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# Host Preferences of Blood-Feeding Mosquitoes

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anthropophily, behavior, disease vectors, host choice, plasticity, zoophily

## Abstract

Mosquitoes use plant sugars and vertebrate blood as nutritional resources. When searching for blood hosts, some mosquitoes express preferential behavior for selected species. Here, we review the available knowledge on host preference, as this is expected to affect the life history and transmission of infectious pathogens. Host preference is affected by myriad extrinsic and intrinsic factors. Inherent factors are determined by genetic selection, which appears to be controlled by adaptive advantages that result from feeding on certain host species. Host preference of mosquitoes, although having a genetic basis, is characterized by high plasticity mediated by the density of host species, which by their abundance form a readily accessible source of blood. Host-selection behavior in mosquitoes is an exception rather than the rule. Those species that express strong and inherent host-selection behavior belong to the most important vectors of infectious diseases, which suggests that this behavioral trait may have evolved in parallel with parasite-host evolution.

## INTRODUCTION

Mosquitoes belong to the most important group of disease vectors, as exemplified by the large number of species involved in the transmission of human and animal parasites and pathogens. Several of the world's most prevalent infectious diseases, notably malaria, lymphatic filariasis, and dengue, as well as less common diseases such as Japanese encephalitis, chikungunya, Rift Valley fever, West Nile virus, and Usutu virus, are transmitted by mosquitoes. Transmission between vertebrate hosts is achieved by the blood-feeding habit of the mosquitoes, which enables the disease agents to successfully become established in and be transmitted by their arthropod hosts. Selection of a blood host that is essential for the parasite/pathogen to successfully complete its life cycle is therefore important. The blood-feeding habit of mosquitoes is part of their intrinsic character, as blood proteins are essential nutrients for egg production and reproductive fitness (18, 20). In addition to plant sugars, blood also serves as a source of metabolic energy, depending on the internal state of the insect (20, 130). Many blood-feeding mosquitoes express a nonspecific host preference, suggesting that blood source and quality are irrelevant for reproductive fitness. However, studies have shown that blood quality, and hence host species, may affect reproductive output (see Reference 66 for an overview. Moreover, many of the disease agents transmitted by mosquitoes are host specific (*Plasmodium falciparum*, *Plasmodium vivax*, *Wuchereria bancrofti*, dengue virus); hence host preference is likely to be more common than was previously assumed given the evolutionary association between insect vector and pathogen.

Here we discuss the current knowledge on mosquito host preference, as well as the extrinsic and intrinsic factors that have shaped this behavioral characteristic. We define host preference as the trait to preferentially select certain host species above others. For the purpose of this review, "hosts" are restricted to vertebrates, although plant feeding is also an important aspect of mosquito biology. This review aims to provide data that allow the reader to understand how mosquitoes have developed host preference, the advantages that are associated with this behavior, and what this behavior means for the transmission of vector-borne diseases.

Blood feeding in insects is thought to have evolved when plant-sucking insects accidentally bit vertebrates and then developed a digestive physiology that allowed for metabolic uptake and use of the protein-rich nutrients (145). Another evolutionary route may have been through the close association between chewing insects and vertebrates, in which the insects became adjusted to vertebrate-specific cues and occasionally chewed on vertebrate skin (66). When blood became the single most important nutritional resource of these insects, a strong and closely associated parallel parasitic evolution occurred between the vertebrate host and the insect. During this process, the insect came to depend on host-specific cues that enable it to accurately identify its host in a heterogenic environment. Hence the host preference can be explained as an adaptive trait that leads to optimal reproductive fitness of the parasitic insect (75).

As with many other insect species, some mosquito species are generalists and express an opportunistic feeding behavior while others are specialists, feeding on a selected host species. This selective behavior has a great influence on disease transmission. Differences in host preference resulting from selective behavior exist not only between different species, but also between populations of the same species and even within a population (46, 75). These differences are caused by extrinsic and intrinsic factors (see below). **Figure 1** provides an overview of the preference for humans by some of the most important mosquito vector species and illustrates the differences that exist between these species.

