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Mosquitoes as potential bridge vectors of malaria parasites from non-human primates to humans

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Malaria is caused by *Plasmodium* parasites which are transmitted by mosquitoes. Until recently, human malaria was considered to be caused by human-specific *Plasmodium* species. Studies on *Plasmodium* parasites in non-human primates (NHPs), however, have identified parasite species in gorillas and chimpanzees that are closely related to human *Plasmodium* species. Moreover, *P. knowlesi*, long known as a parasite of monkeys, frequently infects humans. The requirements for such a cross-species exchange and especially the role of mosquitoes in this process are discussed, as the latter may act as bridge vectors of *Plasmodium* species between different primates. Little is known about the mosquito species that would bite both humans and NHPs and if so, whether humans and NHPs share the same *Plasmodium* vectors. To understand the vector-host interactions that can lead to an increased *Plasmodium* transmission between species, studies are required that reveal the nature of these interactions. Studying the potential role of NHPs as a *Plasmodium* reservoir for humans will contribute to the ongoing efforts of human malaria elimination, and will help to focus on critical areas that should be considered in achieving this goal.

Keywords: apes, cross-species transmission, host preference, mosquito behavior, *Plasmodium*

NON-HUMAN PRIMATE *PLASMODIUM* PREVALENCE

Non-human primates (NHPs) often serve as reservoir of pathogens of human diseases. The yellow fever virus (Ellis and Barrett, 2008), Chikungunya virus (McCrae et al., 1971; Labadie et al., 2010), and the protozoa *Giardia lamblia* that cause diarrhea (Kowalewski et al., 2011), are all examples of pathogens that originate from NHPs and are infectious to humans. Malaria is caused by parasites of the genus *Plasmodium* that can infect a wide range of vertebrate hosts from reptiles, birds to mammals. Only five *Plasmodium* species are known to cause malaria in humans: *Plasmodium falciparum*, *P. knowlesi*, *P. malariae*, *P. ovale*, and *P. vivax*. Of these five species, *P. falciparum* is most common and most lethal (WHO, 2011).

Plasmodium parasites are, however, also found in other primates than humans. *Plasmodium reichenowi* was the first *Plasmodium* species identified in NHPs, isolated from an infected chimpanzee (Coatney et al., 1971; Rayner et al., 2011). Other NHP *Plasmodium* species have been identified (Coatney et al., 1971; Rayner et al., 2011) and their identity can be studied in more detail since the development of molecular tools. A recent study in which mitochondrial, apicoplast, and nuclear gene sequences from 2700 fecal samples from wild-living African apes have been analyzed, showed that *Plasmodium* species are widely distributed in NHPs and with high prevalence (Liu et al., 2010). The detected parasites could be classified into six discrete major clades, all belonging to the subgenus, termed *Laverania*, which discriminates them from more divergent *Plasmodium* species (Liu et al., 2010; Rayner et al., 2011). Interestingly, some of these *Laverania* clades were only associated with chimpanzee (*Pan troglodytes*) samples and others only with samples from western lowland gorilla's (*Gorilla gorilla*).

Although infections with *Plasmodium* parasites appear to be host-specific, chimpanzees, and gorillas were nevertheless found to be infected with mitochondrial DNA similar to that of human *P. vivax* (Liu et al., 2010). Chimpanzees were also found to be infected with *P. ovale* and *P. malariae*, which may have contributed to the perseverance of these human malaria parasites in Africa (Duval et al., 2009, 2010; Hayakawa et al., 2009; Krief et al., 2010; Duval and Ariey, 2012). Several studies performed between 1940 and 1956 showed that these species can be transmitted from apes to humans (Rodhain and Dellaert, 1955a,b; Garnham et al., 1956; Rayner et al., 2011). *P. falciparum* has not been found in wild NHPs but has been detected in captive chimpanzees and bonobos (Liu et al., 2010; Rayner et al., 2011). Interestingly, mitochondrial sequence analysis has revealed that western lowland gorillas probably served as the source of human *P. falciparum* (Liu et al., 2010) and *P. falciparum* diverged between 112,000 and 1,036,000 years ago (Baron et al., 2011).

