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Malaria mosquitoes, *Plasmodium* parasites and skin microbiota, towards control of malaria: A review

Annette Obukosia Busula *

Department of Biological and Agricultural Sciences, Kaimosi Friends University (KAFU), Kenya.

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Abstract

Vector-borne pathogens are transmitted by bites of infected arthropod species. The pathogens require two different host species to complete their lifecycle, usually a vertebrate and an invertebrate host, of which the latter transmits the pathogen between vertebrate hosts. Blood-feeding mosquitoes are important vectors of several human pathogens, including arboviruses namely: chikungunya, dengue fever, Rift Valley fever, yellow fever and Zika transmitted by Aedes mosquitoes amongst others. Culex mosquitoes on the other hand transmit Saint Louis and Japanese encephalitis, lymphatic filariasis, West Nile fever and Rift Valley Fever virus while Anopheles mosquitoes transmit malaria. The contact rate between vectors and their vertebrate hosts affects the intensity of pathogen transmission, and hence disease epidemiology. The ability of vectors to locate their blood hosts therefore is crucial in disease maintenance and perseverance. Host odour is known to play an important role in mosquito host-seeking behaviour and hence influences the contact rate between vectors and hosts. This literature review focuses on interactions between malaria parasites, humans, mosquitoes and how skin bacterial volatiles mediate host-seeking behaviour of mosquitoes.

Keywords: P*lasmodium*; Host; Vectors; Anopheles; Mosquitoes; Volatile; Microbiota

1. Introduction: Malaria

Malaria is a major vector-borne disease, caused by protozoan *Plasmodium* parasites (WHO, 2015b). Transmission of the parasites to humans is through bites of infected female Anopheles mosquitoes (Cowman et al., 2016). In 2021, approximately 247 million malaria cases, an increase from 245 million in 2020 were reported due to disruptions of services during COVID-19 pandemic (WHO, 2021) and the number of deaths declined slightly from 625,000 to 619,000 worldwide (WHO, 2022). Malaria, the leading cause of morbidity and mortality in Sub-Saharan Africa (RBM, 2013) is estimated to cost USD 12 billion every year, absorbing to a maximum of 40% of the health expenses in Sub-Saharan countries (RBM, 2013).

2. Life-cycle of malaria parasites

Malaria parasite species that infect humans are *Plasmodium falciparum*, *P. vivax, P. malariae, P. ovale* and *P. knowlesi* (White et al., 2014). Females of the *Anopheles gambiae* sensu lato sibling species complex (*An. gambiae* sensu stricto [hereafter termed *An. gambiae*] and *An. arabiensis*) and *An. funestus* are the principal vectors of malaria in most African countries (Okara et al., 2010), while a higher diversity of vector species occurs in other parts of the world (Sinka et al., 2012). Dominance of African malaria vectors is largely due to their preference for human blood, high vector competence and high daily survival rates. The malaria transmission cycle starts when an infected female mosquito injects sporozoites into a human host while blood-feeding (Figure 1). The sporozoites travel to the liver where they produce merozoites, which, in turn, infect red blood cells (*P. falciparum* does not have hypnozoites, a dormant liver stage). Inside

* Corresponding author: Annette Obukosia Busula

the red blood cells, the parasite reproduces asexually until the cells burst, causing fevers and other symptoms of malaria. Eventually, some parasites develop into gametocytes that may be taken up by another mosquito while ingesting a blood meal. Inside the mosquito's midgut, the parasite reproduces sexually, producing sporozoites that migrate to the salivary glands, thereby closing the cycle (White et al.,2014).

