partnerships with MSU.

(iii) Community

In addition to the MSU Innovation Center, MSU also assists in supporting entrepreneurs in local communities to develop and launch new product and service ideas into the food, agricultural, and bioenergy markets through the **MSU Product Center**. The Product Center (https://www.canr.msu.edu/productcenter/) connects entrepreneurs with MSU's technical expertise, research, and outreach services and provides services such as concept development, business development, and market research and analysis.

SHARING MSU EXPERIENCES WITH THE GLOBAL COMMUNITY

(i) International educational training and capacity building programs in IP management and tech transfer

As a global university, MSU's outreach mission extends beyond the boundaries of Michigan to the rest of the world. MSU is known for its success in collaborative research, building global knowledge partnerships, and training and educating researchers, scientists, policy makers, and others worldwide, especially in international agricultural development. Over 1,000 faculty and staff members are engaged in international research and teaching. MSU has 25 internationally focused centers, institutes, and offices and more than 325 partnership agreements with international institutions in over 80 countries.

MSU's World Technology Access Program (WorldTAP; https://www.canr.msu.edu/worldtap/) is actively engaged in building IP management and technology transfer capacity in developing countries, specifically in the areas of agriculture and agricultural biotechnology[3,4]. WorldTAP works in close collaboration with MSU-T and the MSU College of Law in offering international training courses, internships, and workshops. These programs help participants develop and implement institutional IP policies, laws, and management

infrastructure; establish Intellectual Property Offices and Technology Transfer Offices; develop the human resources needed to staff offices, manage programs, develop educational programs, and generate researcher awareness; and create the institutional support and commitment needed for proper IP management[13,14,15,16,17].

A short course on IP management and technology transfer was designed and launched in 1995 and was offered annually for 22 years[18]. Over time, the course evolved to meet the needs of the changing IP landscape, from its original focus on institutional IP policy development, establishing IP offices, and issues related to IP for agricultural biotechnology to its most recent focus on protection, licensing and commercialization of inventions made by public sector institutions[19].

(ii) Successes, Benefits, and Impacts of MSU's IP Management and Technology Transfer Capacity Building Programs

The impact of MSU's international IP management and technology transfer programs has been tremendous in terms of raising awareness and building human resources as well as institutional capacity in IP management and technology transfer at public institutions[20]. During the past 22 years through various programs, MSU has trained more than 500 policy makers, administrators, researchers, lawyers, private sector personnel, and students in various aspects of IP management and technology transfer, and other areas related to technology commercialization. MSU has offered these programs both in the U.S.[21] and internationally (Egypt, Morocco, India, etc.)[22-26], leading to the establishment of new institutional and national policies on IP management and the formation of new technology transfer offices at public research institutions[27].

One notable example is the success of the India IPR project. A 2005 assessment of institutional IP management capacity at public institutions (state agricultural universities; SAUs) in India identified a clear need for a focused program to address and build IP management capacity at the institutional level. Through funding from USAID, MSU, SAUs, and ICAR institutions in India developed and implemented a focused, bottom-up approach to institutional capacity building in IP management and technology transfer, moving beyond generic IPR workshops and seminars to mentorship programs and focused internships and workshops. Institutional IP management policies and IPR Cells and Business Planning and Development Units (BPDs) were first developed and strengthened at

five SAUs and ICAR institutions by 2012[28]. Now, over 100 BPDs are supporting technology IP protection, management, and transfer at public institutions throughout India. More importantly, innovations are getting into the hands of the people who need them most. Other collaborators included U.S. Department of Agriculture- Agricultural Research Service (USDA-ARS), Central Advisory Service on Intellectual Property (CGIAR-CAS-IP), and US Joint Working Group (JWG) in Biotechnology.

Several resources and educational and training materials have been developed through international training and capacity building programs offered by MSU. These include:

(i) The *Basic Workbook in Intellectual Property Management*[29], which is freely available on the website as a global public good (https://www.canr.msu.edu/resources/basic-workbook-in-intellectual-property-management).

(ii) Intellectual Property Rights in Agricultural Biotechnology, 2nd Edition[4].

(iii) Intellectual Property Policies and Technology Transfer Practices in the South Asia Region[25].

(iv) IPR Resource CD was compiled under the India IPR Project and contains various documents and information resources related to IP management and technology transfer.

The enabling environment created through capacity building programs is also leading to licensing of MSU technologies to private companies in developing countries through public-private partnerships.

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Review Article

ZIKA - AN EMERGING VECTOR-BORNE INFECTION OF SERIOUS PUBLIC HEALTH SIGNIFICANCE IN INDIA

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ABSTRACT

Zika virus (ZIKV), is a new emerging threat in India, similar to dengue and chikungunya mainly spread by infective bite of *Aedes aegypti*. The transmission dynamics of diseases are mainly dependent on Aedes management. Although there are a few more modes of transmission of ZIKV like sexual, mother-to-child, and through infected blood transfusion. In India, serological evidence of ZIKV has been reported as early as 1954,

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although, the first four confirmed cases of ZIKV were reported more than six decades later from the states of Gujarat and Tamil Nadu followed by Rajasthan, Madhya Pradesh in 2018 and Uttar Pradesh during 2021, as well as Telangana and Jharkhand. Till the year 2021 about 527 cases were reported from 11 states in India. The ZIKV development in Aedes is dependent on the optimal temperature and humidity in addition to intrinsic factors of the mosquito. Factors like water storage habits, unplanned urbanization, socio-economy, rapid transport, and tourism are some of the major factors which help Aedes-borne diseases spread in urban and rural settings in India. Better management strategy towards Aedes will be a slingshot for all Aedes-borne diseases i.e. dengue, zika, and chikungunya.

Keywords: *Aedes aegypti*, Transmission, Extrinsic Incubation period, Environmental factors

INTRODUCTION

Zika has made a frequent appearance in India since being reported in Gujarat (3 cases) in 2016, thereafter about 527 cases were reported from different states[1]. The dengue similar mosquito- borne diseases reported high incidences during the same duration about 1,29,166 in 2016, and 1,23,106 in the year 2021[2-3]. Globally zika has made an appearance in 90 countries after its first appearance in 1947 in Uganda and millions are at risk of ZIKV. In India, ZIKV outbreaks were witnessed in seven states since 2016 (Fig. 1). Whereas a study conducted on the samples stored conducted by ICMR–National Institute of Virology showed more cases totalling to 11 states presenting the ZIKV infection including Delhi in 2021[4]. Zika has milder fever disease unlike dengue high-grade fever but it is associated with microcephaly in children and Gullian-Barre syndrome in adult humans[5]. The disease spread is majorly from the infective bites of Aedes mosquitoes. Besides the main vectors, viz., *Aedes aegypti*, and *Ae. albopictus*, the ZIKV had so far been isolated from other vectors *i.e. Anopheles gambiae*, *Mansonia uniformis*, and *Eretmapodites*[6]. In India, primarily *Aedes aegypti* was found to be incriminated for ZIKV transmission[7]. ZIKV can also be transmitted through the sexual route and from mother to child and through infected blood transfusion.

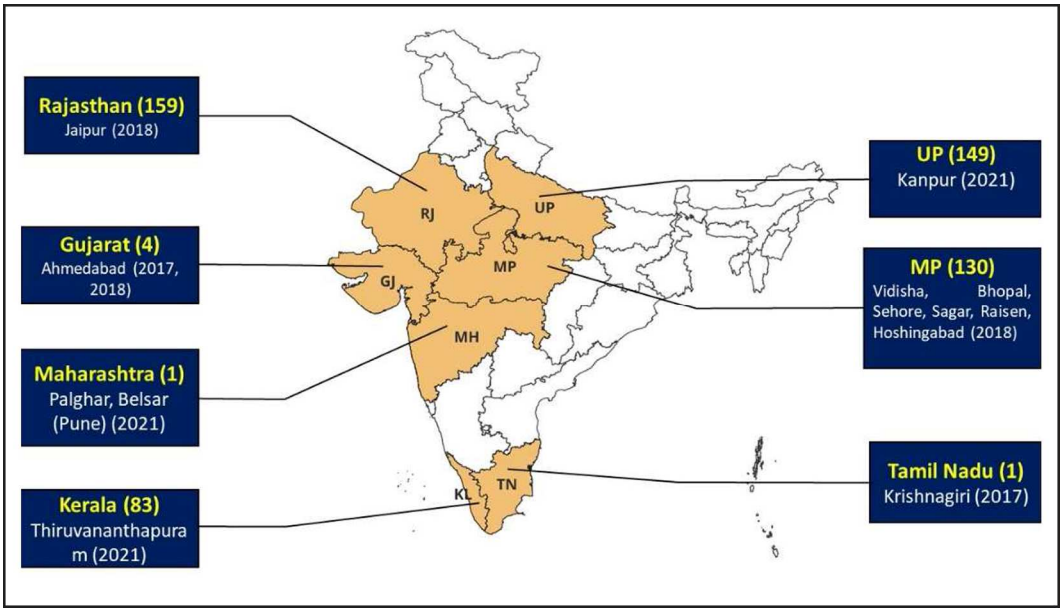

Fig. 1. Outbreaks reported in India from 2016-2021 (*Source*: from authors GIS Based Map of study areas)