Little is known about the ability of NHP malaria parasites to infect humans, except for the fifth human *Plasmodium* parasite, *P. knowlesi*, which was long known only as a parasite of monkeys. The parasite was extensively studied for basic immunological, chemotherapeutic, and biological relationships between malaria parasites and their primate hosts (Collins, 2012). A study in 2004 in Malaysian Borneo revealed that 58% of blood samples from people that had been diagnosed with *P. malariae*, were actually infected with *P. knowlesi* after detection by PCR (Singh et al., 2004). These findings have led people to consider *P. knowlesi* to be the fifth human malaria parasite (White, 2008; Collins, 2012). This example indicates that care should be taken when screening for *Plasmodium* by standard blood smears or rapid

diagnostic tests, which will not reveal if a person is infected with ape *Plasmodium*.

In recent years the diversity and origin of malaria parasites has been studied in detail using advanced molecular techniques (Krief et al., 2010; Liu et al., 2010; Baron et al., 2011; Prugnolle et al., 2011). In several reviews on this topic the potential risk of a parasite exchange between NHPs and humans has been identified (Kevin, 2009; Rayner et al., 2011; Duval and Ariey, 2012). The authors of these studies suggest that: (a) Humans living near wild-ape communities should be tested for zoonotic infections using molecular approaches capable of differentiating between human and zoonotic parasites, (b) Wild NHPs should be screened for *P. vivax*, *P. malariae*, and *P. ovale*, because the evidence for cross-transmission is the strongest for these *Plasmodium* species, and (c). Mosquito species should be identified that could transmit *Plasmodium* parasites between NHPs and humans. Techniques for screening for *Plasmodium* parasites in humans and NHPs have advanced in recent years and have been applied in some of the studies on NHP *Plasmodium* mentioned above. The identification of mosquito species that are likely to transmit *Plasmodium* parasites between NHPs and humans has received little attention and will be discussed below.

THE ROLE OF MOSQUITOES

Mosquitoes play a key role in the transmission of *Plasmodium* parasites between humans. Mosquito species characteristics will therefore influence the *Plasmodium* transmission between humans and NHPs. Transmission studies with malaria vectors have mainly focused on those mosquito species that transmit *Plasmodium* between humans. Mosquito species that are likely to facilitate a cross-species exchange of *Plasmodium* have occasionally been studied for their capability of transmitting *P. knowlesi* in Asia (Collins, 2012). Such studies have not been done in Africa, and consequently knowledge about the role of African mosquitoes as *Plasmodium* bridge vectors is lacking (**Figure 1**).

MOSQUITO SUSCEPTIBILITY

About 30 of the approximately 450 species of the insect genus *Anopheles* are vectors of human malaria (White, 1982). The susceptibility of a mosquito to malaria parasites has a great influence on the effectiveness of a mosquito species as a malaria vector. Little is known about the susceptibility of mosquitoes to the different species of NHP *Plasmodia*, mainly because these *Plasmodium* parasites are not available as a laboratory culture. Experiments with a chimpanzee infected with *P. reichenowi* showed that the malaria mosquito species *Anopheles quadrimaculatus*, *A. stephensi*, *A. maculatus*, *A. dirus*, and *A. culicifacies* could be infected with this parasite species. However, *A. gambiae* s.s. and *A. albimanus* were refractory to the infection (Blacklock and Adler, 1922; Collins et al., 1986), which suggests that not all vectors of *P. falciparum* can equally transmit NHP *Plasmodium*.

