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Vectors that spread malaria: introduction to the microbiome-science of mosquitoes

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Abstract

Amongst six main mosquito species, *Anopheles minimus* responsible for transmitting malaria in India. *Anopheles minimus* is predominant in India particularly northeastern regions and is most accountable for focal infection outbursts marked by an increase in Plasmodium falciparum diseases, and further deaths that can be directly linked to them. According to genetic analysis, *Anopheles minimus* (formerly species A) is the most common species occurring in India, involving the north-eastern provinces and the East-central Odisha state, out of the three species that make up the Minimus Complex, which is distributed throughout Asia. It is documented throughout the year and explains perennial transmission as shown by records of sporozoite infections. This species has been observed spawning year-round in slow-moving seepage water streams. It is also primarily endophilic and endophagic. Malaria is still a serious public health concern in many parts of the world, especially in tropical areas. It is a vector-borne infectious disease. The protozoan parasite Plasmodium, which causes malaria, is spread via the bite of female Anopheles mosquitoes carrying the infection. Insecticide-treated nets (ITNs) and indoor residual spraying are the major methods used in the control interventions aimed at mosquito vectors that have shown great success over the past 20 years (IRS). Unfortunately, natural mosquito populations are developing resistance to the conventional pesticides now employed in public health, which is impeding the efficacy of the existing vector management measures over the long run. Therefore, it appears vital to enhance vector control strategies through the creation of novel, environmentally friendly methods in order to reach the objective of eliminating malaria. Our review article provides background for describing the biology, information gaps, and possible public health danger of Anopheles viruses.

Keywords: *Anopheles minimus*, Northeastern India, Anopheles viruses, sporozoite, public health

Introduction

The knowledge of the links between malaria vector species and disease has significantly improved in current ages thanks to the outline of genetic systematics-aided methods [1, 2]. In-depth research on malaria vectors is regaining importance with the global push to eradicate the disease due to efficient vector management. With the goal of reducing the transmission of malaria and entering the pre-eradication stage by 2017, India newly linked with the Asia Pacific Malaria Elimination Network (APMEN) (www.apmen.org).

Moreover in India, a number of Anopheles species transmit malarial agents, and the epidemiology of the disease is complicated because of the diverse ecology and contextual variables [3, 4]. In accordance to the World Health Organization (WHO), 2020 [5-6] still malaria is regarded as the most difficult tropical disease to treat. It is instigated by parasites belonging to the genus Plasmodium and spread via the bite of infested female Anopheles mosquitoes. Nonetheless, in most affected areas this disease seriously threatens public health and causes a severe and dangerous illness. [The World Health Organization, 2020] reports that malaria is a serious ailment that can be fatal, particularly in children under 5 years old and pregnant women in sub-Saharan Africa, where the disease is most prevalent and where mortality rates are highest.

Insecticide-treated nets (ITNs) with pyrethroids and indoor residual spraying (IRS) with organophosphates and carbamates are the main methods used in the current vector control programmes.

These traditional technologies are used to either prevent human-vector contact or lower density of vector below the needed threshold for dissemination [7]. Anopheles mosquitoes are among the most significant malaria vectors in areas where the disease is prevalent [8]. Anopheles gambiae, Anopheles arabiensis, Anopheles coluzzii, and Anopheles funestus, as well as the recently identified Anopheles stephensi, are the predominant vectors of Anopheles causing human malaria particularly in African nations [9-11].

Numerous entomological studies in this context confirmed the presence of *Anopheles minimus* in northeast India and re-indicted it by finding records of sporozoite infections [12–17]. However, there are no records of its return in the Terai region of Uttar Pradesh [18], but it has just made a comeback in the state of Odisha particularly in eastern parts nearly after 45 years [19–22]. Its status as the chief vector species in the foot-hill valley regions of northeast & eastern India has been unambiguously established once more, necessitating further efforts for its efficient control. It was necessary to assess its behavioural traits, particularly plasticity [23], in light of the rapid ecological changes brought on by the population growth, project development, and migration of human deforestation, which might affect the ecology of mosquitoes.

However, it was essential to evaluate the bionomical traits and infestations connexions of mosquitoes due to the rapid ecological changes brought on by the rapid growth of the human populace, advancements in projects, disforestation, and migration of humans. In light of global efforts to eradicate malaria and the declining prevalence of the disease, this information is thought to be crucial. We present the most recent and up-to-date information on *Anopheles minimus* status inside the system. To develop species-specific management measures to lessen spread with regards to space and time, consider minimus, its bionomical features, and its distribution in India. (Shown in figure-1).