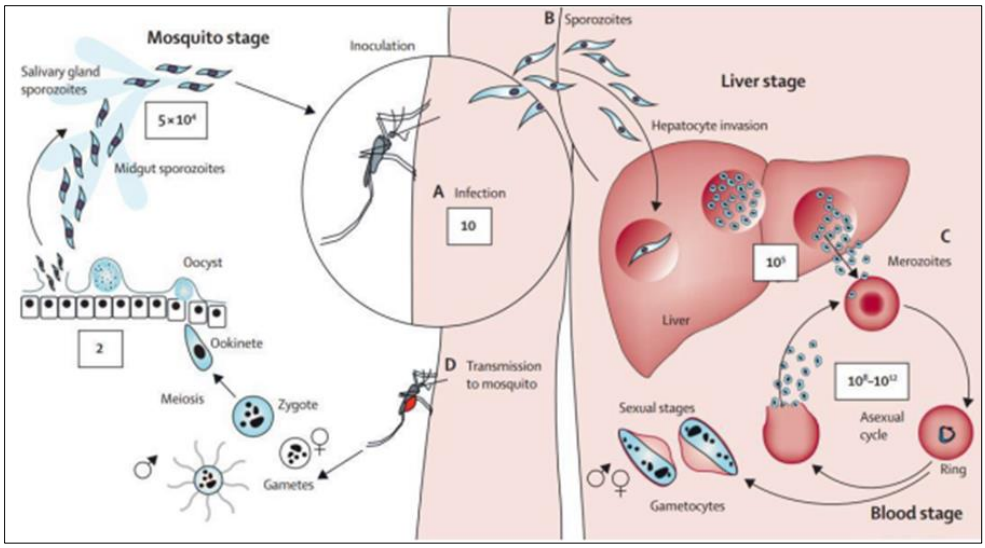

Figure 1 Life cycle of the malaria parasite *Plasmodium falciparum*. Infected female Anopheles mosquitoes pass *Plasmodium* sporozoites to a human who gets infected (A), while male and female gametocytes are the stages taken up by female mosquitoes from the blood stream of infected hosts in order to mediate disease transmission (D). Source: (White et al., 2014)

Diagnostic tools to identify malaria infection include microscopic analysis of blood films, rapid diagnostic tests (RDTs) (Batwala et al., 2010; Okanda et al., 2023), real-time quantitative polymerase chain reaction (qPCR) (Hermsen et al., 2001) and the quantitative nucleic acid sequence-based amplification (QT-NASBA) that allows highly sensitive stage-specific quantification of malaria parasites (Bousema et al., 2006). Treatment of malaria in all endemic countries in the world is mainly by artemisinin-lumefantrine, which kills all stages of malaria parasites (Gonçalves et al., 2016).

2.1. Mosquito host-seeking behaviour

Mosquitoes use (volatile) chemical cues to locate their blood-meal hosts. They have a highly developed chemosensory system located on the antennae and maxillary palps (Zwiebel & Takken, 2004). These cues are more important to vectors that have a specific host requirement (Zwiebel & Takken, 2004). Anthropophilic mosquitoes are sensitive to a narrow range of chemical stimuli and they primarily take blood meals from humans. More opportunistic vectors have a more general sensitivity to a wide range of chemical volatiles, which enables them to feed on humans and animals (Carey et al., 2010).

To find a host, mosquitoes engage in upwind flight behaviour using carbon dioxide (CO_2) (Dekker et al., 2001). The universal kairomone, CO_2 , acts as an activator and attractant for host-searching mosquitoes (Spitzen et al., 2008). Thereafter, they begin a directional flight towards humans when they encounter long-range host-kairomones up to around 70 m distance from the host, whereafter they initiate a landing response using volatiles emanating from human skin (Healy & Copland, 2000) and physical cues like heat, when at close range of their/the blood-meal host (Spitzen et al., 2013). The host-seeking behaviour of mosquitoes can be exploited using traps. Combining natural host odours, synthetic odour blends or skin bacterial volatiles with CO_2 causes an increase in mosquito catch in such traps (Verhulst et al., 2011a). Consequently, odour-baited traps can be used to catch malaria vectors in the field, hence reduce transmission of malaria (Homan et al., 2016).