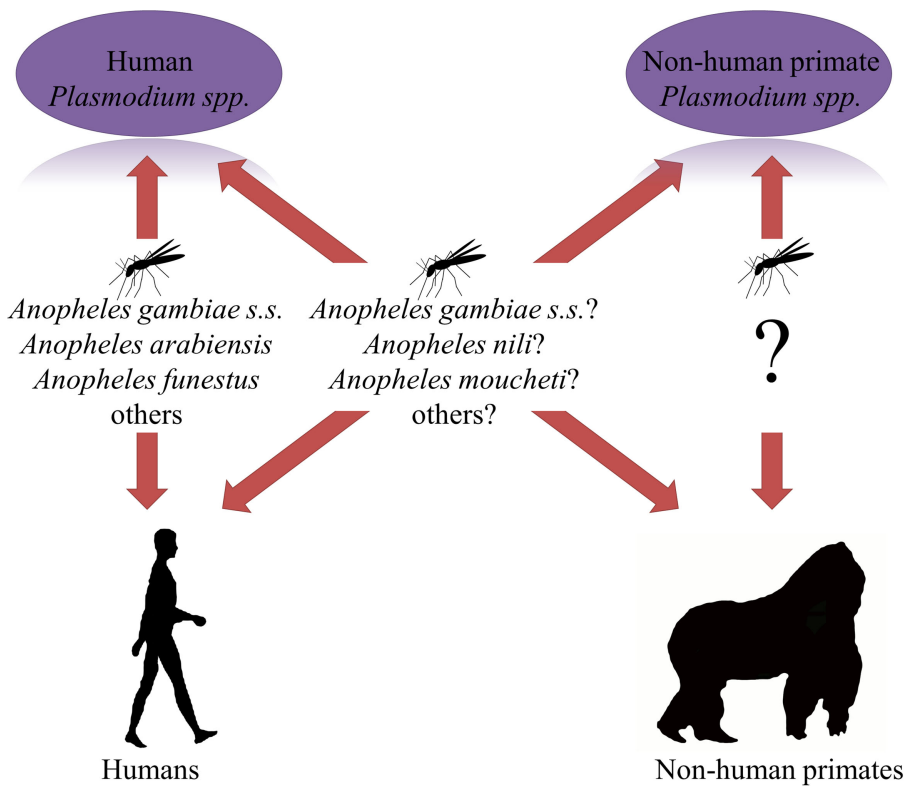

FIGURE 1 | Interactions between mosquitoes, their hosts, and human and non-human primate *Plasmodium species* in Africa. Question marks indicate unidentified vectors.

Studies that nowadays would be considered unethical have shown that mosquitoes infected with NHP *Plasmodia* can transfer the parasites to humans and cause illness (Coatney et al., 1961; Schmidt et al., 1961; Bennett and Warren, 1965; Contacos et al., 1970). Current molecular tools should make it possible to identify mosquitoes in the field that are infected with NHP *Plasmodium* parasites. Detection of parasites in wild apes and humans living near wild-ape communities will support the potential of these mosquitoes as a bridge vector.

MOSQUITO HABITAT

Anopheles gambiae s.s. and *A. funestus* are important African vectors of human malaria partly because they prefer semi-open and open areas and these are the areas that are often more populated by humans. In forested areas other mosquito species become important as malaria vectors for humans. *A. nili*, for example can breed in shaded streams and plays a role in the transmission of malaria in localized rainforest areas (Carnevale et al., 1992; Guerra et al., 2006). *A. moucheti* is considered a forest species and is often reported to be the main vector of human malaria in rainforest areas of Africa (Ollomo et al., 1997; Fontenille et al., 2003; Guerra et al., 2006; Antonio-Nkondjio et al., 2008).

Although studies on mosquitoes that transmit human malaria in rainforest areas are scarce, *A. nili*, *A. moucheti*, and other forest *Anopheles* spp. are possible candidates for malaria parasite transmission from NHPs to humans or vice versa (**Figure 1**). Deforestation, mining, and agriculture may lead to more open areas, thereby giving other mosquito species, like *A. gambiae* s.s. and *A. funestus*, which are known to be effective vectors of human malaria (Gillies and Coetzee, 1987), the opportunity to populate