ZIKV is a positive sense RNA arbovirus with ~1100bp genome and belongs to flaviviridae family. It is closely related to dengue, yellow fever, JE, and West Nile viruses. Similar to the dengue virus it is also transmitted through mosquitoes, it is perplexing to note that the ZIKV incubation period in the mosquito is very less *i.e*. 2-7 days only in contrast to the Dengue virus which is about 7-14 days (Fig. 2). The less incubation period shows more efficient multiplication in the mosquito to become infective which may be one of the reasons to have more cases in a short duration. The study also showed that the virus may alter the oviposition preference of *Aedes aegypti*[8]. It was also observed that the presence of the virus in the mosquito system hampers the viability of the eggs and their number[9].

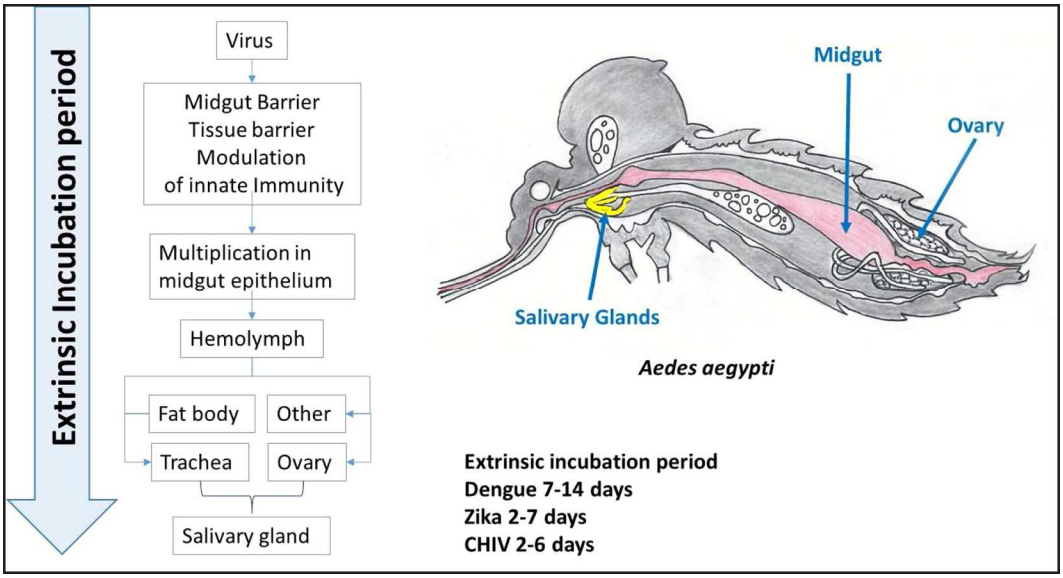

Fig. 2. Virus multiplication in mosquitoes.

ZIKA VIRUS MULTIPLICATION

While biting an infected person, the mosquito picks up ZIKV along with the blood, which it collects in the mid-gut. Being a major barrier most of the pathogens are discarded due to mosquito's innate immunity whereas, in the case of ZIKV and other arboviruses, they have attachment potential with mid-gut they cross the barrier and multiply in the mid-gut epithelium. The virus then infects fat bodies ovaries *etc*. and at last, attracted to the salivary gland for maturation the duration required for this is known as the extrinsic incubation period which is reported ass 2-7 days in ZIKV in contrast to dengue (7-14 days) and chikungunya (2-8 days)[10] (Fig. 2).

FACTORS AFFECTING VIRUS MULTIPLICATION

(1) Temperature: The mosquito longevity and dispersal depend upon ambient temperature; at 25-27 °C optimal growth of ZIKV was studied in *Aedes aegpyti*[11]. Temperature not only impacts on survival of vectors but also alters the susceptibility status of mosquitoes to viruses and other pathogens[12,13]. In addition to external factors like temperature, pH, humidity, and rainfall some

intrinsic factors like susceptibility to the virus, immunity, gut flora, and presence of *Wolbachia* may also alter the capacity of virus development in the mosquito. During the colder season, due to low metabolic rates, the virus multiplication slows down as a result incubation period extends and infectivity in the mosquito is delayed and less lifespan is available for transmission (hypothetical) unlike in warmer optimal temperature conditions of 25-27 °C which supports longer life span and shorter incubation period[11] (Fig. 3).

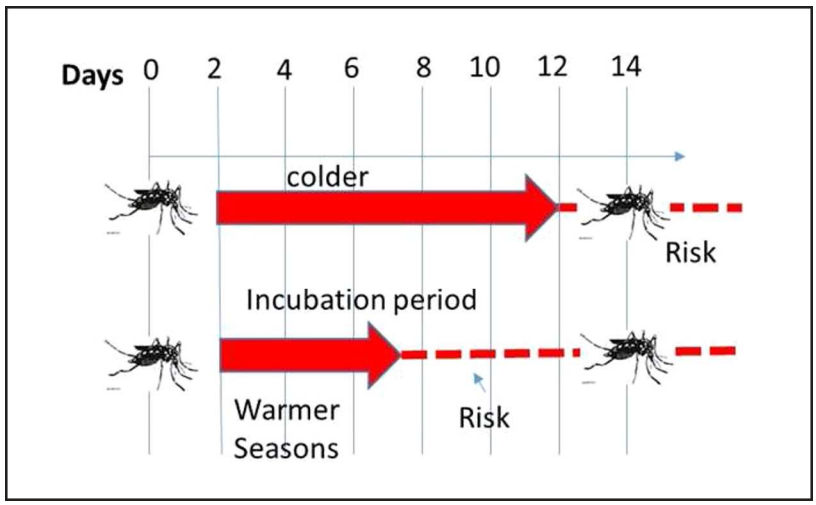

Fig. 3. Role of Temperature in increasing transmission risk during different seasons

(2) Rainfall: Rainfall reduces interspecific computation by increasing the availability of breeding sites in the rainy season it reduces the temperature of summer extreme and provides ambient humidity quotient Studies have shown that there is a lag period between rainfall and the appearance of cases due to incubation periods in mosquitoes and human after built-up mosquito density in the rainy season (October-November)[14]. Rains have a positive correlation with the transmission of mosquitoes hiding inside houses due to extreme temperature and low humidity during May-June get change for dispersal in August and September due to ambient conditions outside. The seasonal pattern in cases is witnessed due to rains[14].

CONSTRAINTS FOR *AEDES*-BORNE DISEASES

Aedes is a highly anthropophilic invasive and efficient vector for DENV, ZIKV, and CHIK viruses. There are several other factors like day biting and multiple host feeding increase the vectorial capacity many folds. *Ae. aegypti* was found to be more competent to transmit zika than *Ae. albopictus* and *Cx. quinquefasciatus*[15]. As a day biter mostly the biting site remains hidden working places are never considered a site of infection as a result of which these sites remain out of any control activity if they are contributing to transmission. The host may not remember the exact place where he might have been bitten by mosquitoes as the outcome of diseases comes after an incubation period of 8-10 days. Due to this pre-patent period (incubation period), the host remains healthy and may transmit to several other places due to the fast and easy transportation system locally and overseas as well.

Transovarial transmission (TOT) studies have shown that once Aedes vectors get an infection by arthropod-borne viruses these can be transmitted to their coming generations demonstrated that the dengue virus can be transmitted for up to 7 generations and this acts as a natural reservoir for virus stocks in the dried eggs also which can hatch after one year also[9]. Studies have shown that *Aedes aegypti* and *Aedes albopictus* both can vertically transmit ZIKV to the next generations whereas Culex could not propagate the virus to the next generation[16-18].