3. Role of skin bacterial volatiles in attraction of mosquitoes

Volatiles from human skin microbiota are attractive to the anthropophilic mosquito *An. gambiae*, but not all skin bacterial species attract mosquitoes (Verhulst et al., 2009; Verhulst et al., 2011b). This suggests that *An. gambiae* selects its blood hosts based on specific bacterial volatiles released from the human skin (Verhulst et al., 2010a). Humans are differentially attractive to malaria mosquitoes based on bacterial species on their skin (Verhulst et al., 2010a). Highly

attractive individuals harbour higher densities, but a lower diversity of bacteria on their skin, compared to poorly attractive individuals (Verhulst et al., 2011b). This therefore suggests that attractiveness of humans to mosquitoes based on microbial diversity and/or density can have an effect on the number of mosquito bites received per person, hence the risk of malaria infection (Takken & Knols, 1999).

4. Mechanisms of odour production by specific bacteria

Different bacterial species on human skin have specific metabolism for generation of specific odour profiles. Corynebacteria generates volatile fatty acids which produce odour and only these bacteria transform long chain fatty acids into short and medium-chain fatty acids (C2-C11), causing malodour (James et al., 2004). Micrococci and Brevibacteria metabolize the short and medium-chain fatty acids even further (James et al., 2004). Staphylococcus species convert amino acids to highly odorous short-chain amino acids (James et al., 2004) that are available as host-seeking cues (Smallegange et al., 2009).

5. Manipulation of vertebrate hosts by *Plasmodium* parasites

Besides variation caused by skin bacteria in attractiveness of healthy humans, it is also expected that the presence of diseases/parasites can alter host attractiveness. To optimize *Plasmodium* transmission, malaria-infected mosquito vectors carrying transmissible stages (sporozoites) should preferentially bite non-infected hosts, while infected hosts carrying transmissible stages (gametocytes) should be more attractive to healthy vectors than hosts without transmissible stages. Various studies in non-human systems indeed demonstrated altered mosquito feeding behaviour such as probing, persistence and engorgement rate upon *Plasmodium* infection (Hurd, 2003), suggesting manipulation of mosquito vectors by *Plasmodium* (Cator et al., 2012). *Anopheles gambiae* mosquitoes infected with sporozoites also showed increased attraction to the odour of healthy humans compared to non-infected mosquitoes (Smallegange et al., 2013).

In addition to changes in infected vectors, infected rodent and bird hosts received more bites from mosquitoes than non-infected hosts (Cornet et al., 2013a, 2013b). Kenyan children infected with transmissible stages of *P. falciparum* (gametocytes) attracted significantly more mosquitoes than non-infected children (Lacroix et al., 2005; Busula et al., 2017), suggesting that malaria parasites may also manipulate their human hosts to enhance transmission. The mechanism underlying this manipulation are thought to include changes in the infected individual's breath or body odour (Lacroix et al., 2005).

6. Conclusion

Interventions such as insecticide treated bed-nets and indoor residual spraying combined with effective anti-malaria drugs have reduced vector-host contact and reduced the malaria burden significantly (Bhatt et al., 2015). This reduction in malaria is aided by increased funding towards malaria control strategies (WHO, 2012; WHO, 2015a). However, due to the changing malaria transmission landscape with secondary vector species becoming more important (Sriwichai et al., 2016), outdoor residual transmission (Russell et al., 2013), continued emergence and spread of parasite resistance to antimalarial drugs, resistance of mosquitoes to insecticides (WHO, 2015b) and lack of a standardized reliable vector control tool (Alonso et al., 2011), additional knowledge and/or alternative methods for vector control are urgently needed. This is especially important because a single strategy may not be effective in all malaria-endemic countries as some countries/regions have set targets on elimination of malaria.

Compliance with ethical standards

Disclosure of conflict of interest

The author declares no conflict of interest.

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