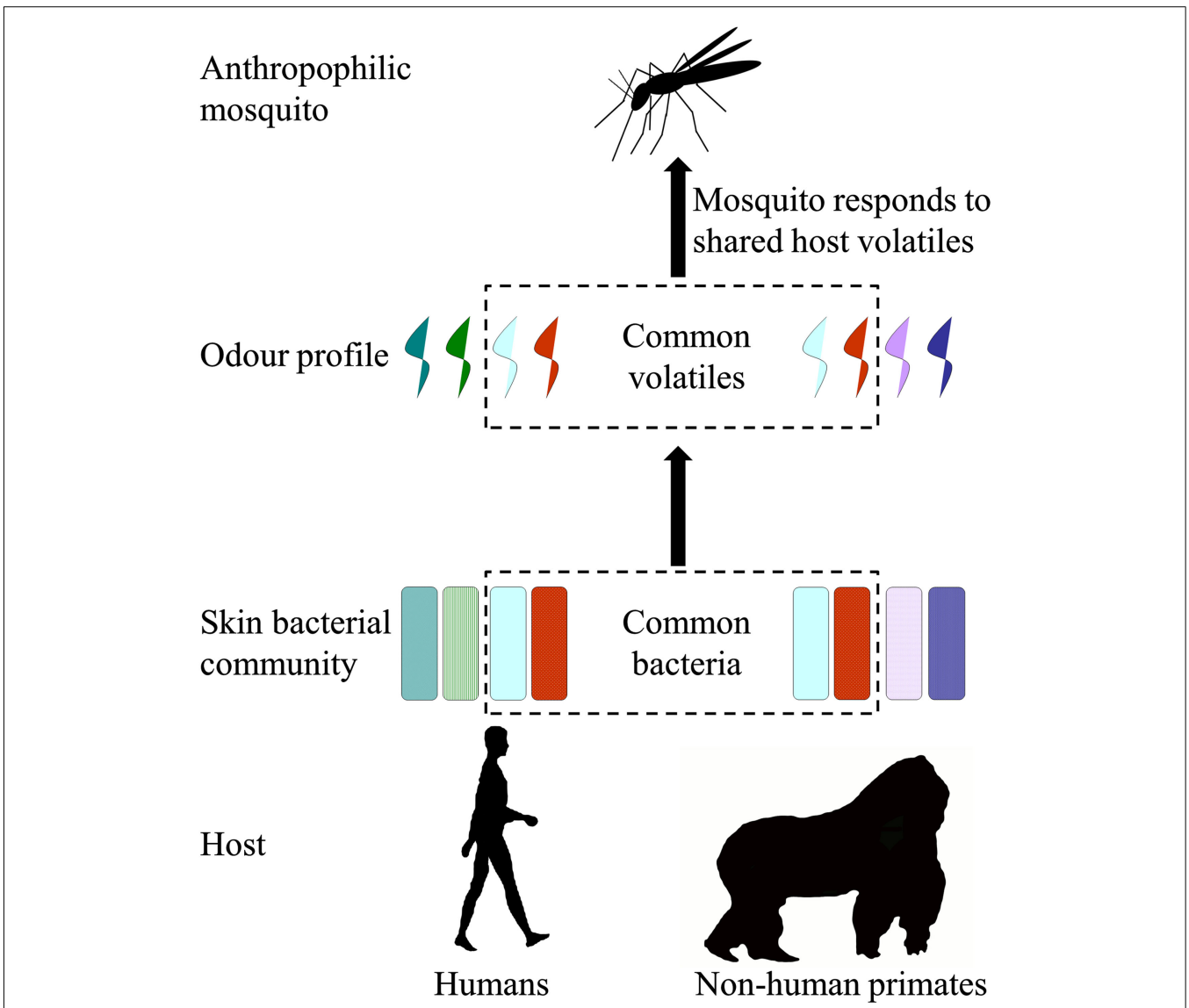

FIGURE 2 | Mosquito-host interactions and the possible response of anthropophilic mosquitoes to volatiles shared by humans and non-human primates.

these regions. These human activities will also lead to closer contact between NHPs and human beings, thereby increasing the risk of disease transmission.

Identification of mosquito species that act as malaria vectors in rainforest areas is essential when trying to eliminate or eradicate human malaria, because these species may possibly transfer *Plasmodium* from NHPs to humans or vice versa. In addition to this, the prevalence of NHP malaria parasites in forest mosquitoes and humans living in these areas should be investigated. This will help to focus on critical areas that should receive additional interventions when trying to eliminate or eradicate malaria.

HOST PREFERENCE

Host selection by mosquitoes drives the transmission of *Plasmodium* parasites between humans, and will play a key role in the frequency and efficiency of an exchange of *Plasmodium* parasite between humans and NHPs. Yet, next to nothing is currently known about the mosquito species that could facilitate such an exchange (**Figure 1**; Rayner et al., 2011).