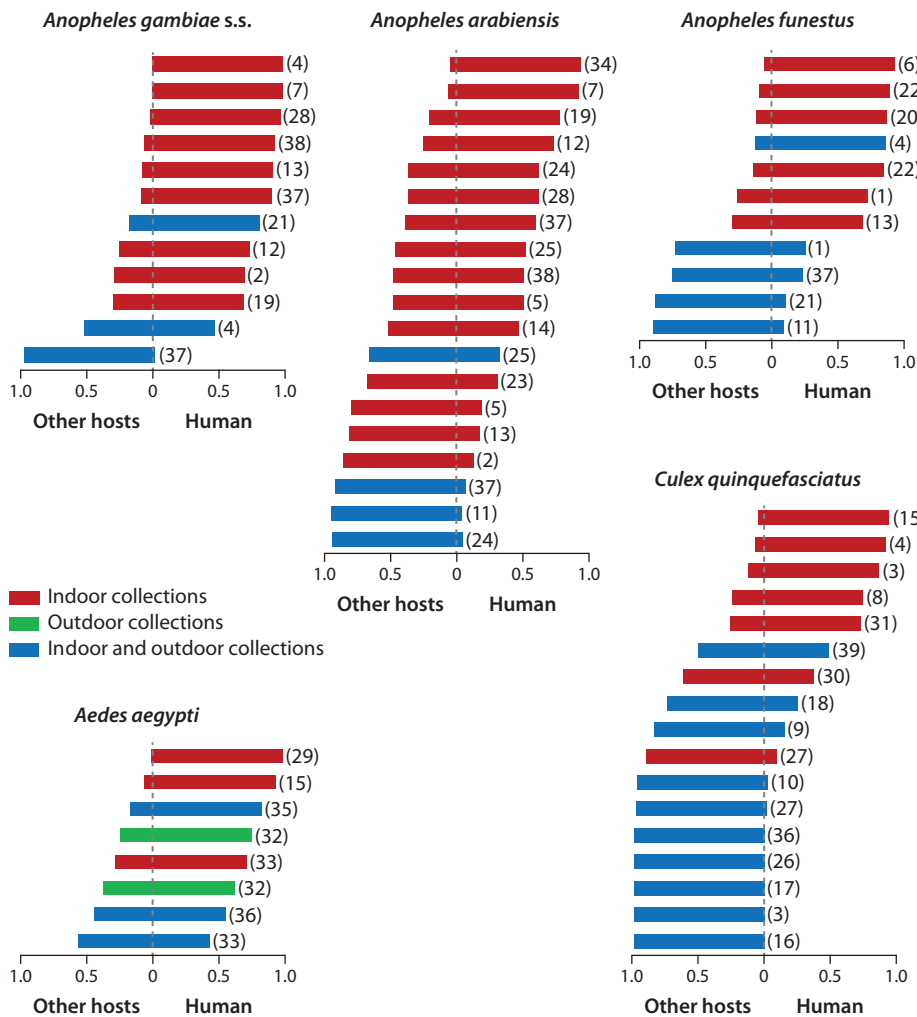
## METHODS TO DETERMINE HOST PREFERENCE

Mosquitoes utilize a range of senses to locate hosts (see Reference 131 for an overview). Of these, olfaction is considered the most important sense, providing mosquitoes host-associated

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**Figure 1**

Overview of the proportion of human blood meals compared to those of other blood hosts of five major disease vectors. Only studies were assessed in which no vector control tools were used, to avoid interference from these vector control tools with the blood-feeding behavior of the mosquitoes. Bar numbers refer to the references listed in the supplemental material (follow the **Supplemental Material link** from the Annual Reviews home page at <http://www.annualreviews.org>) of this paper.

attractive cues in a heterogeneous environment (66, 131, 154). Rudolfs (115) and van Thiel (140) demonstrated the importance of semiochemicals in the host-selection behavior of mosquitoes and provided the basis for our current understanding of host preference. Host preference has been studied in the laboratory and field using a range of tools. These include choice assays such as olfactometers, indoor observational rooms, traps, semifield containment facilities, and experimental huts.

For those mosquitoes that can be kept in culture, laboratory behavioral studies include observations in dual-choice olfactometers, wind tunnels, and choice chambers (124). The principle of these devices is that mosquitoes are exposed to two or more host odors simultaneously in a choice situation and then express a positive response to a particular host by an upwind flight and



(sometimes) landing (26, 46, 65, 102). One limitation of this approach is that by culturing insects in the laboratory for many generations, certain genetic traits may get lost by stress, selective breeding, and the lack of exposure to natural environmental conditions (42, 61). After many generations, the preference for feeding on a selected host species may also be lost, for example, an anthropophilic mosquito species feeding for many generations on laboratory animals (46, 59).

Studies on mosquito host preferences in the field are conducted by examining the blood meal origin of field-collected specimens (44) and by observing mosquito behavior in choice situations (90). Blood-fed wild mosquitoes are sampled from indoor and outdoor collections with resting boxes, (mechanized) aspirators, and resting sites created in dugouts (109). The origin of blood meals can be assessed by multiplex PCR (87, 106), microsphere assay (134), microsatellites (3), enzyme-linked immunosorbent assay (ELISA) (64), or precipitin test (133). The results of these samples are often biased in favor of the most abundant host species locally available, which may not be the most preferred host. For example, collections of blood meals in houses are more likely to collect human-fed mosquitoes, and those collected in animal dwellings are more likely to collect animal-fed mosquitoes (129). Although this observation is unsurprising, it highlights the technical difficulties of getting an accurate estimation of the biting preferences of a population of vectors. Behavioral observations using choice tests, therefore, provide a more objective tool for assessing host preference. These competitive experiments may often represent what a mosquito experiences in nature when a host-seeking mosquito encounters more than one potential host source. Nonetheless, it is possible that many hungry mosquitoes may simply feed on the first available host they find. Natural host choice is examined with choice assays in semifield (91) and field (32, 137) by observing the response of mosquitoes to odorants from entire hosts or parts of their body (25, 48, 92).

Choice tests with live hosts or host-derived odor samples may give a reliable indication of host preference. Some mosquito species, however, show a reduced trap entry response, although they do express a positive response toward the odor source (29, 31). Choice tests in which a trap entry response from the mosquito is not required, for example, electric nets or odor-baited traps that provide suction, are therefore preferred (137, 153). The development of synthetic odorants that mimic human scent has allowed for a more in-depth study of host preference under natural field conditions (89, 99).

