

Sweaty skin: an invitation to bite?

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***Anopheles gambiae sensu stricto* and *Aedes aegypti* have a preference for human blood, which determines their importance as vectors of pathogens responsible for human diseases. Volatile organic chemicals are the principal cues by which humans are being located. Human sweat contains components that are attractive to anthropophilic mosquito species, and variation in sweat composition causes differential attractiveness to mosquitoes within and between individuals and also between humans and other mammals. Characteristics of skin glands and skin microbiota define the odorous organic compounds emitted by sweat, thereby the degree of attractiveness of the host to mosquitoes. Carboxylic acids in particular appear to characterize humans. Thus sweat-associated human volatiles are probably the primary determinant factor in the host preference of anthropophilic mosquitoes.**

Is human sweat unique?

In recent decades, the incidence of dengue has grown dramatically around the world, and today approximately two-fifths of the world's population are at risk from dengue [1]. Also the number of yellow fever cases has increased over the past two decades, and the risk of large outbreaks in urban areas in Africa is more probable than ever [2]. Despite recent reports of reduction of malaria cases in several countries, still half of the world's population is at risk of contracting malaria, with most malaria cases and deaths occurring in sub-Saharan Africa [3,4].

The most important vectors of these life-threatening diseases are the mosquito species *Anopheles gambiae* Giles *sensu stricto* (malaria) and *Aedes aegypti* L. (dengue and yellow fever) (Figure 1), presumably because of their high degree of anthropophily (i.e. preference for humans over animals as their blood host) and strong association with human communities [5,6].

Vector control is one of the cheapest and historically most successful approaches to fight vector-borne diseases [7,8]. Existing tools such as insecticide-treated nets and indoor-residual sprays are effective but also have limitations because of insecticide resistance. Therefore, novel vector-control tools are needed. Odour-baited mosquito traps can be effective control tools, especially when integrated with other methods [8,9].

Visual, physical and especially chemical cues play an important role in the host-seeking process of mosquitoes [5]. Because of the high degree of anthropophily of both *An. gambiae s.s.* and *Ae. aegypti*, it is probable that several of

these chemical cues are similar for these species. There is indeed a clear overlap among the kairomones to which both mosquito species respond: carbon dioxide (CO₂), ammonia, lactic acid, and other aliphatic carboxylic acids play a role in the host-seeking process of both species [10]. With the exception of CO₂, these compounds are present on the human skin and in human sweat [11,12].

In Y-tube bioassays, an odorous blend consisting of ammonia, lactic acid, and two other carboxylic acids was almost as attractive to *Ae. aegypti* as an extract of human skin residues [13]. A more complex blend of CO₂, ammonia, lactic acid, and seven other carboxylic acids, developed based on results obtained in a dual-choice olfactometer [14], attracted three to five times more *An. gambiae sensu lato* females into experimental huts than sleeping humans [15]. These results show the potential of these blends for use in vector control programs.

The skin microbiota plays an important role in human odour production, especially in the conversion of odourless sweat into sweat with its characteristic odour [16]. Interestingly, human sweat incubated with bacteria is more attractive to *An. gambiae s.s.* than odourless sweat, coinciding with an increase of ammonia levels [12,17]. In addition, microorganisms present on the human skin have recently been shown to produce volatile organic compounds, which include aliphatic carboxylic acids, which are attractive to *An. gambiae s.s.* [18]. Considering all of this evidence, should we conclude that human sweat has a distinctive smell, different from other mammals, which anthropophilic female mosquitoes use to locate their favourite blood host?

Mammalian sweat and mosquito host specificity

What proof supports this hypothesis? First, what is known about sweat produced by humans compared to sweat of other mammals? The distribution, function and secretion of the different types of human skin glands (sebaceous, apocrine and eccrine) are briefly described in Box 1. Eccrine glands are the best developed and most abundant glands in humans and are widely distributed over the general body surface. By contrast, in most mammalian groups (including prosimians, monkeys and apes, with the exception of great apes) eccrine glands are limited to the friction surfaces of the hands, feet and tail. Apocrine glands, which play an important role in chemical communication, have a restricted distribution in most mammals including humans. In hoofed animals such as the donkey, cow, horse and camel, and in canids, apocrine glands can be found over the general body surface and have a function in evaporative cooling. All prosimians, monkeys, and apes have thermal apocrine glands associated with hair follicles. The chimpanzee and

