A laboratory study assessing the attractiveness of the malaria vector *anopheles* to rabbits treated with a long-acting ivermectin formulation

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Abstract

Mass treatment of humans and livestock with ivermectin is seen as a promising strategy in the fight against malaria vectors. However, before implementation of this approach, it is essential to assess whether hosts treated with ivermectin display varying attractiveness to mosquitoes. Our study aimed to assess the attractiveness of *Anopheles (An.) coluzzii* to rabbits treated with ivermectin.

Fourteen rabbits were divided into two groups: an ivermectin-treated group (subcutaneously injected with a long-acting ivermectin formulation, herein IVM) and a control group (subcutaneously injected with the adjuvant of the formulation, herein VHC). Laboratory-reared female *An. coluzzii* mosquitoes were released into a dual-choice olfactometer impregnated with the odors of IVM-treated or control rabbits between 7 PM and 2 AM, based on four odor combinations (VHC *vs* IVM; IVM *vs* empty; VHC *vs* empty; and empty *vs* empty). The activation and trophic preference of *An. coluzzii* were measured in relation to these different odor sources.

The results showed that treatment with IVM did not have a significant impact on the attractiveness of *An. coluzzii* to rabbits [X^2_2= 47.111; p = 0.48]. However, a slight preference of *An. coluzzii* towards IVM-treated rabbits was observed at days 14 and 28 after injection [X^2_2 = 2.9587; p = 0.048]. Ivermectin treatments of rabbits seem not to pose a risk of trophic diversion of the malaria vector *An. coluzzii*. However, due to

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the varying attractiveness of *Anopheles* mosquitoes depending on vertebrate hosts, field trials with natural alternative hosts of *Anopheles* are required for more powerful conclusions.

Key words: Malaria, *Anopheles coluzzii*, ivermectin, attractiveness, rabbit.

Introduction

Long-Lasting Insecticidal Nets (LLINs) and Indoor Residual Spraying (IRS) are the principal vector control strategies used to combat malaria, which continues to kill a large number of people, particularly children under 5 years of age in Sub-Saharan Africa (1). Although these tools have contributed to significantly reducing the burden of malaria between 2000 and 2015, this decrease has since stalled, and an increase in malaria incidence has even been reported in several countries including Eritrea, Namibia, Angola, Botswana, Burundi, the Comoros and Madagascar (2). Several factors are hindering the effectiveness of LLINs and IRS, including insecticide resistance (3,4), behavioral changes (biting early or outdoor) (5,6), and feeding on livestock (7). To mitigate mosquito resistance to insecticides and target mosquitoes that feed on livestock, new strategies will be required.

Entomological studies have revealed the heterogeneity of trophic choices among *Anopheles* species (8,9). In addition to humans, the primary host species, these vectors also feed on livestock, depending on the availability and relative densities of humans and animals (10). In Burkina Faso, significant trophic diversion of *An. gambiae s.l.* to domestic animals, particularly cattle and sheep in the Kou Valley, has been observed (9). Female *An. gambiae s.l.* showed zoophagy in several locations in Senegal, and those of *An. funestus* were significantly more zoophilic in the southeast of the country (8,11). Current malaria control strategies poorly integrate this trophic plasticity of *Anopheles* vectors, which contributes in part to maintaining vector populations at a density conducive to transmission. Furthermore, studies in Senegal have shown that malaria transmission rates were higher in households with animals (12), highlighting the importance of considering the animal aspect in malaria control. Mass treatments of humans and animals with ivermectin are a focal point of this approach.

The systemic insecticidal effect of ivermectin on certain species of *Anopheles* vectors that are blood fed on ivermectin-treated hosts has

been proved (13–15) sparking renewed interest in this medicine in malaria treatment. Ivermectin is an anthelmintic drug widely used in domestic animals to combat internal and external parasitic infestations (16), but it is also in humans to combat filariasis, particularly onchocerciasis (17,18).