It is frequently reported that when exposed to a group of (same-species) hosts, host-seeking mosquitoes express a preference for one individual above the others (108, 54). Even if under a no-choice situation, the mosquito's response to host cues is similar; when two of such hosts are tested in a dual-choice system, mosquitoes may select one host significantly more often. This preference is likely caused by the natural variation in odorants between individuals, which affect the insects even at very low concentrations, and demonstrates the high sensitivity of the odorant receptors to semiochemicals (154). Between-species differences in host preference of mosquitoes, though, are generally highly robust because these are based on actual differences in odor composition (46).

## EXTRINSIC DETERMINANTS OF HOST PREFERENCE

External factors may affect host preference, such as when the preferred host species is not available and the response threshold for host selection has been reduced owing to low metabolic energy (20) or when adverse weather prevents mosquitoes from venturing far from the residential habitat (152).

### Odorants (and Their Production by Skin Bacteria)

Olfaction is the principal way in which mosquitoes detect a host (11, 131). The olfactory receptors located on the antennae, maxillary palpi, and labellum (58, 63, 105) are tuned to respond to specific

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odorants released by the blood host (15, 110). Carbon dioxide is a general cue for all hematophagous arthropods, causing activation (47) but also attraction (112, 116, 123). Because carbon dioxide is exhaled by all vertebrates, it should be considered a general cue signaling the presence of a host (80) and not thought to affect host preference other than indicating the potential suitability of a host. Skin emanations contain host-specific cues, and in specialized mosquitoes these play a role in host preference (12, 128). For example, (S)-lactic acid is an excretory product of humans and an important cue in the host selection process of the anthropophilic mosquitoes *Aedes aegypti* and *Anopheles gambiae* s.s. (29, 125). Bacteria present on the human skin affect mosquito host selection and preference (144). Whether such microbiological interactions also affect mosquito-host interactions with other animals is unknown.

### Blood Quality/Host Species

In the tsetse fly, *Glossina morsitans*, blood source has a strong impact on fecundity (62), with those feeding on pig blood producing more offspring than those feeding on cattle blood. However, when tsetse flies fed on a range of different wild host species, there was no difference in fecundity or survival, and it was concluded that the nutritional value of the various blood sources was of no consequence for the fecundity of the flies (88). Such information is relatively scarce for mosquitoes (75), although available data suggest an association between reproductive fitness and host species. Takken et al. (132) reported differences in fecundity between *An. gambiae* s.s. and *An. quadriannulatus* when fed human and cattle blood. Several of these studies report, remarkably, no relationship between the preferred host and optimum reproductive output. *An. gambiae* s.s. did not derive a fitness advantage from feeding on human blood (76), and *Ae. aegypti*, also a highly anthropophilic species (Figure 1), expressed the highest fitness when it fed on birds (75).

### Color

Mosquitoes' sense of vision enables them to navigate successfully through the environment (8). Their sense of color, however, is poor (150) and is unlikely to play a role in host preference. Nevertheless, color is reported to affect the oviposition response of several mosquito species (68, 84).

### Body Heat

Mammals and birds exude heat resulting from metabolic activity. Mosquitoes respond to such heat sources (35, 51, 103). It is not known whether differences in body heat affect the preference for particular hosts in choice situations. Body heat creates convection currents that affect the dispersal of semiochemicals and hence affects host-seeking behaviors (28, 100).

### Relative Humidity

As with temperature, mosquitoes also have an accurate sense of relative humidity and are capable to detect, at close range, small differences in moisture (20, 59). However, humidity seems to increase the effect of odorant cues rather than affect host preference on its own (100).

### Body Mass

The size of a body may affect host preference, presumably because a larger host would exude a higher quantity of olfactory cues. A well-known example is the production of metabolic carbon

dioxide, which is positively associated with body size (138) and affects the range of attraction of mosquitoes (48). Young children are bitten less often by mosquitoes than their parents are (16, 126). Whether this preference is due to different odorant patterns between children and adults, body size, or both is not known.

### Gender

Mosquitoes express different degrees of preference for humans. These preferences are presumed to be associated with differences in odor profiles, which differ between men and women, as well as between people of the same sex (49, 148). *Ae. aegypti* expressed varying degrees of attractiveness to women owing to the estrogen content of their urine (114). Lindsay et al. (69) demonstrated that *An. gambiae* s.s. were more attracted to pregnant women than to women who were not pregnant. Qiu et al. (108) found that gender had no effect on the preference of *An. gambiae* s.s. to humans. Differences in attraction to humans by mosquitoes were correlated with the composition of the microorganisms on the skin, which is highly variable among humans (144), as well as between men and women (38) (see sidebar, Variations in Attraction to Humans by *Anopheles gambiae*). The latter study, however, did not examine this effect on mosquitoes. It seems likely that the variation in bacterial communities between individuals overrules a potential difference in attractiveness of a gender.