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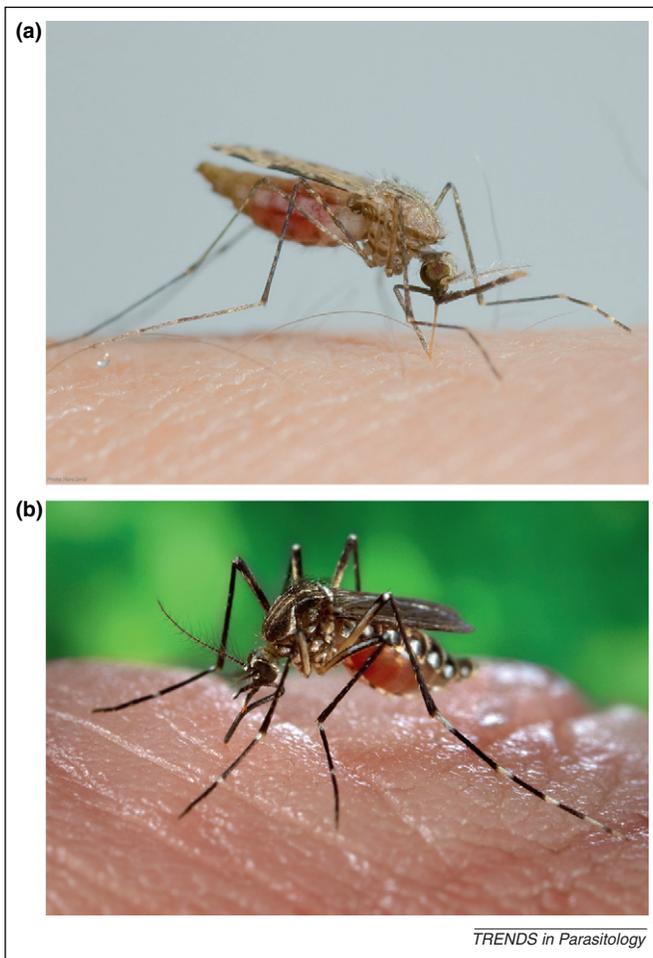


Figure 1. Mosquito vectors. (a) *Anopheles gambiae* s.s. (photo by H. Smid, Bugsinthepicture, The Netherlands); (b) *Aedes aegypti* (courtesy of F.H. Collins, University of Notre Dame, USA).

the gorilla exhibit a distribution ratio of approximately 40% apocrine to 60% eccrine sweat glands, whereas monkeys, the gibbon, and orangutan have a 50:50 distribution. By contrast, humans mainly possess eccrine and relatively few apocrine glands [19,20].

Most information on the composition of and odour production by sweat has been retrieved from humans [11,21]. Axillary odour especially has received much attention [22,23], not only because humans prefer to mask this odour, but also because the armpits are considered prime candidates for the release of human pheromones [24]. The extensive aggregation of both apocrine and eccrine glands in the axillae is only found in humans and African apes (and are somewhat developed in orangutans) [20]. Remarkably, more volatile organic compounds (VOCs) are present in human axillary sweat than in human urine or saliva [22].

Eccrine glands produce odourless sweat, primarily consisting of water, with small traces of salts, proteins, amino acids, urea, ammonia and lactic acid. Apocrine sweat gland secretion mainly consists of lipids, steroids and proteins. Bacterial action is responsible for the conversion of odourless apocrine sweat into the typical smell. In humans, bacteria of the genera *Propionibacterium*, *Corynebacterium* subgroup A, and *Staphylococcus* break down the secretion of sebaceous glands (odourless sebum that for a large part consists of lipids) into mainly carboxylic acids [16,19,20,25,26] (Box 1). Also the axillary odour of humans contains volatile carboxylic acids [25,27]. Besides axillary odour, malodour produced by human feet is of interest both in research and pharmaceuticals. Although only eccrine glands are present on the feet [28], feet provide an excellent, moist, environment for bacterial species such as staphylococci that convert sweat components into odorous short-chain carboxylic acids, such as acetic, propanoic, 2-methyl