Retention of eggs for more than one year is also another complication. Studies have shown that the eggs remain viable and persist for up to one year in they are laid in shades. There are several cryptic breeding sites where the Aedes select to breed and lay eggs. These sites remain hidden and eggs being small sized[19].

Variability in breeding sites of *Aedes* is another complex feature as it likes to breed in artificial containers of any size from the cap of a bottle to swimming pool-sized tanks mostly clean potable water is selected by *Aedes aegypti,* especially whereas *Aedes albopictus* like mainly outdoor natural habitats like a tree. Inhabitants of different socioeconomic levels store water mostly due to intermittent supply and uncertainty of water supply in metropolitan cities in India. The places like dump yards, solid waste disposal confiscated dump yards, Stores, engineering workshops and police makhanas (Places to keep seized vehicles) always pose a challenge for breeding control in Delhi[20].

Despite efforts from the health department and national program the diseases persist and appear every year this warrant a need for research to find the natural reservoir, asymptomatic contributors, etc. Concurrently vectors are changing behaviour such as biting time, and resting habits, and are continuously developing resistance to existing public health insecticides. Changing land use patterns and villages are developing into cities. In the existing control efforts manpower, the reach of control activities is never adequate due to high population pressure also. It is also evident that vector-borne diseases are increasing their horizon and distribution to several countries and the threat of new vector-borne diseases is always suspected.

Control over the transmission of ZIKV and other Aedes-borne diseases is achievable with efficient awareness programs, community engagement, behaviour alteration towards water storing habits, source reduction, and avoiding bites of mosquitoes. In addition to this strengthening of existing vector control systems adopted by state health departments by integrating newer tools, that have more reach and efficiency over conventional activities. Better urban and rural development and construction planning are required to reduce mosquito genetic conditions through effective engineering. Proper solid waste management is crucial in preventing the breeding of mosquitoes outdoors. An effective control plan should be started very early before the transmission season[21]. There is no or limited surveillance being observed in public places, offices, railway stations community centres, religious gathering places, etc. Inter-sectoral coordination and engagement of officials and staff of these areas can also help in the reduction in transmission of such arthropod-borne diseases.

CONCLUSION

The global risk of Zika is increasing due to the presence of *Aedes aegypti* in most tropical countries. Rapid urbanization, changing bio-ecology, temperature and humidity, faster modes of travel and tourism, vector-borne diseases like dengue, chikungunya, and now Zika have also successfully invaded several states of India. The emergence of Zika has registered attention worldwide and alerted the public health system of the affected countries The global risk of Zika is directly proportional to the increasing habitats of *Ae. aegypti* in most tropical countries There is an urgent need for effective vector management focusing on *Aedes*

mosquitoes through regular surveillance and monitoring for ZIKV in India. We advocate a year-round systematic surveillance program on emerging and re-emerging arboviral infections such as Zika, Dengue, and Chikungunya in the human host as well as the vector species to tackle and prevent impending outbreaks of arboviral diseases in the Country.

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Exploratory Review Article

A PERSPECTIVE ON AEDES-BORNE VIRAL DISEASES, WITH SPECIAL REFERENCE TO DENGUE

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ABSTRACT

The world today is passing through a truly challenging time because of the COVID-19 pandemic and global warming. At the same time, vector-borne viral diseases have been causing about 17% of all infectious diseases globally. Among these about 90% are caused by mosquito vectors and cause a colossal public health problem with their continued emergence and resurgence. In the 21st century well-connected globalized world, the ecology of mosquitoes is likely to be reshaped by the changes attributed to global warming, deforestation, urbanization, and

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changes in land-use patterns with increased trade, travel and commerce. Diseases such as dengue fever (DENV), chikungunya fever (CHIKV), Zika fever (ZIKV), and yellow fever (YFV) are thereby expanding to hitherto unaffected areas causing severe health concerns. A striking commonality between these diseases is that they are all *Aedes*-borne viral diseases. Barring yellow fever, the other three viral diseases namely dengue, chikungunya and Zika have all been endemic to India. However, India is considered to be a 'Yellow fever receptive area'. Another interesting perspective on these *Aedes*-borne viral diseases is that their ancestral roots have all been sourced back to Africa. That being said, there are several other viruses such as Ebola, monkeypox etc. which have similar origins in Africa, and are also potential international challenges indicating a plausible 'African hotspot' for vector-borne viral diseases in humans. In fact, the WHO estimates that the dengue virus puts about 40% of the world's population at risk of infection with more than 100 countries endemic to the disease at present. The NCVBDC data also shows an increase in dengue case incidences from 188401 in 2017 to 193245 in 2021. Furthermore, from the perspective of *Aedes*-borne diseases, in recent times, *Ae. vittatus* and the transmission of Usutu virus disease have emerged as epidemiologically important vector species and arboviral disease respectively. Apart from mosquitoes belonging to the *Culex* sp., the potential of *Aedes albopictus* in the transmission of the Usutu virus has also been reported. However, despite having a wide range of distribution and transmission potential, *Aedes vittatus* has not been given enough attention as the other widely recognized arboviruses vectors like *Aedes aegypti* and *Aedes albopictus*. This study is an attempt to understand and analyze the various eco-epidemiological perspectives of Aedes-borne viral diseases in the changing environment.

Keywords: Aedes-vector, climate change, conservation medicine, deforestation, reservoir, virus

INTRODUCTION

Since time immemorial, viruses have been coexisting with their reservoir hosts through co-evolution, thereby maintaining an ecological equilibrium in nature. However, with the passage of time, the world today is confronted with the emergence and re-emergence of various viral diseases having both epidemic and pandemic potentials[1]. 17% of all infectious diseases are vector-borne and about 60% of all emerging infectious diseases are zoonotic in nature. Additionally, research has shown that 72% of these zoonotic diseases originate from wildlife[2,3,4]. A significant cause of concern from arboviruses continues to generate severe public health and economic burden globally, especially for those living in endemic regions[5]. This could largely be attributed to globalization including changes in land-use patterns, rapid urbanization, rampant deforestation, global warming and climate change; consequently disrupting and altering the ecological niche of the reservoir hosts[1]. Currently there are more than 600 known arboviruses that are recognized by the Centers for Disease Control and Prevention in their list of arboviruses and related zoonotic diseases. Out of these, about 80 of them are recognized as known human pathogens[6]. Interestingly, the human pathogenic flaviviruses, including Yellow fever virus (YFV), Dengue virus (DENV), Zika virus (ZIKV), and the alphavirus Chikungunya virus (CHIKV) have their origin in Africa and are all primarily transmitted by the native African mosquito- *Aedes aegypti*. In fact, the very first origin of humans can also be traced back to Africa, thus indicating a hitherto unexplored coherent connection[5,7,8,9]. The World Health Organization has reportedly estimated approximately 3.9 billion people are at risk of dengue virus infections per year. In recent years, dengue has become a major public health problem, particularly in Southeast Asia and the Americas, with severe outbreaks and dramatic increases occurring in various parts of the world with no specific treatment whatsoever[5,10,11]. It is noteworthy to mention here that all these viruses share common ecological, evolutionary, and epidemiological patterns, having originated in forests and involving transmission cycles between sylvatic forms of *Ae. aegypti* and other wild *Aedes* species such as *Ae. africanus,* playing a supporting and/or complimentary role in virus transmission in semi-urban/rural and sylvan environments[8]. This study is an attempt to understand and analyze the various perspectives of *Aedes*-borne viral diseases, in the context of changing environmental conditions.

METHODOLOGY

The study was conducted using several databases available online including Google scholar, Semantic Scholar, PubMed/Medline, Semantic Scholar, ScienceDirect and ResearchGate up to the year 2022. All searches performed for this review were done using the English language for both peer-reviewed and not peer-reviewed journal articles. The search was initially conducted on PubMed using keywords such as '*Aedes*-vector', 'virus', 'zoonosis', 'Africa', 'global warming', 'climate change' in a combinatorial manner. Later, relevant keywords from within the articles and/ or abstracts were included in our repository to expand the search domain. A similar approach has been followed for all other databases.

The data on case incidences along with the data for deaths for calculation of Case Fatality Rate were collected from the National Centre for Vector-Borne Disease Control website (accessed on 10 Apr 2023). The data on the populations at risk, global disease burden and percentage of emerging infectious diseases were taken from the Factsheet of the World Health Organization (accessed from 10 - 25 Apr 2023).

All the findings, observations and comments mentioned in this study pertaining to the focused topic are based solely on information that has been published and listed in the reference section.