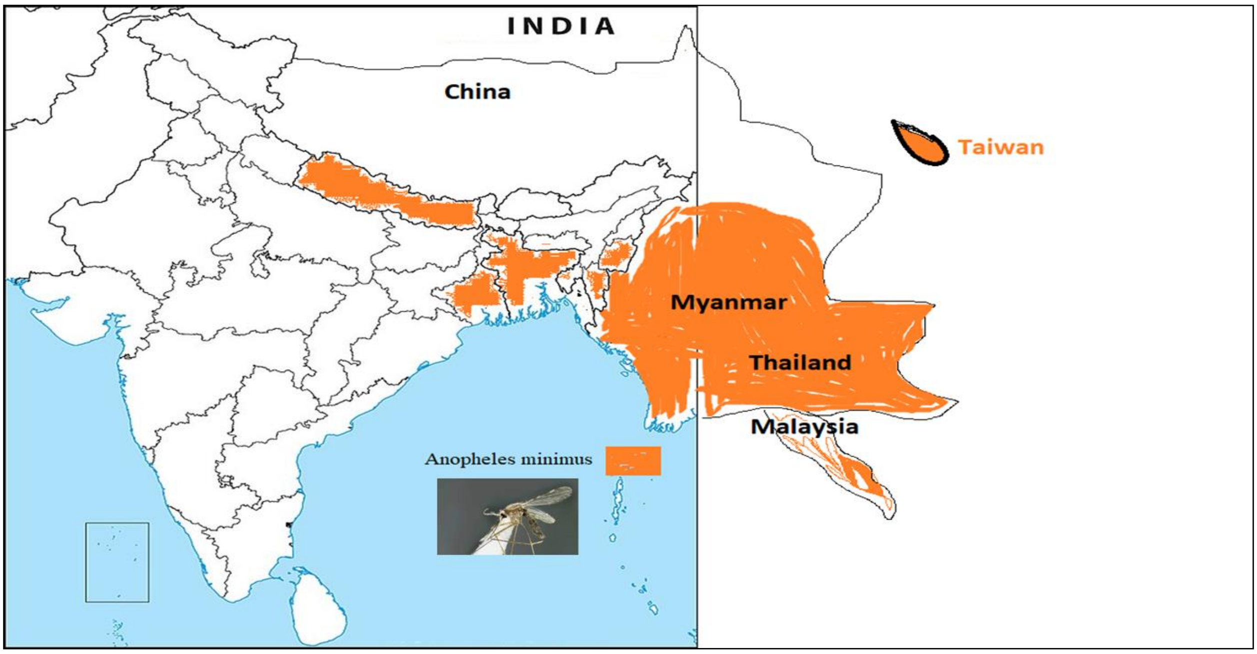

Fig 1: Distribution of *Anopheles minimus* in and around India and surroundings of Malaysia, Taiwan, Myanmar, and Thailand

Microbiome of Mosquitoes

According to the holobiont theory [24-25], microbiomes have emerged as a critical driver of many aspects of host physiology, including development, nutrition, survival, and the ability to transmit pathogens in insect vectors [26]. Due to their epidemiological relevance, research has focused a lot on how the microbiota can intemingle with arboviruses (i.e., arthropod-borne RNA viruses belonging to the families Togaviridae, Flaviviridae, Reoviridae, Bunyaviridae, and Rhabdoviridae) [27]. (Shown n Fgure-2). However, commonly based on laboratory-raised mosquitoes, the majority of the information on microbiota-pathogen interface in mosquitoes requires substantiation from data collected from field [28]. Additionally, sample pooling is used to reduce mosquito populations after processing a lot of field-collected insects.

We can study microbiotic dynamics at the populace level and look at broad species-specific patterns using pooled samples. Although interindividual variety in the populace can be significant and varies between vector species, pooling is unable to capture this diversity [29]. The resolution of inter-individual variance and diversity of individual vector-associated microbiomes has major epidemiological consequences. Because it is a holobiont's most dynamic element, the microbiome can quickly respond to shifting environmental conditions, driving vector adaptation and evolution. For evolutionary innovations to emerge in vector populations, inter-individual heterogeneity among host microbiomes provides favourable conditions.

Thus, the research of the natural microbiome heterogeneity is a necessary step in the ongoing effort to create novel microbe-based vector control techniques. For effective and long-lasting biocontrol, it is essential to comprehend its function in evolution of host, adaptability, and physiology, involving acquisition of pathogen, transmission. and resistance. Despite the fact that Wolbachia-based tactics have been effectively used in a number of tropical regions as part of the World Mosquito Program [30], present methods do not take into account the ecological, epidemiological, as well as evolutionary elements of holobiont.