### Defensive Behavior

The degree to which a host is bitten by mosquitoes is affected not only by body odor, but also by the effectiveness of defensive responses. Healthy mice were bitten significantly less often than malaria-infected mice were, which was ascribed to the more-active behavior of the healthy mice that prevented mosquitoes from biting (27). In addition, blood hosts that express a more effective defensive behavior than other hosts are bitten less often (146) and consequently may be less prone to contracting diseases.

### Parasites and Pathogens

Infection with a human or animal parasite/pathogen affects mosquito feeding behavior, typically increasing the transmission of pathogens (2, 56, 79), leading to increased or decreased blood uptake.

## VARIATIONS IN ATTRACTION TO HUMANS BY *ANOPHELES GAMBIAE*

We define host preference as the preferred response of a mosquito to a selected host species. Within one host species, however, differences in preference between individuals have also been observed (13). This has been studied most with the anthropophilic mosquito *Anopheles gambiae* s.s., which occurs in tropical Africa and a small section of the Arabian Peninsula. Although predominantly anthropophilic, this mosquito significantly prefers certain humans to others (12, 54, 70, 108, 121). Also, age of the human host appears to be a factor, as the mosquito prefers adults to children (10, 16, 21, 126). A gender difference has not been found (108). The difference between human individuals has been ascribed to differences in the composition of microorganisms present on the human skin and not to their absolute quantity (143). The microorganisms produce the skin volatiles that the mosquitoes use for host location (142), and it was found that poorly attractive individuals had a higher diversity of microorganisms compared with the highly attractive individuals (143).

Further, malaria infections in the human host may also affect their attractiveness to mosquitoes (60, 93). Whereas these infections affect the degree of attractiveness of as well as blood uptake on one host species, it is not known whether parasite infections cause a shift in host preference among various host species.

### Climate (Winter Versus Summer Hosts)

Mosquitoes can express different host preference behavior between seasons. For example, *Culex nigripalpus* switches from deer to birds between summer and winter (34). In contrast, *Cx. tarsalis* in California feeds primarily on birds in the summer and on mammals and birds in the winter (122, 135). Similarly, differences in feeding preference between seasons was reported for several mosquito species in France (4). These differences are likely to be associated with an abundance of host species, as they are linked to the migratory behavior of avian species on which the mosquitoes feed in the summer. A direct effect of temperature and humidity on mosquito behavior was reported by Kessler & Guerin (50), but because this study was done under controlled laboratory conditions, it is difficult to extrapolate these findings to field populations.

## INTRINSIC DETERMINANTS OF HOST PREFERENCE

### Physiology

Soon after emergence from the pupae, male and female mosquitoes express a strong behavioral response to nectar (40), which serves as source of metabolic energy needed for flight and anemotactic behaviors (41). Following mating, which takes place 24 to 48 h after emergence, the feeding behavior of anautogenous female mosquitoes switches from sugar to blood. The inherent genetic preference for a specific host is already expressed at this time. Choice experiments with members of the *An. gambiae* complex have shown the preference of *An. quadrimaculatus* and *An. arabiensis* for cow odor while *An. gambiae* s.s. selected human volatiles, demonstrating the high degree of anthropophily of this species complex (30, 102). Nonetheless, the nutritional state of the insects may overrule the inherent host preference, because the principal strategy of the insect is to safeguard reproduction, for which (animal) blood is required. Under such circumstances, the mosquitoes lower their threshold for host preference and may feed on a nonpreferred host. Age of the mosquito does not affect host preference, but adaptive learning, through a memorized host encounter, was shown to affect the choice for a specific host species (19).

### Genetics

Host choice depends not only on the innate host preference of the mosquito species, but also on the tendency of the mosquito to feed indoors or outdoors and the time of feeding. These behavioral characteristics may be driven by selection and therefore have a genetic background. The genetic determinants of the innate host preference can be studied in laboratory setups by backcrossing and selection experiments. The genetic determinants of host choice, including the effects of other behavioral characteristics, can be studied by sampling field populations. Problems encountered in these field studies, however, may include sampling bias, variation due to other biological determinants, and plasticity in host preference. **Figure 1** shows the host preference of a number of important mosquito disease vectors with respect to the degree of anthropophily. For those species that are strongly anthropophilic, it is easier to reveal these genetic determinants because of a small sampling bias. Controversially, for species with a variable degree of anthropophily, biological determinants are more influential, for example, the abundance of host

**Anthropophily:** feeding predominantly on human blood

**Plasticity:** the trait of switching behavioral preference, usually when conditions become unfavorable



**Zoophily:** feeding predominantly on animal blood

species, proximity of mosquitoes to host species, and type of environment in which the study took place.

In Muheza, Tanzania, Gillies (46) performed a simple study that clearly revealed a genetic basis for host preference. *An. gambiae* females were released in an experimental hut that was divided into three rooms. One room was occupied by a man and another by a cow. Mosquitoes were released from a small room in the middle of the hut. Blood-fed mosquitoes were collected in the calf room or human room, and their F1 progeny were marked with fluorescent dust and released in the experimental hut to determine whether the offspring would have the same host preference as their parents. Within a few generations it was possible to select for strains that differed significantly in their host preference (46). Similar results were obtained for *An. vestipennis* (139) and a zoophilic strain of *Ae. aegypti*, but not for an anthropophilic strain of *Ae. aegypti* (94). These experiments showed that there is a genetic polymorphism in host preference on which selection can operate under both laboratory and natural conditions.