Box 1. Human glands, skin microbiota, and mosquito attraction

A. Distribution, function and secretion of human glands (See [16,19,20,26,28]).

	Apocrine glands	Eccrine glands	Sebaceous glands
Distribution	Deep in the dermis of the skin, associated with hair follicles, and mainly situated in the axillae, and in the perineal and genital area	Most numerous on the palms and soles, then in decreasing order on the head, trunk, and the extremities	All over the body, except on the palms and the soles; the largest and most numerous sebaceous glands are in the skin of head, forehead, cheeks, and chin
Function	Contribute little to thermoregulation and suggested to play a role in chemical communication	Thermoregulation	Produce sebum, an oily secretion that lubricates and protects the skin surface and hair; not involved in thermoregulation
Secretion	Lipids, steroids, and proteins	Primarily water, with small traces of salts, proteins, amino acids, urea, ammonia, and lactic acid	Sebum, which consists mainly of lipids

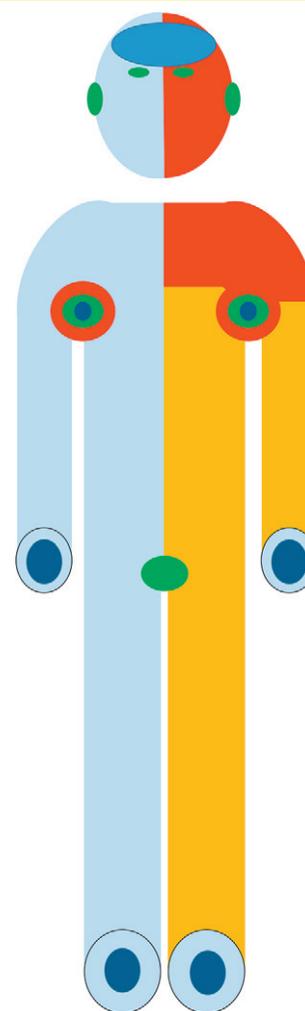
B. Human glands and skin microbiota (See [28]).

- *Corynebacterium*, *Micrococcus*, *Propionibacterium* and *Staphylococcus* are examples of genera of microorganisms that are frequently found on human skin.
- The microbiota composition on human skin is determined mainly by the number and density of apocrine, eccrine, and sebaceous glands at a specific site and whether or not the site is shielded from direct contact with the surrounding air (think of axillae, clothing, and shoes).
- The table provides examples of bacterial genera common on specific human body parts.

Body part	Gland type	Microbiota density	Microbiota genera present
Head and body	Many sebaceous Eccrine present Apocrine local	High	Dominated by propionibacteria and staphylococci
Axillae	Many sebaceous Apocrine present Eccrine present	High	Dominated by corynebacteria and staphylococci
Arms and legs	Few sebaceous Few eccrine No apocrine	Low–moderate	Mainly staphylococci and micrococci
Hands	Many eccrine No apocrine No sebaceous	Moderate	Mainly staphylococci
Soles	Many eccrine No apocrine No sebaceous	High	Dominated by staphylococci

C. Production of volatile carboxylic acids by skin microbiota and mosquito attraction.

- Skin lipids present in human sebum are catabolized by propionibacteria, corynebacteria, and staphylococci into long-chain carboxylic acids, which are subsequently converted by corynebacteria into short-chain carboxylic acids (C1–C12) [25].
- Metabolism of branched aliphatic amino acids, present in eccrine sweat, by staphylococci also results in short-chain carboxylic acids (C2–C12) [30].
- Many short-chain carboxylic acids increase the attractiveness of ammonia and/or lactic acid, present in eccrine sweat, to *An. gambiae* s.s. and *Ae. aegypti* females. The effect of VOCs on mosquito attraction depends on concentration, ratio, and combination of the compounds within a blend [10].
- Examples of short-chain carboxylic acids produced by human skin bacteria are propanoic and 3-methylbutanoic acid, both highly volatile compounds, which have, to the human nose, a sweaty odour [25,29,30].
- Most studies on VOC emanation from different human body parts have been restricted to hands, feet, and axillae [18,22,23,27,29,34,55,57]. Nevertheless, based on gland distribution in relation to skin microbiota, one can speculate which body parts emit ammonia, lactic acid, and/or carboxylic acids: Because eccrine glands are distributed over the entire body (Figure 1), although in different densities, ammonia and lactic acid can be emitted from the entire body. As several skin bacterial species convert skin lipids into short-chain carboxylic acids, it is probable that these VOCs are not only emitted from the axillae [22,27], but also from the head and upper trunk where many sebaceous glands are also present [27,35]. However, because amino acids, which are present in eccrine sweat, are metabolized into short-chain carboxylic acids as well, it is probable that these compounds can be found also on other body parts, as has been published for hand palms and foot soles [18,34,46,57]. Depending on the local bacterial composition and density [35,59], different body locations will differ qualitatively and quantitatively in VOC production, including carboxylic acids. This could have an effect on biting site selection of mosquitoes. In addition, because many human skin bacteria produce CO₂ [28], small amounts will be emitted by the skin. However, much higher amounts of CO₂ are found in human breath. This compound augments the attractiveness of human skin emanations to both *An. gambiae* s.s. and *Ae. aegypti* females [10]. Because interpersonal variability in skin microbiota composition is high [58,59] and because the correlation between the microbial and chemical odour profile is disturbed by personal habits and living conditions [55], further characterization of the human skin microbiota and its metabolism is needed before it will be possible to create a general map of the odour production by the different parts of the human body [16].