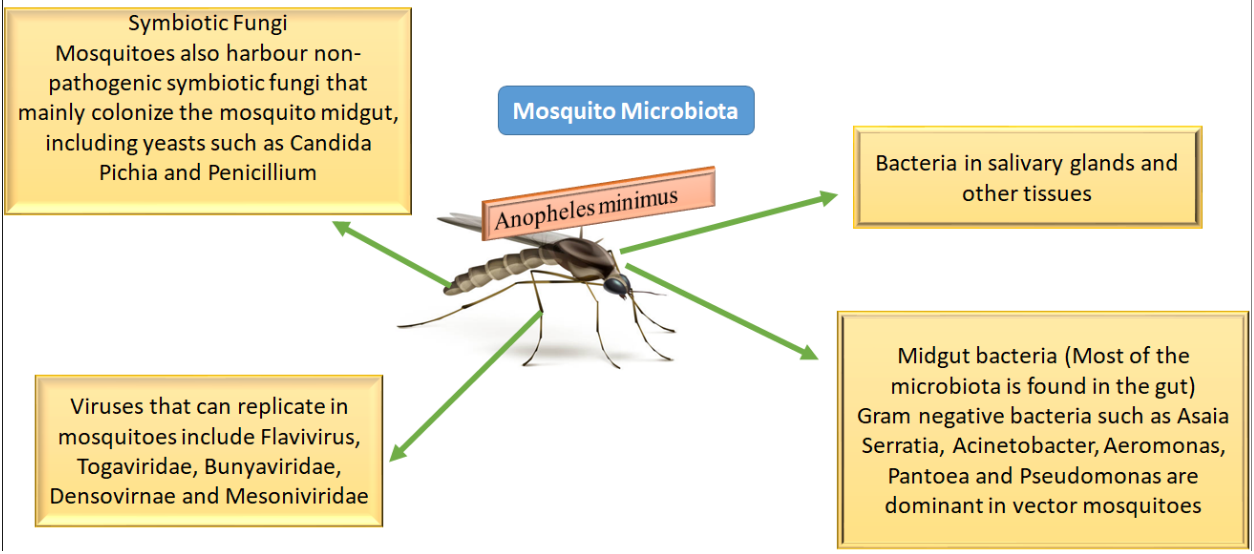

Fig 2: Illustrates the microbiome of mosquito and its interaction with pathogens

Factors Changing the Gut Microbiota in Vector Mosquitoes

Throughout the lifespan of the mosquito, the symbiotic microbiota is very variable in composition. The composition of the microbiota can be influenced by a variety of circumstances, including developmental stages, habitat, dietary habits, and even pathogen infection.

Mosquito larvae are aquatic; hence they primarily acquire their gut microbiota from their surroundings [31]. The microbiota of the larvae may be impacted by changes in the breeding bacterial communities. For instance, hotter water encourages the development of Betaproteobacteria, a common phylum of gut bacteria that is regarded to be advantageous for the development of Anopheles larvae [32]. The proliferation of microorganisms in water contaminated by fertilisers high in phosphorus and ammonium can be a substantial source of food for mosquito larvae [33]. Due to the reduction or eradication of specific bacterial taxa, residual antibiotics in water also have an impact on the microbiota of mosquito larvae [34].

The larval peritrophic matrix (PM) wraps the midgut bacteria during pupation to create the meconium. The majority of the gut microbiota is lost when the freshly hatched adult mosquito ingests the meconium [35, 36]. All three vector mosquito taxa were examined by Moll *et al.* [37], who discovered that the bacterial load is highest in larvae, decreases with age, increases in the pupa, and is very low in just hatched adults. According to Wang *et al.* [38], the variety of gut bacteria is larger in larvae than in adults. Additionally, they discovered that in larvae and pupae, cyanobacteria predominate in the gut, whereas in adult intestines, proteobacteria and bacteroidetes predominate, with Enterobacteriaceae and Flavobacteriaceae being the main species during a blood meal. Mosquito-microbiota interactions are intricate. The microbiota has a role in mosquito digestion, nutrition, growth, fertility, and immunity, and mosquito variables can influence its composition and growth [39].

Condition of insecticide sensitivity

Since the start of the control campaign in 1953, An. minimus has been regularly shown to be DDT sensitive both over geography along with time in India. The northeastern Indian region was tested for the sensitivity of various populations of this species to diagnostic concentrations of DDT (4%), malathion (5%), and various pyrethroids, such as alpha-cypermethrin (0.10%), deltamethrin (0.05%), and permethrin (0.75%), used in long-lasting insecticidal nets for vector control (Table 2). Similar findings have been reported from the eastern state of Odisha, where a comeback has been staged after a 45-year hiatus [40]. Except for northern Vietnam, where there has been documented resistance to permethrin & lambda-cyhalothrin, An. minimus does not exhibit pyrethroid resistance elsewhere in Southeast Asia [41].