To determine how strongly genes involved in host preference are fixed in a population, genes may be crossed with genes from a closely related species with a different host preference. Crosses with two strains of *Ae. aegypti* and two strains of *Ae. simpsoni* with different host preferences showed that interstrain hybrids and their backcrosses were intermediate in host preference between their parental strains (94). This finding confirmed the existence of genetic control for the behavioral differences between the strains, although none of the behavioral preferences was strongly fixed in the population. However, this was not the case when the highly anthropophilic *An. gambiae* s.s. was backcrossed with the more zoophilic *An. quadriannulatus* (101). Even after three backcrosses with *An. quadriannulatus*, the anthropophily of *An. gambiae* s.s. did not change. It was expected that after three backcrosses, 15/16 of the genes would have been derived from *An. quadriannulatus*, which would have indicated that the anthropophilic behavior of *An. gambiae* s.s. is a dominant trait that is strongly fixed in the population. However, a field study in Burkina Faso suggested that nonendophilic and nonanthropophilic *An. gambiae* s.s. populations may exist (113). An analysis of single-nucleotide polymorphisms in larval pools suggested the existence of two populations of *An. gambiae* (113). The adults of one of these populations, now termed the Goundry subgroup, however, were not caught in both indoor and outdoor sampling with odor-baited traps (N.O. Verhulst, personal communication), whereas members of the other population were readily collected. This indicated that the Goundry subgroup is not as endophilic and anthropophilic as *An. gambiae* s.s., although the exact feeding preferences and the potential of this new subgroup malaria vector remain to be investigated.

So far, little is known about the genetic determinants that affect host preference. There is evidence, however, that host preference may be correlated with specific polymorphic chromosomal inversions. Parallel indoor/outdoor collections in Kano, Nigeria, of polymorphic populations of *An. arabiensis* and *An. gambiae* show that adult mosquitoes carrying certain inversion karyotypes do not distribute at random in relation to the human environment. Certain chromosomal inversions occur significantly more frequently in outdoor- than in indoor-collected mosquitoes (24). Populations of the *An. gambiae* complex carrying these chromosomal inversions would generally be more difficult to control by residual house spraying than if the target mosquito population lacked these polymorphisms (23).

The association of certain chromosomal arrangements with mosquitoes collected indoors may also explain the higher rates of *Plasmodium* infection found in mosquito populations with a specific chromosomal inversion (104). The causes of intraspecific variation in rates of *Plasmodium* infection could also be due to many interrelated factors, including differences in longevity, susceptibility to *Plasmodium*, and behavior. Host preference, however, could not explain these results because there was no difference in chromosomal inversions in mosquitoes collected with human- and

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cow-baited traps (104). When mosquito populations in two Kenyan villages were studied, there was evidence in only one village that chromosomally distinct individuals had different preferences for resting sites (86). The conclusion of this study was that host feeding may reflect host availability not genetic variation.

Although polymorphic chromosomal inversions may play a role in the endophilic behavior of mosquitoes (24, 86), most studies do not support the hypothesis that chromosomal inversions also mediate host preference. A study in Ethiopia, however, showed a possible correlation between the host preference of *An. arabiensis* populations and their polymorphic chromosomal inversions. *An. arabiensis* populations possessing a 3Ra chromosome inversion were more likely to feed on cattle than on humans (74). These results should be confirmed by field and laboratory tests in which mosquitoes with or without the 3Ra inversion are given a direct choice between human and cow (odor).

Polymorphic chromosomal inversions conserve groups of genes, so finer-resolution genetic studies may identify single genes or smaller groups of genes that affect host preference. These genes may be discovered through exploratory approaches such as mapping polymorphic chromosomal inversions, quantitative trait loci mapping, microarray studies, single-nucleotide polymorphisms, functional genomics (e.g., RNA interference), and comparative genomics (7, 97). Although these techniques have been used to study population differences or genes involved in gustatory, odorant, and visual processes (7, 73, 85, 147), they have been used only to a limited extent to study innate host preference or host choice. Research on odorant perception, for example, was initiated in *Drosophila* and is now developing rapidly in mosquitoes. Comparing odorant perception and genetic background of closely related mosquito species with different host preferences, for example, by whole-genome sequencing, may help unravel the genetic basis of mosquito olfaction.

## PLASTICITY IN HOST PREFERENCE

### Learning

There is growing evidence that mosquitoes learn and thereby adapt their behavior to a positive or negative experience. Associating a blood meal with a specific location or host cue may thereby increase subsequent feeding success.

Although learning is very common in other insects, studies that show learning behavior in mosquitoes are rare (83). Offering *Cx. quinquefasciatus* (136) or *An. gambiae* s.s. (19) an odor with a blood meal as a reward revealed that these species learn to respond to an unconditioned stimulus in association with a conditioned stimulus. Field experiments should confirm whether mosquitoes also learn from a positive blood meal under natural conditions and whether this will influence host choice. Mwandawiro et al. (96) tested the host preference of *Cx. vishnui* under semifield conditions and showed that when mosquitoes were given a host choice by being released into a net containing both cows and pigs, they exhibited a tendency to feed on the host to which they had been attracted in an initial experiment. This feeding preference was not shown by the offspring, suggesting physiological/behavioral conditioning in the host preference of the parents (96). Similar experiments with *Ae. aegypti*, however, did not show any learning abilities (1).