RESULTS

(1) Dengue Virus (DENV) and Chikungunya (CHIKV)

The 21st century world is faced with a challenge from emerging and re-emerging mosquito-borne viral diseases flaring up in several countries including India, such as Dengue, Dengue Haemorrhagic fever (DHF) as well as Chikungunya (CHIKV) which were formerly under control[12,78]. Dengue is one of the most widespread Flavivirus considered to be a neglected tropical disease and a re-emerging pathogen which has expanded to its full potential both regionally and globally[6,13,14]. The WHO estimates that half the world's population are now at risk for dengue with 5.2 million case incidences in 2019 and an estimated 100-400 million infections occurring each year. Case fatality rates (CFR) of dengue have shown to vary from 0.17% in 2017 to 0.07% in 2022 (Fig. 1). Additionally, the dengue case incidences are shown to vary from 188401 in 2017 to 193245 in 2021 indicating a steady

increase (NCVBDC). Dengue virus has a single-stranded positive-sense RNA genome which encodes three structural (C, capsid; prM/M, precursor of membrane; E, envelope) and seven non-structural (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) proteins with genetic variation between each of its identified serotypes[15,16]. There are four distinct dengue viruses- DENV-1, DEN-2, DENV-3 AND DENV-4, which differ both phylogenetically and antigenically. While infection with one type provides long-term immunity to that specific kind, it does not confer immunity for the other three types[18,19].

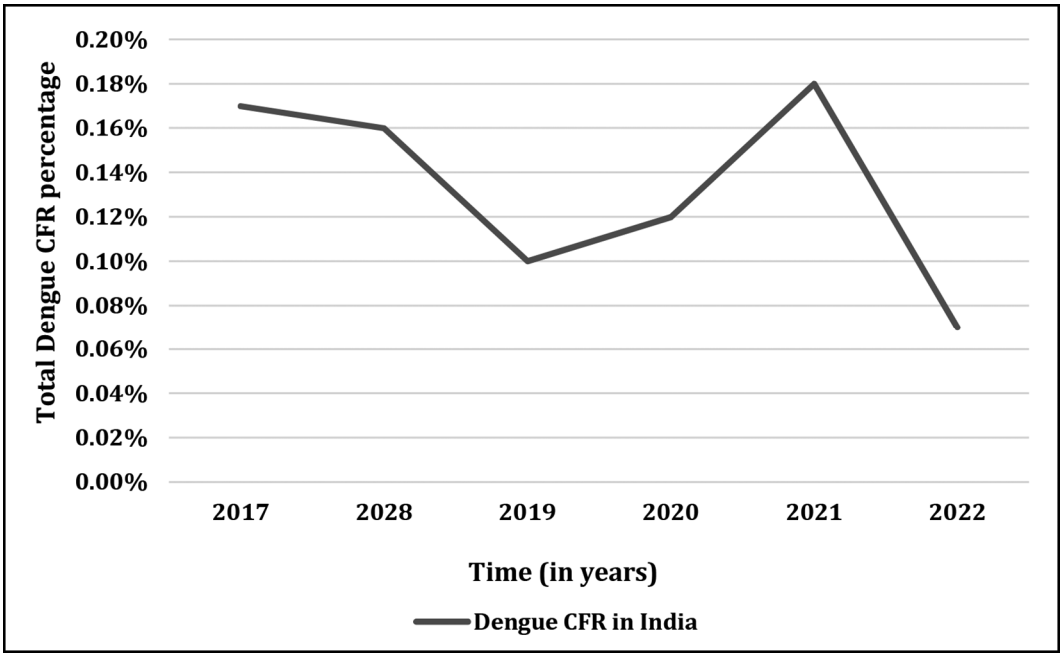

Fig. 1. Projection of Case Fatality Rate (CFR) of dengue across India between 2017- 2022 (NCVBDC Data)[17]

Similarly, Chikungunya (CHIKV) has also been identified as one of the major re-emerging mosquito-borne viral diseases, especially in India, although has now spread to various parts of the world[9,12,20]. At present, CHIKV has been identified in more than 110 countries with a two-fold increase in case incidences in 2022, reporting a total of 2,73,685 cases[21]. Although the case fatality rate (CFR) of Chikungunya is relatively low, the number of suspected CHIKV cases increased

from 67769 in the year 2017 to 108957 in the year 2022 (NCVBDC). The CHIKV genome is made up of a positive sense single-stranded RNA having 3 distinct genotypes, namely, Western African, East Central South African and Asian[12,79].

It is, however, noteworthy to mention here that according to the reported data by the National Center for Vector Borne Disease Control (NCVBDC), the incidences of dengue cases are found to be significantly higher than that of chikungunya cases (Fig. 2).

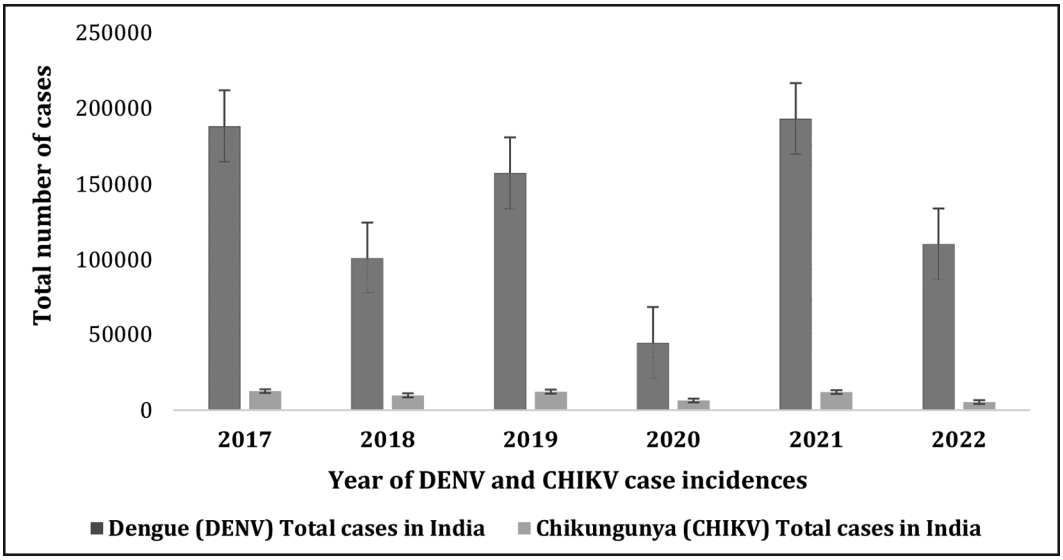

Fig. 2. Comparison of confirmed DENV and CHIKV cases in India between 2017-2022 (NCVBDC Data)[22]

(2) Zika virus (ZIKV) and Yellow-fever virus (YFV)

Zika virus is a Flavivirus which was first identified and isolated in the year 1947 from sentinel rhesus monkeys from the Zika forest in Uganda, Africa[23,24,25]. Before 2007, only 14 known human infection cases of ZIKV were reported, Although it was endemic in certain parts of the world[23,26]. Since then, it spread to various parts of Africa, Asia, the Americas and the Pacific with WHO declaring it as a Public Health Emergency of International Concern (PHEIC) in the year 2016. The very first report of Zika virus reported from India has been from Gujrat and recent reports of its incidence from Kerala have been confirmed in 2021[27].

Alongside ZIKV, the Pan American Health Organization reports that the Yellow Fever Virus (YFV) of the *Flaviviridae* family has been estimated to cause nearly 30,000 deaths with around 2,00,000 cases every year globally. Interestingly, YFV having originated in Africa and subsequently spreading to various parts of the world similar to the other arboviruses, there have been no reports of YF case introductions in India and it continues to be a "Yellow fever receptive area" despite having a conducive environment for its transmission[28,29]. A strong hypothesis may suggest that high population sero-prevalence of dengue, JE and other flaviviruses such as WNV and Zika in Asia, may result in a cross-protective immunity to the introduction of YF in Asia. Another possible explanation of the same could be a difference in the strain variation of *Ae. aegypti* throughout the world. The Asian strains of *Ae. aegypti* showed lower vector competence than their African and American counterparts[30,31,32,33]. Nevertheless, the 21st century world, a well-connected globalized village, with its means of air and water mobility has facilitated the probability of many imported cases of viral diseases that were originally absent in that region and yellow fever is no exception[31,33,34]. Besides that, the usage of such viruses in the context of bioterrorism and biological weapon warfare by the enemies of humanity is a possibility that might not be ruled out entirely. Hence, the authors are hesitant to be complacent at this critical juncture as this does not necessarily disregard the possibility of a future outbreak of Yellow Fever Virus in India.