Given the importance of this molecule, a roadmap anticipated that ivermectin would be available as a complementary tool for malaria control(19). For now, the lethal effect observed with *Anopheles* mosquitoes is 3 days for the human oral formulation (20) and 28 days for the subcutaneously injected formulation in domestic animals (15). These lengths of efficacy are potentially too short to have an impact on mosquito population densities and then on *Plasmodium* transmission; therefore, it is necessary to repeat treatment administrations of the currently recommended therapeutic doses which pose logistical and cost challenges. A way to override this limitation is the use of slow release formulation as a new slow-release injectable formulation developed and tested in collaboration with Institut de Recherche pour le Développement (IRD), Institut de Recherche des Sciences de la Santé (IRSS), and Centre International de Recherche-Développement sur l'Elevage en zone Subhumide (CIRDES), allowing for a slow release of lethal concentrations of ivermectin to *Anopheles* for a period of 6 months (21,22).

However, like all insects, *Anopheles* mosquitoes identify their host from a complex mixture of odors (23–25). Yet, a person's body odor can vary depending on various factors such as emotional state (stress), age, diet (alcohol), menstrual cycle, perspiration, and medication intake (26). Also, some medications are linked to body odor and perspiration (27); ivermectin could also alter the odor profile of treated hosts, making them more or less attractive to vectors. Similarly, the metabolites of ivermectin or adjuvants of formulations could also modify the degree of attraction of mosquitoes to treated hosts.

Before large-scale deployment of this approach, it is important to characterize the effect of treating vertebrate hosts on the relative attraction of *Anopheles*. Studies have shown that mosquitoes are attracted to different bodily compounds such as ammonia, carbon dioxide, or lactic acid (28–30). In this case, it cannot be excluded that the ivermectin formulation could modify the odor profile emitted by the treated vertebrate host, thereby making it more or less attractive. Additionally, the metabolites of ivermectin or adjuvants of

formulations could also modify the degree of attraction of mosquitoes to treated hosts. This long-acting formulation is manufactured using biocompatible solvents and biodegradable polymers, the most commonly used being lactide/glycolide copolymers, lactide polymers, and poly-ε-caprolactone (31). Thus, during the degradation of these polymers in the body, they are hydrolyzed to produce products easily assimilated by the organism (32). For example, PLGA is degraded into lactic and glycolic acids. Lactic acid being one of the volatile compounds attractive to *Anopheles* in the search for a host, the presence of this degradation product in the tested formulation could thus, in addition to or in place of ivermectin, further increase the effectiveness of the approach.

To our knowledge, no studies have been conducted to evaluate this aspect of ivermectin use in animals or humans as a method of vector control against *Plasmodium*. Indeed, the possibility of modifying host attractiveness could represent a barrier to field deployment of the approach (in the case of mosquito repellency by treated hosts and thus the risk of human overexposure to bites), or conversely, an attractive effect could represent a benefit, allowing for greater effectiveness. In this context, it is therefore important to characterize the effect of ivermectin on attractiveness.

The objective of the study was to evaluate the attraction of female *An. coluzzii*, one of the main malaria vector species, to vertebrate hosts treated with ivermectin. Rabbits were selected for this preliminary experiment because of their docility, their suitable size, and the ease of their handling in a confined environment.

I. Methods

I.1. Rabbits housing and care

Fourteen male rabbits of local breed (Bobo breed), with an average weight of 1.81 (± 0.22) kg, were used in this study. The rabbits received Tétracolivit® and Anticox® to prevent respiratory and digestive diseases. They were housed in the animal facility at the International Center for Research and Development on Livestock in the Subhumid Zone (CIRDES) throughout the experimental period. The rabbits were fed with a compound feed (corn bran, cottonseed meal, fish meal, mineral salts, and essential amino acids) in the form of rabbit pellets, manufactured by the Centre de Promotion de l'Aviculture Villageoise (CPAVI). Water was provided *ad libitum*. These rabbits were

acclimatized to the CIRDES breeding conditions before starting the experiments.