Identification of mosquito blood meals by multiplex PCR (Garros et al., 2011) may lead to identification of mosquito species that feed on both humans and NHPs. Collected mosquitoes may also be used to determine *Plasmodium* infections in mosquitoes, but the number of mosquitoes needed to confirm such infections is high given the relatively low natural infection rate of human *Plasmodium* infections in mosquitoes (Marchand et al., 2011). Blood-fed mosquitoes can be caught nearby human dwellings with resting boxes, clay pots, or pitfall traps (Service, 1993; Odiere et al., 2007; Qiu et al., 2007). However, the collection of blood-fed mosquitoes in areas where NHPs are naturally abundant may require specific arrangements.

To find their blood host, mosquitoes use physical cues like heat, moisture, vision in addition to chemical cues like carbon dioxide and body odor (Takken and Knols, 1999). Mosquito species with a certain host preference use body odor components to distinguish between different host species (Costantini et al., 1998; Takken and Knols, 1999; Pates et al., 2001). *A. gambiae* s.s. is one of the most important and best studied vectors of human malaria. It is a highly efficient vector because of its restricted, anthropophilic, host range, and preference to feed indoors (Costantini et al., 1998; Takken and Knols, 1999). Interestingly, its sister species, *A. quadriannulatus* and *A. arabiensis*, have a wider host range that is more zoophilic (White et al., 1980; Hunt et al., 1998; Torr et al., 2008) or opportunistic (Costantini et al., 1996, 1998), respectively. Volatiles released by the human skin provide essential cues that guide *A. gambiae* s.s. to its human host (Smallegange and Takken, 2010). Recently, it was found that the human skin microbiota plays a critically important role in producing these volatiles and thereby in mediating mosquito-host interactions (**Figure 2**; Verhulst et al., 2009, 2010, 2011).

The volatiles that are released from the human skin have been studied intensively and this resulted in the identification of more than 350 compounds (Bernier et al., 1999, 2000; Curran et al., 2005; Penn et al., 2007; Gallagher et al., 2008). Less is known about the volatiles released by NHPs. Skin glands and their associated bacteria determine which volatiles are produced and therefore play an important role in the attractiveness of human sweat to mosquitoes

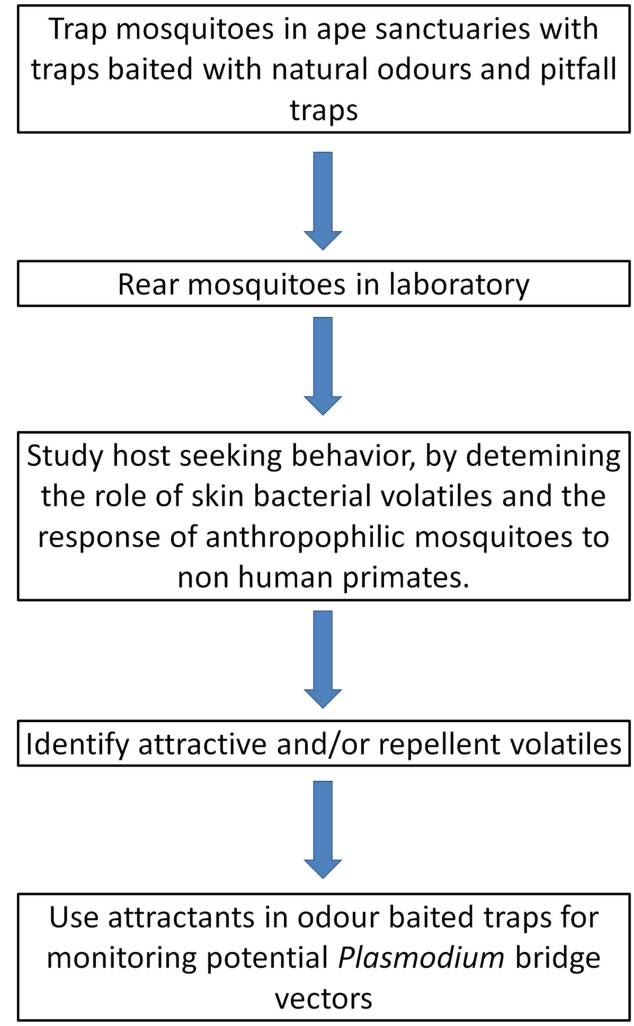

FIGURE 3 | Study design for the identification of mosquito species that may act as bridge vectors of *Plasmodium*.