VECTORS, VIRUSES AND VERTEBRATE RESERVOIRS

Arboviruses survive by virtue of alternation between vertebrate and invertebrate hosts in a cycle where man gets the infection tangentially on an accidental intrusion in the pathway. However, the interaction between animals and arboviruses is a dynamic phenomenon and as time passes, some of the vertebrate hosts could eventually transform in epidemiologically crucial ways and consequently attain the status of a potential reservoir/amplifying hosts of the virus, especially considering the changing climate and environment due to anthropological activities[36]. The point of origin for ZIKV and CHIKV evolution, much like YFV, is believed to have occurred in the arboreal cycles involving nonhuman primates (NHPs) and sylvatic mosquito vectors of the *Aedes* genus in sub-Saharan Africa[37,38,39,40]. The diseases being primarily zoonotic in nature, these viruses exist primarily and primitively in wild homoeothermic vertebrate hosts such as mammals or birds and are thereby

disseminated by sylvan or wild vectors. They can be maintained in enzootic and epizootic sylvan cycles in non-human primates[35,36]. It might be noteworthy to mention here that the isolation of ZIKV, DENV and CHIKV from mosquito species other than *Aedes* such as *Cx. quinquefasciatus* has added a new dimension to the disease epidemiology with some of them acting as complementary vectors. As a matter of fact, there have been several conjectures on a kind of adaptive coevolution existing between *Aedes* with that of ZIKV and DENV creating stabilizing selection pressure on different viral genotypes that can have a catastrophic effect for the future[15,23]. The different vectors, reservoirs and suspected reservoirs of these arboviruses are provided in Table 1.

Table 1. Vectors and reservoirs of arboviruses

Virus family	Arboviruses	Major vector(s)	Reservoir/ Suspected reservoir(s)	Endemic region(s)	References
Flavivirus	DENV (DENV-1 DENV-2 DENV-3 DENV-4)	*Ae. aegypti* *Ae. albopictus*	Primates (monkeys and humans)	Africa, Asia, South America, Pacific	5, 6, 8, 41, 42, 69
	ZIKV	*Ae. aegypti* *Ae. albopictus*	Non-human primates	Africa, America, Asia, Pacific	5, 6 69, 70, 71, 72, 73, 81
	YFV	*Ae. aegypti* *Ae. albopictus*	Primates	Africa, South America	5, 6, 69, 74, 75
Alphavirus	CHIKV	*Ae. aegypti* *Ae. albopictus*	Primates, bats, rodents	Africa, Asia	5, 6, 76, 77

DISCUSSION

(i) Global warming, deforestation and *Aedes*-borne viral diseases

Arboviruses by definition are those viruses which are transmitted by arthropod vectors to a mammalian host[6]. Apart from dengue (DENV), other Aedes-borne arboviral diseases include chikungunya (CHIKV), Zika (ZIKV) and yellow fever (YFV)[5,7,41,42]. These viruses have a long history of infecting humans, but in recent years their spread has been facilitated by the 21st century globalization of a well-

connected world and the expansion of interconnected communities with changes in land use patterns coupled with travel, trade and commerce[15,37]. Mosquitoes only become the vectors of the arboviruses when they get infected while taking a blood meal from an infected host and these are the viruses which are characterized by either a single-stranded RNA genome or a double-stranded DNA[5,6,43]. It has been widely identified that single-stranded viruses, as a matter of fact, appear to mutate much faster than double-stranded viruses do and therefore have a great potential for genetic variability[15,44]. Nevertheless, climate change in addition to rampant deforestation may act as a selection pressure for these viruses, increasing their probabilities of mutation[45]. Hales *et al.,* reported an association between climatic variables such as temperature, rainfall and humidity to dengue outbreaks[12,80]. Currently, anthropogenic activities such as mining, road construction, mining, logging and agricultural development altogether pave the way for large-scale felling of trees, consequently leading to deforestation. The trend in urbanization as a result of rampant deforestation is thought to have provided ample opportunities for the vectors to interact directly with these arboviruses which have expanded their territory[46]. As a consequence, viruses such as Dengue, SARS, Ebola etc. have emerged and re-emerged in the past decade as a concern of global importance. Similarly, several other viral diseases such as Zika fever or Yellow fever have expanded and/or have found potential to expand to newer territories, causing massive outbreaks[47].

(ii) Africa- An evolutionary hotspot for vector-borne viral diseases in humans

The role of *Aedes aegypti* and *Aedes albopictus* as primary and/or complimentary vectors respectively, in maintaining and eventually transmitting arboviral diseases, has already been established[9,15,48,49]. It is interesting to note here that out of those 3,500 species of known mosquito vectors, it is *Aedes aegypti* which has been the cause of almost all major *Aedes*-borne viral epidemics including Dengue, Zika, Chikungunya and Yellow-fever[9]. *Aedes aegypti* is a mosquito vector which is native to Africa and has become particularly well suited to urban environments[14,50,51,52]. It is noteworthy to mention here that several findings have confirmed the origin of the first modernized humans from Africa as well.[82] Additionally, there also seems to be a disproportionately large percentage of mosquito-borne arboviruses, such as Zika, yellow fever, chikungunya and likely the dengue virus as well, originating from Africa, which has a severe public health impact globally[9,28]. Monkeypox and Ebola

virus have caused severe human epidemics, once again having their origin and emergence in Africa[2], indicating Africa to be an evolutionary hotspot for emerging infectious zoonotic diseases and their vectors. Moreover, at present the "domesticated" variant of *Ae. aegypti* has begun exploiting new niches and breeding in man-made artificial containers, albeit, they were previously breeding in natural containers *i.e*. tree-holes. Evidently[9,53,54,56], an all-encompassing view of the current situation of arboviruses and their vectors suggests an exemplary example of an "African evolutionary hangover" of their origin, emergence and behaviour.

Currently, the projections from the United Nations indicate the likelihood of an increase in the global human population from the current 7 billion people with Asia and Africa as developing countries, contributing about 86% of the world's urban population growth overall.[28,55] This has huge implications in the context of globalization of human trade and commerce, developmental advancement, and air and water travel links, increasing the risk for diseases, and thereby obliterating virus-vector boundaries.

(iii) Arboviral vectors: Recognized, undervalued and neglected

In the preface of rising arboviral disease, both *Aedes aegypti* and *Aedes albopictus* have thoroughly taken advantage of climate change, rapid urbanization, rampant deforestation and international trade and travel, to transmit the dengue virus[57]. It is believed that both these vectors have already become endemic to many novel geographical regions[6]. The geo-political boundaries between vectors and hosts have been blurred as a result of rampant deforestation and large-scale urbanization. Consequently, the virus may accidentally spill over to humans and other novel hosts[12,23]. Transovarian transmission of viruses has also been reported from these *Aedes* species. In the urban scenario where non-human hosts are unavailable, survival of these viruses within their vectors in nature is possibly maintained by both male and female *Aedes* vector species as a result of transovarial transmission, especially in the inter-epidemic period[15,23,58]. While *Aedes aegypti* is widely distributed worldwide, particularly in the tropical and subtropical regions, *Ae. albopictus* is a mosquito having enhanced ecological flexibility and representing a greater geographical expansion, thus referring to it as a 'global vector'[6,23,50,56,59,60]. Recent findings in the North Bengal district of West Bengal, India, have shown several patients to be affected by either dual, triple or all four serotypes of DENV, all at the same time in different combinations, thereby creating a 'Super-

infection'[13,15,61,62]. These different serotypes of dengue exhibit intra-codon recombination events that in turn maintain extensive purifying selection pressure[15,61]. They exhibit antigenic variation and are seen to quickly adapt to different eco-climatic zones leading to the emergence of genetically diverse viral strains and a potential reason behind the emergence of a new variant serotype- DENV-5[15,44,63]. However, further reconfirmation about the status quo of DENV-5 is required.