I.2. Insectary-rearing of *An. coluzzii*

The experimental colony of *An. coluzzii* was established at the CIRDES in collaboration with the IRSS, between October and December 2019. The *An. coluzzii* colony was established from gravid female Anopheles mosquitoes collected between 06:00 and 08:00 inside dwellings in the Kou Valley (Bama), located 30 km from Bobo-Dioulasso (11°23'14" North -4°24'42" West). Females were collected using mouth aspirators and placed in cages (30 X 30 X 30 cm), then transferred and raised in the insectary under standard breeding conditions (temperature of 27±2°C, relative humidity of 75±10% with a photoperiod of 12 hours). In the laboratory, female mosquitoes were forced to lay eggs individually. All females that laid eggs were analyzed by PCR-RFLP (33) to confirm that all laid eggs were exclusively from *An. coluzzii*. All eggs were placed in water, and the larvae that emerged were raised under the same standard environmental conditions, receiving a diet based on TetraMin® Baby Fish Food (Tetrawerke, Melle, Germany). After emergence, males and females were daily fed with 5% glucose serum soaked on a cotton pad.

I.3. Ivermectin formulation and rabbit treatment

The slow-release formulation of ivermectin (Medincell® F23) used in this study was described in a previous work from our team(22). It has been shown to be effective in killing *Anopheles* mosquitoes that fed on cattle treated with this formulation for up to 6 months. To measure the attraction of *An. coluzzii* to rabbits treated with ivermectin, two (2) groups of seven (7) rabbits each were constituted:

- Group 1, corresponding to the treated arm, received subcutaneously a double dose of Medincell® F23 (2.4 mg/kg of body weight, equivalent to 0.4 mg/kg per month).

- Group 2, the control arm, was injected with a double dose (2.4 mg/kg) of the adjuvant used to manufacture the Medincell® F23.

I.4. *An. coluzzii* behavioral assay using an olfactometer

A dual-port olfactometer (Figure 1) was used to assess the olfactory responses of *An. coluzzii* mosquitoes to the odors of rabbits compared to outdoor air, as previously described (34). The system consisted of

two cubic plexiglass boxes, each 40 cm high, containing the rabbits (odor sources). These boxes were positioned outside the release room building (L x W x H = 60 x 40 x 40 cm). Inside the room, a mosquito release cage was placed, connected to two glass collection boxes (L x W x H = 40 x 20 x 20 cm) through two parallel cylindrical tubes. Two (2) odor evacuation ducts, each 12 meters long, were connected to the boxes containing the odor sources and led into the collection boxes of the olfactometer. Fans, located in the middle of the ducts, were used to draw air from the odor sources into the collection boxes. The air velocity entering the olfactometer arms ranged from 0.15 to 0.18 m/s. The device (Figure 1) was thoroughly cleaned between two experiments with 70°C alcohol to prevent contamination.

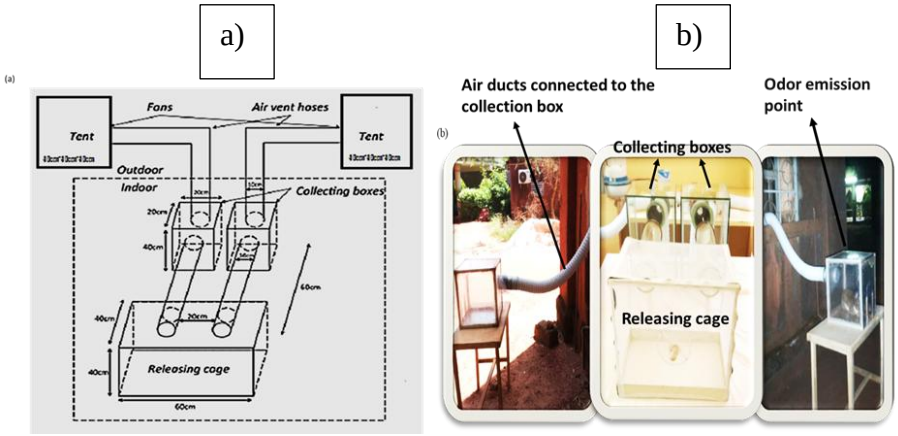

Figure 1. Diagram of the Olfactometer: a) Double-entry tunnels (34). b) Photographs of the experimental setup.