Key:

- Apocrine glands
- Eccrine glands, high density
- Eccrine glands, low density
- Sebaceous glands, high density
- Sebaceous glands, low density

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Figure 1. Distribution of apocrine (green), eccrine (blue/light blue), and sebaceous glands (red/orange) on the human skin surface [28]. The low density of eccrine glands (light blue) present on the head, trunk, arms, and legs are only shown for the left side of the body, whereas the sebaceous glands (red and orange) present on the head, trunk, arms and legs are only shown for the right side of the body.

propanoic, 3-methylbutanoic and decanoic acid [29,30] (Box 1).

Comparisons of sebum of several mammalian species revealed that distinct differences in skin surface lipid composition exist between families, whereas within families, many similarities have been found among species. Human skin lipid composition differs remarkably from other mammals, consisting mainly of triglycerides and their breakdown products such as free carboxylic acids. Mammalian skin surface lipids, including primates, contain little or no triglycerides or free carboxylic acids [31–33].

Several carboxylic acids, short- and long-chain, are present in human skin emanations [11,34,35]. These odorous compounds are believed to contribute to the distinctive olfactory signature of humans [31]. The latter brings us back to mosquito host specificity. Anthropophilic mosquitoes might locate humans using carboxylic acids, which humans uniquely emit. Fifteen of the 20 aliphatic carboxylic acids (C1–C18) that were tested for their attractiveness to *An. gambiae* s.s. and *Ae. aegypti* had a positive effect [10]. In addition to carboxylic acids, many more compounds (over 300) present in human body odour have been identified [22,34,35]. By contrast, significantly fewer volatile emanations were reported to emanate from the skin of other mammals and birds [36,37]. Only a few carboxylic acids have been detected in extracts of chicken feathers and giraffe hair, among which acids that have a positive effect on the attractiveness of lactic acid or lactic acid + ammonia to *Ae. aegypti* or *An. gambiae* s.s., respectively [10,13,14,36,37].

At first glance, two of the other compounds that are attractive to both mosquito species, CO₂ and ammonia, do not seem to be obvious cues to differentiate between possible blood hosts. Carbon dioxide is a major component of vertebrate breath [38], whereas ammonia is mainly produced from animal urine and faeces [39–41]. Vertebrates, however, release CO₂ at various rates, depending on body size, and the concentration exhaled depends on the metabolic rate of an animal [38]. Also for ammonia, host-specific levels of emission from the skin or breath can exist. Similarly, measurements of the amount of lactic acid in skin-rubbing extracts of 13 mammals and chicken revealed that humans have, on average, a much higher amount of lactic acid on their skin [42]. Skin odour of three mammals (calf, goat or cat), which was not or only slightly attractive when offered alone, became as attractive as human odour to *Ae. aegypti* when lactic acid was added [43].

Summarizing the above shows that *Ae. aegypti* and *An. gambiae* s.s. are attracted to human sweat components either secreted by the skin glands (ammonia and lactic acid) or produced by skin bacteria (carboxylic acids) after conversion of skin gland secretions (lipids and amino acids) (Box 1). Because the bacterial composition on human skin depends largely on the number and density of the three types of skin glands [28], it is clear that these glands play an important role in the attractiveness of human sweat to these mosquito species. To be able to elucidate whether this is also true for other mammals, more knowledge is needed of mammalian skin gland distribution and secretion, and mammalian skin microbiota composition, density and VOC production.

Human sweat and mosquito host selection

Even though anthropophilic mosquitoes can distinguish humans from other animals based on body odour, human individuals are not all equally attractive to *Ae. aegypti* and *An. gambiae* s.s. [44–46]. Which sweat-related characteristics are responsible for this differential attractiveness of people to mosquitoes?