Although *Ae. aegypti* and *Ae. albopictus* are globally recognized vectors of arboviral diseases, few studies have also highlighted the role of another mosquito belonging to the *Aedes* species, namely *Aedes vittatus* having a significant role in the epidemiology of DENV, ZIKV, and CHIKV as well as YVF. The serotype DENV-2 has also been isolated from *Ae. vittatus* in Africa, which although does not cause any form of human infection but has been shown to circulate in sylvatic populations[46]. Despite having reports of isolation of the virus from the wild-caught *Ae. vittatus*, it has hitherto been neglected and/or undervalued. Similarly, *Culex quinquefasciatus* has also been suggested as an important vector surrounding the aforementioned viruses, barring YFV. Although *Cx. quinquefasciatus* has been associated with other diseases, the importance of this 'smart vector'[15] in the transmission of SLEV, ZIKV, CHIKV, WNV, JEV and VEE has been overlooked. Nevertheless, although the mere isolation or detection of a virus from the mosquito does not confirm its vectorial status[1,15], the authors are hesitant to disregard the potential of these vectors in future epidemics, if any. On the other hand, there have been several reports suggesting the isolation/detection of Usutu virus (USUV), a *flavivirus* belonging to the Japanese Encephalitis Virus serocomplex from *Aedes albopictus* as well as from *Culex* species[8,65]. The Usutu virus was discovered in South Africa in 1959 and evidence suggests that its life cycle requires mosquitoes as vectors with birds as amplifying hosts. The virus may spill over to humans and horses accidentally during its transmission[65]. Recently, different genetic strains of the USUV are seen to be co-circulating with the West Nile Virus (WNV) in different areas and spreading to a number of European countries. This raises an important epidemiological concern of public health importance and deserves enough attention and increased awareness from the public health sector and authorities.

(iv) One health and conservation medicine

The complex interrelationship between emerging and re-emerging zoonotic diseases and deforestation resulting in biodiversity loss has a crucial role in the emergence

of novel pathogens and altering the disease dynamics in multiple ways. In such a scenario the authors rely on the approach towards 'One-health policy'[68] and 'Conservation medicine'[66,67] that practically focuses on sustainable environmental health altogether, taking together humans and the flora and fauna and thereby developing health management policies and practices. Since the loss of biodiversity globally affects the welfare of both man and animal accompanied by the variations in climate and environment exacerbating the situation, 'Conservation Medicine' stands as a truly collaborative and integrated endeavour to mitigate the rising concerns for controlling and preventing all the emerging and re-emerging infectious diseases. The 'One-Health' concept together with 'Conservation medicine' could be an effective strategy to contain and prevent the spill-over of vector-borne zoonotic viral diseases and thereby reduce their disease burden. However, the assumptions for this approach require further validation by structured studies in this direction[67].

CONCLUSION

Aedes-borne viral diseases, particularly dengue, pose a significant public health threat in many countries. The incidence of arboviral diseases has increased dramatically in recent years, with dengue emerging and re-emerging as an endemic in many tropical and subtropical regions. Even with the global expansion of these arboviral diseases of public health importance, not enough attention is given to its vector surveillance, control and prevention. The primary vector for transmission of these arboviruses is *Aedes aegypti* and in some situations *Aedes albopictus*. Hence, prevention of *Aedes*-borne viral diseases relies on a combination of vector control and personal protective measures. In this regard, an inclusive understanding of the interactions between the host and virus is essential to completely assess the factors that modulate their expansion to newer geographical locations. There is currently no specific antiviral therapy or supportive treatment available. Thus, fully comprehensive genome sequencing studies and molecular analysis of such *Aedes*-borne viruses and their strains are required to study the evolutionary trends so as to come up with necessary therapeutic measures. Apprehensions are being raised in certain quarters regarding the hitherto undervalued and neglected vectors of these tropical and sub-tropical diseases. Early recognition of these severe diseases and prompt management of complications is critical in reducing significant morbidity and mortality. Moreover, it is also necessary to assess these *Aedes*-borne viral diseases in light of their origin from a single ancestral root in Africa. In such

changing epidemiological scenarios with environments conducive to emergence, re-emergence and the sporadic outbreak of all these *Aedes*-borne diseases, the authors strongly emphasize a 'One-health Policy' approach having a structured public-health policy, sustained surveillance, vaccine reinforcement, formulation of area-wise strategy and epidemic preparedness with thorough approval from public health policymakers to combat and contain the future outbreak, if any.

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Conflict of Interest

There is no conflict of interest.

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Original Review Article

PROBABILITY OF ELIMINATION OF TARGETED VECTOR BORNE DISEASES BY 2030: INDIAN PERSPECTIVE

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ABSTRACT

Malaria, Lymphatic Filariasis (LF) and Visceral leishmaniasis (VL) are the three vector-borne diseases targeted for elimination in India in pursuit to achieve the SDG goal. There have been significant achievements in reducing 89% of malaria cases in India. Population living at risk for LF has been reduced as only 134 out of 328 districts are undergoing the preventive chemotherapy of mass drug administration (MDA) and in rest, MDA has been stopped. VL cases have also been reduced to

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1276 cases in 2021 as opposed to 8000 in 2015. The regular assessment and feasible course correction in strategic approaches viz., diagnostics and treatment with incentivization to grass root workers have led to globally recognised achievements. Considering the last mile challenge, emphasis has been to focus on intensified implementation of programme activities with enthusiastic and committed implementers prioritizing integrated or a mix of integrated and vertical approaches. It is important as the process of validation and certification of having achieved elimination are time-consuming. Validation for malaria elimination requires evidence for no indigenous case, subnational validation, ensuring prevention of reintroduction (PoR) policy, claim for national certification and then wait for response of WHO. Similarly for LF, validation requires evidence of successful completion of three transmission assessment surveys (TAS) at the interval of 2 years between each TAS. In addition, establishment of Morbidity Management and Disability Prevention (MMDP) clinics in all endemic units and implementation of vector control need to be reflected in the dossier for certification of elimination. In case of VL, the preconditions of epidemiological surveillance, adequate access to diagnosis and treatment need to be fulfilled followed by sustenance phase of cases below 1 per 10 000 population for at least three consecutive years. Validation process starts when such reports are submitted to WHO and the international validation team (IVT) reviews them. The probability of achieving elimination thus depends on evidence of zero indigenous malaria cases, clearance of TAS by all LF endemic districts and sustenance of VL cases below 1 per 10000 population in all endemic blocks for 3 years. All such processes, guidelines and risk factors in achieving elimination therefore need to be repeatedly disseminated which should be user-friendly and feasible so that target is achieved by the year 2027 and remaining period of 3 years is used for validation.

Keywords: malaria, filariasis, kala-azar, elimination, validation, vector borne disease

INTRODUCTION

In India, the major vector-borne diseases, namely malaria, lymphatic filariasis (LF), kala-azar, dengue, chikungunya and Japanese encephalitis (JE), are covered under the National Centre for Vector-Borne Diseases Control (NCVBDC), which runs an umbrella programme National Vector-Borne Diseases Control Programme (NVBDCP), under overarching of National Health Mission for prevention and control of these vector-borne diseases[1]. Of these, malaria, kala-azar and lymphatic filariasis (LF) have been targeted for elimination. The states are responsible for programme implementation, whereas the NCVBDC, Dte. GHS, MoHFW, and GoI provide policy guidance, and logistics to the states. During the last 4 decades, the country has witnessed an increasing load of vector-borne diseases, causing many morbidity and mortality. Diseases like dengue, chikungunya, Japanese encephalitis, and tick and mite-borne diseases are spreading to newer areas and continue as a crucial public health concern[2].

In pursuit of global strategy and commitment, India has initiated the elimination campaign of three vector-borne diseases, namely malaria, lymphatic filariasis and kala-azar. The goal of achieving elimination has been rescheduled aligning with sustainable development goals (SDG)[3] in respect of malaria and LF whereas for kala azar, it is targeted by the end of 2023.

Before the probability of elimination of these VBDs is discussed, it is important to understand the situation of these diseases and the challenges in achieving the elimination.

MALARIA

It is well known that about 95% population in the country (approximately over 1.2 billion) resides in malaria-risk areas, and 80% of reported malaria cases are from 20% of the population residing in tribal, hilly and hard-to-reach areas[4]. India achieved a reduction of about 86% in malaria morbidity between the years 2015 and 2021 reporting about 158326 cases against 1169261 in 2015[5]. The significant reduction in malaria cases has led to the shrinking of the malaria map in recent years and thus optimism for achieving its elimination by 2027 with zero indigenous cases and sustaining it for the next three years to realize the goal by 2030. The high-burden states have achieved the status of low burden category as shown in Fig. 1.