Although some studies have shown that mosquitoes can learn from a positive stimulus such as a blood meal, it is still unclear whether learning influences host choice under natural conditions. Studies with *Cx. quinquefasciatus* (136) and *An. gambiae* s.s. (19) indicated that mosquitoes may learn from a negative experience. If mosquitoes could associate the odor of insecticide-treated bednets (ITNs) with not being able to feed, this would lead to avoidance of ITNs and increase the risk for people not sleeping under a bednet.

ITNs: insecticide-treated bednets



**IRS:** indoor residual spraying

**HBI:** Human Blood Index

### Insecticide-Treated Bednets and Indoor Residual Spraying

The use of ITNs and indoor residual spraying (IRS) reduce the number of malaria cases and deaths (67, 107), and these were adopted by the World Health Organization as the most valuable malaria interventions (151). ITNs prevent people from being bitten by repelling mosquitoes or killing them when they land on the net. IRS kills female mosquitoes resting in a house and can repel other mosquitoes from entering. A mosquito population may adapt to ITNs and IRS by developing resistance against the insecticide used or changing its behavioral characteristics, thereby avoiding contact with the insecticide.

After the application of IRS or the introduction of ITNs, mosquitoes may change from feeding indoors to feeding outdoors (111, 117) or a resident outdoor mosquito population may be revealed that had previously gone unnoticed. Another way to avoid contact with an ITN is to bite earlier at night (78, 82). Often a decrease in the Human Biting Index (HBI, which represents the proportion of blood-fed mosquitoes on people) is observed after the introduction of ITNs, IRS, or both. This decrease may be caused by a reduction in the number of humans as potential hosts or by the repellent effect of the ITN or IRS. This reduction in the number of available human hosts will be more challenging for strongly anthropophilic mosquitoes such as *An. gambiae* s.s. than for opportunistic mosquitoes such as *An. arabiensis* (Figure 1) that may readily switch to other hosts. The number of *An. gambiae* s.s., for example, often decreases in areas where ITNs are introduced (5, 9, 17, 78). The population of a highly anthropophilic strain of *An. arabiensis* in Zambia also decreased after the introduction of ITNs (39). The HBI of this *An. arabiensis* strain remained high after the introduction of ITNs, indicating that the species was not able to adapt to the intervention and shift its host preference. Opportunistic members of the *An. funestus* complex, however, may shift to feeding on ruminants, and *Cx. quinquefasciatus* tends to feed more on birds when ITNs are introduced (9). The introduction of IRS also lowers the HBI of several mosquito species, although this not as well documented (14, 43, 120).

Gillies (46) showed that it is possible to select for strains of *An. gambiae* s.s. that differ significantly in their innate host preference (see above). If humans become less available in an area with intense use of ITNs or IRS, such a change in innate host preference can be expected. Although the studies mentioned above showed a change in host choice after the introduction of ITNs or IRS, to our knowledge only one study also addressed the innate host preference of the mosquitoes studied. In an area in Burkina Faso with high bednet coverage, the proportion of feeds taken on humans by *An. gambiae* s.s. was approximately 40% (64). In contrast, 88% of *An. gambiae* s.s. collected in the field “chose” a human-baited trap over a trap baited with cow odor, indicating a preference for humans but a zoophilic pattern of host selection (64). Although this study showed that *An. gambiae* displays plasticity in feeding behavior in this area, it is unclear why the innate preference did not change after all these years of positive feeds on cows.

### Host Abundance

The abundance of a certain animal species often determines the host choice of a mosquito, especially if this mosquito species is opportunistic (52, 122). However, the host choice of mosquitoes with a clear host preference may also change when their preferred host becomes less abundant (64, 149). As mentioned above, both IRS and the use of ITNs reduce the availability of humans as a host, thereby forcing mosquitoes to feed on other hosts. Other, more natural causes may also lead to a shift in host abundance and thereby affect host choice. Edman (33) studied to what extent host preference and host availability determine feeding rates. Mosquitoes were sampled in three areas for four years in Florida and host abundances were calculated in each area. Mammals

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were the preferred host of all mosquito species caught, but the distribution on mammals differed among species. Host abundance changed over the years and between areas and affected mosquito host choice. Although both innate host preference and host abundance affected feeding rates, the influence of either of these factors depended on the mosquito species (33).

Many *Culex* species have a preference for feeding on birds. The abundance of birds, however, often fluctuates throughout the year because of migration. When the availability of their preferred host declines, *Culex* species may switch to other hosts, including humans (33, 52, 122).

### Physical Barriers

Mosquito-proof housing is an effective strategy to reduce the number of mosquito bites and thereby malaria transmission (53). Simple modifications to the design of indigenous houses, such as screening windows and doors and closing eaves, can readily protect people from mosquitoes and malaria (71). Installing a ceiling in a house can be very effective against *An. gambiae* s.l., which enters through the eaves (72), but less effective against culicines that enter mostly through doors and windows (98). To our knowledge, the effect of mosquito-proof housing on the host choice of mosquitoes is unknown, although the results will probably be similar to those of intervention with ITNs.