Infants and children have been reported to be bitten less frequently by *An. gambiae* mosquitoes than adolescents and adults [44], which might be caused by differences in body mass or physiological differences. The most obvious change in relation to human sweat and body odor production is that apocrine and sebaceous glands mature during puberty [19], and are then colonized by bacteria [47]. So even though parents can recognize their preadolescent children by olfaction [48,49], children have a less ‘pungent’ body odour compared with adults.

Moreover, children produce sweat at a lower rate compared to adults. Both boys and girls have higher levels of lactate in sweat produced during the first 20 minutes of a heat exercise than men and women, dropping to similar levels in a subsequent heat exercise. No gender differences and similar levels of ammonia for children and adults were found [50]. Both *Ae. aegypti* and *An. gambiae* s.s. do not exhibit an age preference when considering adult persons [45,51], which might be explained by only small age-related differences in VOCs from healthy adults [35].

Men have been found to be more attractive to *Ae. aegypti* mosquitoes than women [51], whereas *An. gambiae* s.s. did not discriminate between human individuals based on gender [44,45]. No significant differences relating to gender in VOCs of non-axillary human skin exist [35]. Gender-specific axillary sweat components have been identified, but these compounds are not unique for either sex [22]. By contrast, humans are able to discriminate between body odours of men and women, which might be because of different intensity [52]. In general, individuals vary in the relative abundance of VOCs emitted [53]. Because the behavioural effect of semiochemicals on mosquitoes depends largely on their concentration [10], variations in body odour intensities could contribute to differential attractiveness of individuals to mosquitoes.

Men produce more sweat than women during exercise and more sebum is produced per cm² male skin, presumably because of differing hormonal levels between the sexes [26]. Nevertheless, no differences in concentrations of volatile carboxylic acids related to subjects’ gender or age have been found [54]. The latter could be because of the large number and variety of saturated and unsaturated carboxylic acids synthesized by the human skin [31]. In relation to the latter, sweat appears to have a characteristic individual signature, which is relatively consistent over time [22,55], and axillary sweat samples from identical twins are more similar than those of unrelated persons [56]. Individuals can even be distinguished based on human hand odours alone [57]. An interesting point in this context is that the composition of microbiota on human skin, which is strongly correlated with human body odour, is unique for each person [58] and stays relatively stable over time [59]. The density and variety of microorganisms colonizing the human

skin is higher for men than women, influenced by pH, sweat and sebum [60].

In brief, differential attractiveness to anthropophilic mosquitoes between children and adults emphasizes the importance of the production of lipids by skin glands and the conversion of these lipids into odorous carboxylic acids by skin bacteria. Moreover, the unique skin microbiota composition of each individual in connection with the unique odour profile of a person's sweat appears to determine the differential attractiveness between human individuals.

Conclusions and future directions

Sweat plays an important role in the attractiveness of vertebrates to mosquitoes, and the unique composition of human sweat appears to explain its tantalizing effect on anthropophilic mosquitoes. Based on differences in types of skin glands distributed over the body, it is expected that different vertebrates, including humans, produce sweat at a varying rate and composition. By metabolizing the sweat substances, microorganisms present on the body have a strong influence on the body odour components produced and therefore on mosquito behaviour. In contrast to the microbiota of human skin, little is known about skin microbiota of other vertebrates. A study on the correlation between mosquito host preferences and the microbiota present on the skin of a variety of vertebrate species could elucidate this.

Besides differences in CO₂ emission rates from breath among vertebrate species, humans have a large variety of carboxylic acids and a high amount of lactic acid on their skin. These unique characteristics might enable anthropophilic mosquitoes to distinguish humans from other vertebrates. Ammonia and lactic acid, mainly present in eccrine sweat, in combination with the carboxylic acids resulting from microbial conversion of sebaceous and apocrine gland secretions, seem to be, at least partially, responsible for attraction of *Ae. aegypti* and *An. gambiae* s.s. to humans. Individual differences in sweat production and composition play a role in differential attractiveness of humans to anthropophilic mosquitoes. Sweat is thus an important cue for these mosquitoes, and the composition of VOCs emanating from sweat indeed provides an invitation to bite. Further research will establish to what extent opportunistic mosquito species rely on these VOCs in their host-seeking behaviour.

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