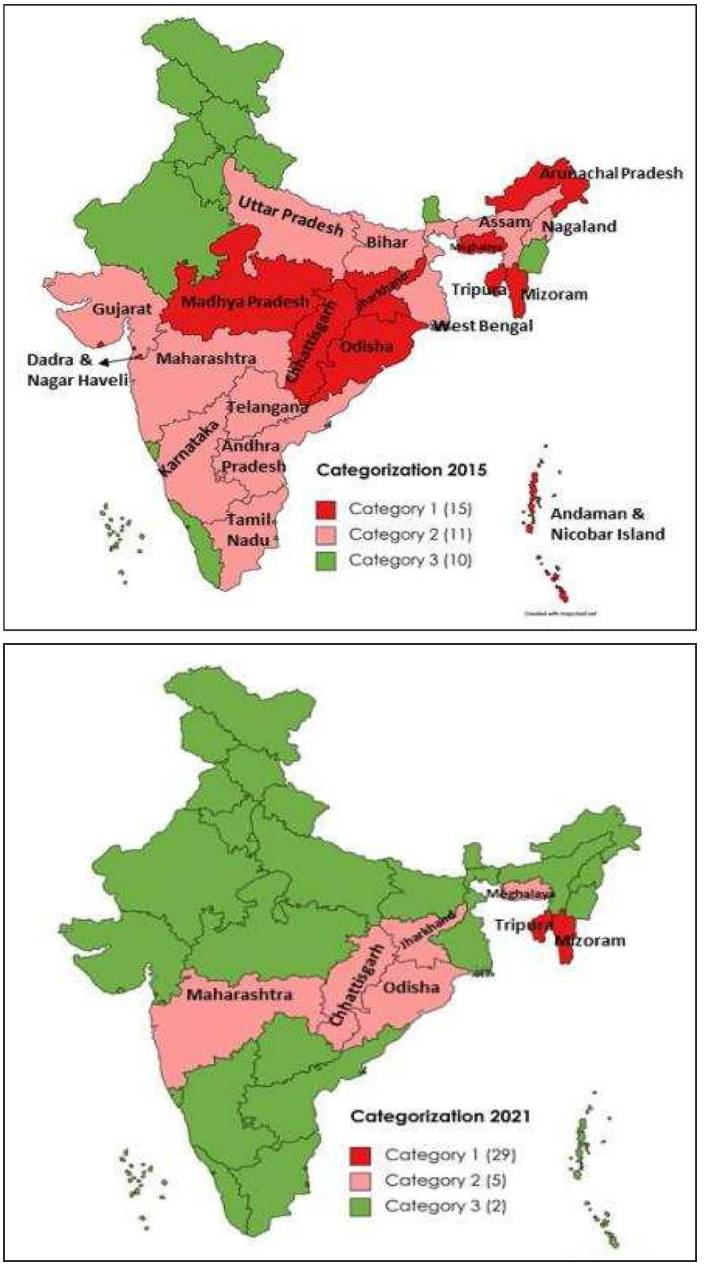

Fig. 1. Categorization of districts as per Annual Parasite Incidence (API) for the years 2015 and 2021.

The challenges, however, are also many in achieving elimination. These are also known since a long but the main issue is how to resolve them. The basic challenge starts from low priority to malaria programmes in low-burden areas both in terms of financial allocation and deployment of human resources. Surveillance involving the private sector and reporting from all to have the real burden in a timely manner is another issue which may need a regulatory framework. The reporting from difficult areas including tribal districts needs attention as the people have belief in various traditional healers[4].

Urban Malaria is one of the biggest concerns as it is mainly transmitted by *Anopheles stephensi* which now is not limited to identified towns, rather it has invaded all townships due to developmental activities and rapid urbanization which necessitates water storage practices- preferred breeding sites for this vector[6]. Limited coordination of municipal corporations with state and intersectoral coordination are also considered limiting factors in surveillance, treatment and preventive measures. Entomological surveillance across the country is suboptimal due to limited entomological capacity in the majority of states as well as at the central level which limits the appropriate advisory under integrated vector management (IVM) as to which tools and technology to be used in different situations like low, or high endemic areas and also in an outbreak situation. Last but not least, the actions for prevention of reintroduction of malaria cases after achieving zero indigenous malaria cases including cross-border malaria are issues to be resolved which need to be regulated by a policy framework[7].

LYMPHATIC FILARIASIS

This disease is targeted for elimination in line with the global target. Over 700 million population are reportedly living at risk of LF. India started a lymphatic filariasis elimination campaign in 2004 through Mass Drug Administration (MDA) in 250 endemic districts[8,9] which has been extended to 272 districts (328 after bifurcation or trifurcation of districts) during the journey of LF elimination. In India, the efforts to scale MDA and tackle LF have shown success because the number of districts requiring MDA has been reduced from 328 to 134 in 2022 (Fig. 2). This update has been documented in WHO weekly epidemiological record[10].

The current strategy for the elimination of Lymphatic Filariasis with annual MDA was to reduce the microfilaria rate below 1% so that transmission is

interrupted, and the new generation will not contract the disease. During scaling up the programme has switched from single-drug Diethylcarbamazine citrate (DEC) to a two-drug combination of DEC plus Albendazole and now with three drugs, i.e., Ivermectin with DEC plus Albendazole. The affected people with lymphoedema/elephantiasis are covered under the Morbidity management and disability prevention (MMDP) strategy of ELF by augmenting home-based lymphedema care through simple washing and drying[11]. The people affected by hydrocele are motivated for surgical intervention. The programme has enlisted lymphoedema and hydrocele cases which are updated every year. Integrated vector management (IVM) has also been advocated by WHO as a supporting pillar to sustain the gains achieved and made a part of the dossier though optional for submission of validation of elimination claim[12].

Though India has shown significant achievement towards LF elimination, the last mile challenges in generating evidence for the current status of LF endemicity in non-endemic districts, identifying and liquidating new foci in non-endemic districts with treatment and vector control under IVM and sustaining the achievements gained so far cannot be ignored.

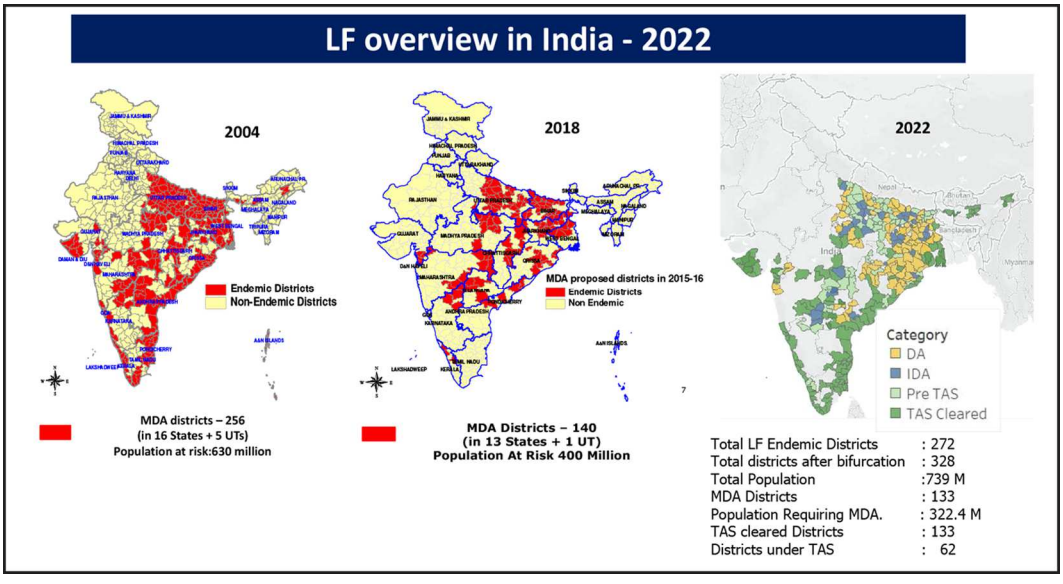

Fig. 2. Number of districts selected for MDA (*Source*: NVBDCP)

The challenges in LF elimination are suboptimal compliance to MDA drugs &acceptance of multiple drugs by the community[13]. Fear of side reactions due to DEC has initially been one of the factors in poor compliance. Inadequate IEC and mobilization of the communities at the ground level especially matching the needs of the programme have contributed to less awareness. Matching and timely requirement of drugs, as well as diagnostics, has resulted in staggering MDA and doing transmission assessment surveys. These mismatches need to be resolved with a greater number of implementation and evaluation units under block-level IU & Small EU strategy. The establishment of morbidity management and disability prevention (MMDP) clinics at each IU and conducting entomological surveillance for undertaking integrated vector management need focused attention as these are part of the dossier for claiming certification of elimination[14].