### HOST PREFERENCE AND DISEASE TRANSMISSION

The Ross-Macdonald model (77) is historically the most important model to predict the transmission risk of malaria and other vector-borne diseases. Although the model has often been adjusted and expanded, the human-biting rate remains one of its most important parameters (127, 141). The importance of the human-biting rate is also reflected by the predominantly anthropophilic behavior of vectors of malaria and dengue fever, probably the two most important vector-borne diseases today. Both *Plasmodium falciparum* and dengue virus can be transmitted by different *Anopheles* and *Aedes* species, respectively, but only a few species are of major importance in disease transmission because of their strong anthropophilic behavior (7, 119, 131).

The influence of host preference on disease transmission can be more complex. Some *Culex* species, such as *Cx. pipiens*, have a preference for specific birds, in this case the American robin (*Turdus migratorius*) (52). This preference is the most influential parameter in the intensity and peak of West Nile virus (WNV) in *Culex* mosquitoes (37, 122). When the American robin migrates, *Culex* mosquitoes shift from their preferred avian host to humans, thereby increasing WNV transmission to humans (52). The initial increase in WNV transmission with increasing feedings on humans will stop when the fraction of feedings on humans (which are dead-end hosts for WNV) becomes so large that transmission is inefficient (37).

### DISCUSSION AND CONCLUSION

This review shows that many mosquitoes express an opportunistic trait of host choice, but that some species are truly host specific. In species with a strong innate host preference, such as *An. gambiae* s.s., this is assumed to lead to the highest levels of reproductive fitness (75, 76). The host choice of opportunistic mosquitoes is often determined by the host species that is most abundant or readily available. An example of this is the variable host preference of *Cx. quinquefasciatus*, which varies from 100% mammalophilic, with many meals taken on humans, to a high degree of ornithophily (Figure 1). This variation is determined, not geographically, but by local ecotypic factors. For example, in New Delhi, India, 26.3% of blood meals were taken on humans (57), while in Kerala, India, more than 74% of blood meals originated from humans (118). In Kenya,

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**WNV:** West Nile virus

**Mammalophilic:** a general preference for feeding on mammals, but occasionally on birds or reptiles/amphibians

**Ornithophilic:** a general preference for feeding on birds, but occasionally on mammals or reptiles/amphibians

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*Cx. quinquefasciatus* was 100% mammalophilic, with 3–9% of meals originating from humans (95), whereas in Tanzania, the species had a strong anthropophilic behavior (81). In North America, mammalian feeds of this species may range from less than 10% to 52.5% and depend greatly on host abundance (36, 37). The high degree of plasticity in host preference of *Cx. quinquefasciatus* as shown from these studies suggests that, although inherent preferences may prevail locally, this species is exquisitely adapted to obtaining blood under many different circumstances, where the most abundant host species seems to be favored. This behavior contrasts that of the specialist *An. gambiae* s.s., which is inherently anthropophilic and maintains this behavior under different circumstances (**Figure 1**), although occasionally derivations of this behavior are reported, presumably when human hosts are scarce.

Studies reporting high degrees of anthropophily of mosquitoes often refer to indoor collections of mosquitoes, where the insects are most likely to encounter only humans. Thus, a strong bias for a particular host can occur when circumstances limit host choice, although the species has an inherent opportunistic feeding behavior (**Figure 1**). True host preference may best be tested by using choice tests with live hosts or host-derived odor samples. These tests can be performed in the laboratory for mosquitoes that can be kept in culture (102, 124) or in a field setup for wild mosquitoes as demonstrated by Dekker & Takken (30) and Torr et al. (137).

A few mosquito species, such as *An. gambiae* s.s., *An. funestus*, and *Ae. aegypti*, express a high, genetically fixed species preference (**Figure 1**). Even under conditions where humans are scarce and other hosts abundant, high feeding rates on humans, mediated by olfactory senses that are tuned to human-specific cues, may occur (131). Therefore, in order to make correct inferences about host preferences of a mosquito, it is necessary to take into consideration the abundance and availability of a particular host. Such information is essential for planning strategies to control vector-borne diseases, in which the vector associated most strongly with humans should be the principal target while non-human-feeding species can be ignored.

Of the three important disease vectors, *Ae. aegypti*, *An. gambiae* s.s., and *Cx. quinquefasciatus*, there are surprisingly few studies on the host preference of *Ae. aegypti* compared with the other two species (**Figure 1**). The behavior of *Ae. aegypti* has been studied extensively in the laboratory, but behavioral field studies with this mosquito are rare. For example, laboratory studies have shown a very strong preference of *Ae. aegypti* for human odorants (6, 45), but confirmation of this behavior from field studies is lacking. Given the very important role of this mosquito species in dengue transmission, detailed knowledge on the presumed host association of this mosquito from wild populations would be essential for designing effective tools for mosquito control.