Mosquito microbiome modification and manipulation

Controlled microbiota alteration may be necessary to answer some mosquito microbiome research issues. It is common practice to research the impact of particular bacteria on vector competence and physiology by empirically starting microbes from field mosquitoes into lab chamber colonies, as seen, for example, in [42-43]. The usage of axenic or gnotobiotic mosquitoes may be necessary to answer several research problems involving microbiota change. Until recently, antibiotics were used in these studies, but they may have an effect on the physiology of mosquito or competence of vector irrespective of how they affect the microbiome [44], (ii) nevertheless, they do not totally clear the mosquitoes' microbiome [45], and (iii) mosquitoes have revealed to harbor antibiotic-resistant microbes [46]. Axenic and/or gnotobiotic mosquitoes have recently been developed, and these advances [47] offer hopeful answers to these problems and have highlighted the crucial function of the microbiota in larval development.

Microbiota's effect on the frequency of vector bites

The average number of bites per unit of time, or vector biting rate, can be influenced by the microbiome through altering feeding habits and host preferences. An increased biting rate leads to a higher vectorial capacity, since the vector has more possibilities to acquire and transmit infections. When Anopheles mosquitoes are exposed to heat-killed E. coli [48] or Chromobacterium [49], their feeding behaviour is interrupted, as is that of Ae. aegypti [50], which is affected by Serratia. Through modification of their chemosensory system, microbiota has the capacity to influence host-seeking behaviour as well. Symbionts in D. melanogaster determine the larval pheromone preference [51] and have an impact on the adult olfactory system, which affects food preference [52-54]. Furthermore, vitellogenin expression in Ae. albopictus is known to control host-seeking behaviour [55], and gut bacteria are known to modify vitellogenin gene expression levels in the true bug Riptortus pedestris [56]. Therefore, more research should be done to determine whether the microbiome has the potential to affect host seeking behaviour, maybe through modulation of vitellogenesis.

Siderophores' Potential Use in a Future Paratransgenesis Campaign

The heterologous production of one or more exogenous biomacromolecules to lower parasite burden in Anopheles mosquitoes is a current paratransgenesis approach [57]. Due to its presence in the A. stephensi microbiome naturally and its capacity to vertically propagate across multiple generations of mosquitoes in a laboratory setting, S. marcescens AS1 has been used as a heterologous host in previous investigations. This is a promising path for potential malaria control as the expression of several antimalarial effector molecules in S. marcescens As1 significantly lowers parasite load within A. stephensi [58]. Because their well-studied biosynthetic gene clusters (BGCs) are relatively short in base-pair length compared to large lipopeptide and macrocycle BGCs, siderophores are also appealing candidates for this campaign. This makes it easier to heterologously express and/or manipulate siderophore BGCs for paratransgenesis applications. Serratiochelin A's future potential as a paratransgenesis tool is increased by the combination of its decreased overall fecundity and anti-Plasmodium activity. Fortunately, the BGC to make serratiochelin A is present in wild-type S. marcescens AS1 naturally, therefore genetic modification to constitutively express this BGC in S. marcescens AS1 is a viable alternative or additive strategy to the current effort.

Conclusion

There is growing evidence that many characteristics critical to vectorial capacity can be influenced by the microbiome of the vector. The complexity of microbial communities and the diversity of the mosquito microbiome are also frequently highlighted in studies. Many attempts to unravel this intricacy focus on a single microbe's impact on the host, such as those that take advantage of monoaxenic gnotobiotic infections; however, it is uncertain if these results apply to mosquitoes with a full microbiome made up of a variety of microbes. Understanding microbial interactions are essential because applied techniques must be effective in hosts with diverse microbiomes, which mosquitoes in the field do. However, this complexity can also be handled by grouping microorganisms with similar life histories and interspecific connections, which can then be linked to impacts on the host and then vectorial capability. Advances in omics technologies can help with this. Ultimately, complete knowledge of the acquisition of the microbiome and the processes regulating its composition and abundance will be necessary for the development of sustainable ways to adjust vectorial ability by introducing bacteria into wild mosquito populations. Only then can the microbiome's full potential for vector control be realized. Another factor to take into account is the possibility of many diseases infecting mosquitoes at the same time. The elimination of one pathogen might encourage the spread of another. Therefore, employing a symbiotic microbe with anti-multipathogen abilities would be preferred. Last but not least, it's critical to remember that no tool is 100% effective. A "magic bullet" does not exist to eradicate diseases spread by mosquitoes. Only the simultaneous and coordinated use of the greatest number of tools will be able to control diseases.

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