To assess the attractiveness of IVM-treated rabbits to *Anopheles* mosquitoes, four (4) combinations were tested: the IVM *vs* empty combination (IVM for "ivermectin formulation" and empty: box without rabbit), the VHC *vs* empty combination (VHC for "vehicle" or placebo), the IVM *vs* VHC combination, and the empty *vs* empty combination (Table I). These combinations were tested each week in the olfactometer for one month after rabbit treatments. During each trial, fifty female *An. coluzzii* mosquitoes that had not blood-fed and aged 3-8 days were released and kept for twenty minutes in the olfactometer. At the end of this time, the number of mosquitoes that moved towards the collection boxes (activated mosquitoes) was recorded per arm, in order to calculate the activation and preference of *An. coluzzii* for the four combinations and their preference for the three

odors (empty, IVM, and VHC). Activation is defined as the proportion of mosquitoes captured in the two collection boxes relative to the total number of released mosquitoes. Preference is the ratio between the number of mosquitoes captured in the collection box designated as "test" on the total number of activated mosquitoes. The "test" collection box was the right arm for the empty *vs* empty combination, VHC for the empty *vs* VHC combination, IVM for the empty *vs* IVM combination, and IVM for the VHC *vs* IVM combination.

To align the trials with the time when mosquitoes naturally become active in the field (35), releases began early in the night starting from 7:00 PM. All combinations were tested between 7:00 PM and 2:00 AM. To enhance the mosquito response to host odors in the olfactometer, females were starved for 10 hours before their release in the olfactometer.

Table I. The different odor combinations tested

Combinations	Treated arm	Control arm
Empty *vs* empty	right arm	Left arm
Empty *vs* IVM	IVM	Empty
Empty *vs* VHC	VHC	Empty
VHC *vs* IVM	IVM	VHC

Empty vs empty: only ambient outdoor air.
Empty vs IVM: Ambient outdoor air and odor of formulation containing ivermectin-treated rabbit.
Empty vs VHC: Ambient outdoor air and odor of Vehicule of the formulation-treated rabbit.
VHC vs IVM : odor of Vehicule of the formulation-treated rabbit and odor formulation containing ivermectin-treated rabbit.

I.5. Statistical analysis of the data

The proportions of activated mosquitoes (activation) and those collected in the "test" arm (preference) of the device were calculated and analyzed using the R software.

Activation and preference were the response variables to be analyzed. They were analyzed based on the tested combinations (empty *vs* empty, empty *vs* VHC, empty *vs* IVM, VHC *vs* IVM), the Delay After Injection (7 days, 14 days, 21 days, and 28 days), and the time at which mosquitoes were released (7:00 PM - 2:00 AM). The generalized linear model with a binomial distribution of the error was used to analyze the effect of explanatory variables on activation and preference, followed by Likelihood Ratio Tests (LRT) at a significance threshold of $P < 0.05$

to evaluate the main effects of "combination", "delay after injection (DAI)", and "test time", as well as their biologically meaningful interaction on *Anopheles* activation in the olfactometer.

Analysis of mosquito preference was conducted by "combination" based on "DAI" and "treatment or arm status". Odds ratios were calculated to compare the frequency at which mosquitoes oriented towards the "test" collection box relative to the "control" collection box in the tested combinations

II. Results

II.1. Activation of *an. Coluzzii* by treated rabbits

A total of 7,378 *An. coluzzii* mosquitoes were released into the olfactometer during the entire testing period, of which 608 were activated by the odor combinations, resulting in an average activation rate of 8.2%.