KALA-AZAR OR VISCERAL LEISHMANIASIS

This disease is mainly reported from 54 districts of four states, i.e. Bihar (33 districts), West Bengal (11 districts), Uttar Pradesh (6 districts) and Jharkhand (4 districts). A total of about 140 million population are reported to be at risk of VL in these endemic districts. The country has reported 1276 VL cases in 2021 against 32 803 in 2005 showing over 90 per cent reduction of VL cases since 2005[15]. Though significant achievement has been made in reducing the cases to less than 1 case per thousand population at the block level, the tackling of post-kala-azar dermal leishmaniasis (PKDL) may remain a challenge in addition to other challenges described in other VBDs. The occurrence of sporadic cases from other states will also need to be looked into for taking appropriate measures. Post-elimination vigilance will be crucial for quick response to case notifications.

DISCUSSION

Understanding the situation of diseases targeted for elimination and associated challenges, an analysis was attempted with a few examples of planning, resource allocation, access, availability (provided) and implementation (utilization) of resources[16]. The effective outcome due to reduction at different levels in the channel has been calculated with mathematical formulas shown below:

Situation 1: If planning is made for 100% resource and 50% of it is allocated out of which 80% is accessible and from accessible resources, only 80% is provided. The

expenditure is also 80% of funds provided then the actual outcome is only 25.6%. The diagrammatic flow is indicated in Fig 3.

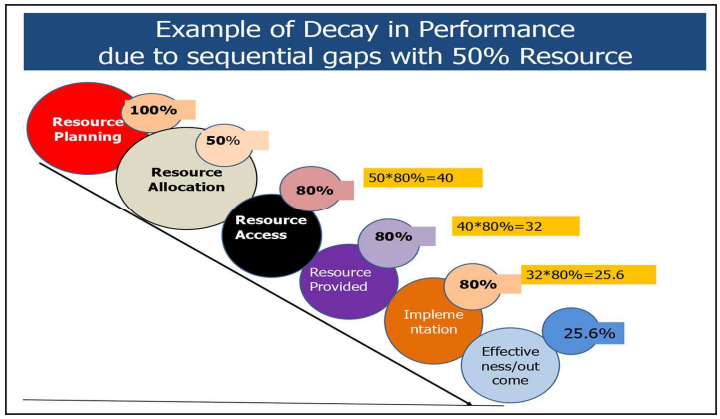

Fig. 3. Example of decay in performance due to sequential gaps with 50% resource.

Situation 2: If planning is made for 100% resource and 80% of it is allocated out of which 80% is accessible and from accessible resources only 90% is provided. The expenditure is also 80% of funds provided then the actual outcome is only 46%. The diagrammatic flow is indicated in Fig. 4.

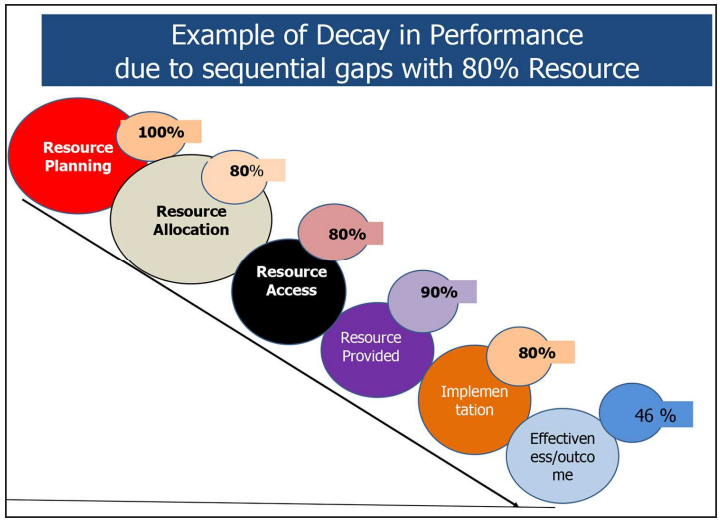

Fig. 4. Example of decay in performance due to sequential gaps with 80% resource.

Situation 3: If planning is made for 100% resource and 98% of it is allocated out of which 60% is accessible and from accessible resources only 90% is provided. The expenditure is also 70% of funds provided then the actual outcome is only 37%. The diagrammatic flow is indicated in Fig. 5.

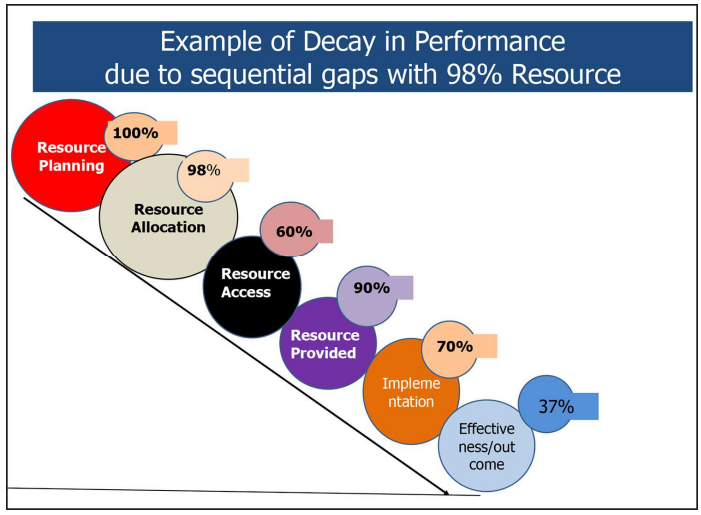

Fig. 5. Example of decay in performance due to sequential gaps with 98% resource.

CONCLUSION

The above discussions reveal that any reduction or ad-hoc arrangements results in the decay of performance due to sequential gaps. Various permutation and combinations can be made with the different scenarios but decay in performance need to be avoided by providing adequate resources and performance monitoring at every stage may be made mandatory with accountability and responsibility.

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[Format for the entire above category except for Original articles – unstructured abstract with key words; Introduction; Materials and Methods (if applicable); Results (if applicable); Discussion.]

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Perspective	2000	-	10
Original Article	3500	8	35
Review/Update Article	4500	8	45
Budding Researcher's Section	3500	8	35
Letter to Editor	500	2	3

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National Vector Borne Disease Control Programme. Dengue/Dengue Haemorrhagic Fever. Delhi: National Vector Borne Disease Control Programme; c2005-2018. Available from:

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Acknowledgements

All individuals who were directly involved with the study but do not qualify to be authors should be acknowledged. Consent should however be taken from these

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Request for contributing manuscripts for the next issue scheduled to be published on December 1, 2023

The power of scientific research lies in its ability to transform people's lives. Helping colleagues, peers and the wider general public to get a better understanding of your research and the impact that it can have on society is a win for everyone involved. Promoting your research helps it reach a wider audience in the arena of your research interests, which could lead to future collaboration and further academic opportunities, such as invites to conferences and commissioned articles.

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Vol. 3, No. 1, of *Journal of Medical Arthropodology & Public Health* (June 1, 2023) was published on date. We take this opportunity to request the scientific fraternity having research interests in medically important arthropods (e.g., insects, arachnids, centipedes, millipedes, crustaceans etc.) to submit their research manuscripts for consideration of publication in the Vol. 3, No. 2 (December 1, 2023) on or before October 31, 2023. For SUGGESTIONS TO AUTHORS please see either this issue or the SOMA website, www.soma16.org.

Expecting your kind understanding and cooperation in this regard, and looking forward to receiving your manuscripts before very long, we remain, with best wishes,

Cordially yours,

Prof. Dr B.K. Tyagi **&** **Dr Rina Tilak**
Chief Editor Exec. Editor

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1. Name of the periodical	**:**	**Journal of Medical Arthropodology & Public Health** **ISSN: 2583-6455 (Online)**
2. Published by the Society	**:**	SOCIETY OF MEDICAL ARTHROPODOLOGY
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5. Address of Publication	**:**	Department of Zoology, University College of Science, Osmania University Hyderabad, Telangana-500007 India
6. Frequency	**:**	Semiannual (Commencing w.e.f. June 1, 2021)
7. Language	**:**	English
8. Date of Declaration	**:**	22nd May, 2023

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