(Smallegange et al., 2011). Mosquitoes also vary in their attraction to different parts of the human body (Dekker et al., 1998). The type of skin glands and associated bacteria determine the difference between, for example, foot odor (eccrine glands) and axillary odor (apocrine glands). In most mammals, eccrine glands are limited to the friction surfaces of the hands, feet, and tail. By contrast, the eccrine glands of great apes and humans are distributed over the general body surface (Smallegange et al., 2011). Also the extensive aggregation of both apocrine and eccrine glands in the axillae is only found in humans and great apes (Folk and Semken, 1991; Smallegange et al., 2011).

While the distribution of sweat glands is relatively similar between humans and great apes, little is known about the body odor profiles of great apes and other NHPs and how these compare to human body odor. It also remains to be investigated if the similarities or differences between ape and human odor are mediated by their skin microbiota (Smallegange et al., 2011). Mosquitoes caught near NHPs in sanctuaries in Africa may be used in the

laboratory to understand how mosquitoes are attracted to NHPs. It is not known if anthropophilic mosquitoes like *A. gambiae* s.s. are also attracted to odorants from NHPs and thereby may bite both humans and NHPs (**Figure 2**). Studying the bacteria that play a role in the attractiveness of humans and NHPs to mosquitoes may lead to the identification of volatiles that specifically attract or repel mosquitoes that may form a bridge between humans and NHPs. Next, these volatiles may be used to trap mosquitoes near wild populations of NHPs to identify potential vectors and the malaria parasites they carry (**Figure 3**). Studying their host-seeking behavior in the laboratory will also reveal which mosquito species would readily bite both humans and NHPs and how restricted this host preference is.

CONCLUSION

In 2007 the Bill and Melinda Gates Foundation, followed by the World Health Organization (WHO) and the Roll Back Malaria (RBM) Partnership declared that the paradigm of malaria control and elimination has been extended to encompass an ultimate goal of malaria eradication (Roberts and Enserink, 2007; Roll Back Malaria Partnership, 2008; Alonso et al., 2011). Since that declaration the discussion on the probability of malaria eradication has intensified (Roberts and Enserink, 2007; Greenwood, 2008; Ferguson et al., 2010; Kappe et al., 2010; Alonso et al., 2011; The malERA Consultative Group on Vector Control, 2011). However, in 2010 there were still an estimated 216 million human cases of malaria and 655,000 deaths and the consequences of malaria may decrease gross domestic product by as much as 1.3% (WHO, 2011).

The possibility that NHPs act as a reservoir for human *Plasmodium* or are a source of NHP *Plasmodium* that may affect human health should be investigated before malaria eradication is considered. Current vector control efforts are focused on human habitats, mainly because the most important vector of human malaria *A. gambiae* s.s. is highly anthropophilic and found only around human settlements (Costantini et al., 1998; Takken and Knols, 1999; Pates et al., 2001). In the process of malaria elimination in any country, emphasis is often laid on monitoring parasite prevalence in humans. The case of *P. knowlesi* has shown that conventional methods of screening for *Plasmodium* parasites will not reveal human infections with NHP *Plasmodia* and therefore humans living near wild-ape communities will need more detailed testing to detect these parasites (Kevin, 2009; Rayner et al., 2011).

The significance of NHPs as a potential source for human infection will largely depend on the vector species that transmit *Plasmodium* between apes, and whether their behavior facilitates transmission to humans. By understanding how mosquito species are attracted to NHPs, and using this knowledge to identify the vectors that may transmit *Plasmodium* between apes and humans, we can understand the zoonotic potential of NHP *Plasmodium* parasites. Identification of the bacterial volatiles that specifically attract mosquitoes that may form a bridge between humans and NHPs may lead to the development of selective odor-baited mosquito traps (Mukabana et al., 2012). These traps can be used for monitoring or mass trapping of mosquito species that facilitate such a cross-species exchange of *Plasmodium* parasites (**Figure 3**). Detailed screening for *Plasmodium* parasites and trapping of vectors in areas where humans and NHPs coexist will help to focus on critical areas that should receive additional interventions when attempting to eliminate or eradicate malaria.

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