The recent discovery of a likely exophilic line of *An. gambiae* s.s. in Burkina Faso (113) calls for behavioral research to assess whether the host preference of this subspecies varies from its closest sibling, which is highly endophilic and readily bites humans. This research cannot be carried out by blood meal analysis only; it should also involve choice assays to examine the olfactory response of both siblings to a range of common hosts. Such studies will elucidate the genetic regulation of olfaction, a subject that has rapidly gained attention in recent years. Thus, a comparison of the olfactory genes of both mosquito lines may reveal important clues to the regulation of anthropophily, a crucial aspect of host preference behavior of mosquitoes.

In recent years the widespread use of IRS and ITNs has led to significant reductions of *An. gambiae* s.s. in parts of Africa (5) but it has also altered its behavioral traits. Increased exophilic behavior has been reported (111, 117). Because the anthropophilic trait of *An. gambiae* s.s. is very strong and genetically fixed, detailed studies on the host preference of these outdoor-biting populations of *An. gambiae* s.s., as well as of sympatric human-biting members of the *An. gambiae* complex such as *An. arabiensis*, are required. This altered behavior has been suggested to lead to increased outdoor transmission of malaria, but this would also require a behavioral adaptation



of these vectors. Alternatively, *An. arabiensis* might become a more dominant mosquito, as the decline of *An. gambiae* s.s. leaves behind a nutritional niche for this opportunistic species. The development of more accurate tools for sampling outdoor anopheline populations (89) promises to provide data that can lead to better understanding of the epidemiology of malaria.

The reported variation in arbovirus transmission due to the annual migration of avian hosts demonstrates that the vector *Cx. pipiens* expresses a certain degree of host preference, i.e., for the American robin. As the transmission risk of West Nile virus varied with the annual migration of the robins (52), associated with high feeding rates of *Cx. pipiens* on robins, it seems that this avian species provides a fitness benefit to the mosquitoes that cannot be derived equally well from other bird species. Is this a common feature in mosquitoes, and therefore does it have consequences for the risk of vector-borne diseases mediated by host preference? In addition to behavioral choice assays, studies on gene-silencing using RNAi technologies may reveal the regulatory mechanisms of such behavior, through identification of the genes that control host preference.

The strong association of anthropophilic behavior with the most important disease vectors calls for investigations of the evolutionary mechanisms of these behaviors. It is likely that the pathogens have exploited this behavioral trait, as human *Plasmodia* and dengue are all anthroponoses, requiring a specialist vector in their life cycle. Hence coevolutionary adaptations in host preference and pathogen-host interactions may have led to this trait, which is clearly beneficial to the pathogen (22, 55). Recent advances in molecular genetics allow for the elucidation of this phenomenon, and these can be used to gain novel insights into parasite-mediated behavior of disease vectors.

The examples discussed in this review show that, in spite of a considerable volume of published work on mosquito host preference, studies that would further clarify the nature of this behavior could help us understand why mosquitoes select some host species more than others and, above all, whether the process of host selection is driven by fitness advantages that make the insect optimize its foraging strategies and host selection. A better comprehension of the host preference of mosquitoes will benefit our understanding of vector-borne disease epidemiology and, ultimately, for the development of effective disease control strategies, for example, by targeting host-specific vector species more accurately.

#### SUMMARY POINTS

1. Host preference of mosquitoes is affected by extrinsic and intrinsic determinants, of which genetics is an important component. Many species express inherent traits in host preference (e.g., a preference for birds or mammals), but this preference is readily overruled by physiological factors (hunger) and physical abundance of available hosts.
2. Many studies on host preference of mosquitoes are biased because of the limited availability of multiple host species to the mosquitoes; host preference then provides data on those hosts that were most readily accessible and may not reflect the true, inherent host preference.
3. True host preference may best be tested by using choice tests that can be performed in the laboratory for mosquito species that can be kept in culture or in a field setup for wild mosquitoes.
4. Mosquito species that are highly anthropophilic are often vectors of important human diseases, suggesting that the evolution of host preference has coevolved with the evolution of pathogen-host interaction. In these mosquito species, the anthropophilic trait appears genetically fixed and dominant.

5. In many mosquito species, host preference exhibits a high degree of plasticity, caused mostly by environmental circumstances when favorite host species disappear or are not accessible.
6. Widespread use of IRS and ITNs for malaria control may have caused shifts in host-seeking behavior, resulting in shifts in the time of or preferred site of host seeking; these changes may affect the innate host preference when preferred hosts are less available.
7. The recent discovery in West Africa of two populations of *Anopheles gambiae* s.s. that express behavioral differences in host preference calls for research on the genetic control of this behavior.
8. Seasonal shifts in host availability may be associated with shifts in the transmission risk of arboviral disease such as West Nile virus.

### DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

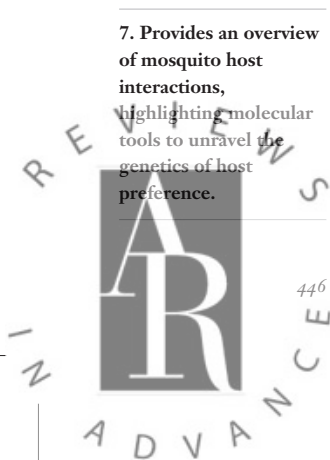
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