Mosquito activation varied among the four odor combinations evaluated (empty *vs* empty, VHC *vs* IVM, IVM *vs* empty, and VHC *vs* empty) [$X^2_3 = 61.046$; $p < 0.001$; Figure 2a)]. It was found to be higher for the empty vs empty combination, while the other three combinations displayed comparable levels of activation (Figure 2a). Mosquito activation per combination differed depending on the time of mosquito release. There was more activation at 7 PM compared to other time slots [$X^2_1 = 79.083$; $p < 0.001$; Figure 2b)]. The combined influence of combination and test time was significant on mosquito activity [$X^2_3 = 45.498$; $p = 0.013$; Figure 2c)]. Additionally, mosquito activation varied considerably depending on the DAI [$X^2_3 = 53.300$; $p < 0.001$]. However, no interaction was observed between odor combination and DAI [$X^2_9 = 48.839$; $p = 0.24$; Figure 2d)].

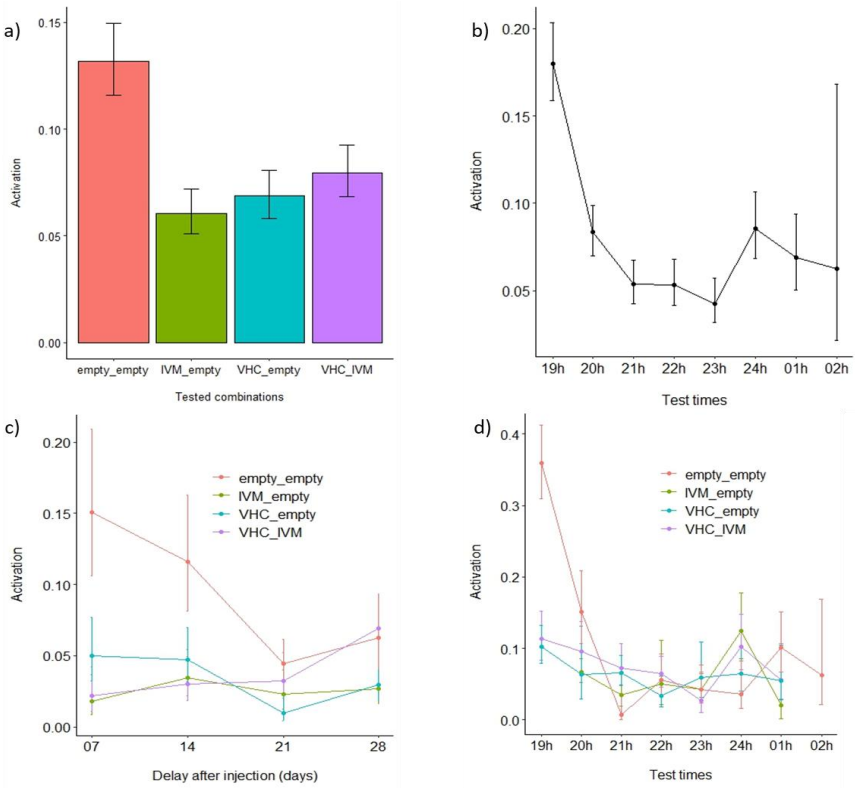

Figure 2. Activation of female *An. coluzzii* based on a) the tested combination; b) the test times; c) the delay after injection; d) the four tested combinations according to the test times.

IVM: rabbit treated with the ivermectin formulation.
VHC: rabbit treated with the vehicle (placebo, solvent) of the formulation

II.2. Preference of *An. coluzzii* based on treatments

The preference for the empty *vs* empty combination was analyzed to verify the reliability of the setup. The result showed that there was no bias in the experimental setup, and mosquitoes did not exhibit any preference towards either arm [Z = 0.071; P = 0.944; OR = 1.01; CI = [0.76; 1.33]]. Analysis of combinations containing rabbit odors (IVM *vs* empty, VHC *vs* IVM, and VHC *vs* empty) showed that the arm status did not affect the choice of *An. coluzzii* (Figure 3a). Similarly, the DAI of IVM to rabbits did not have a significant effect on mosquito preference in each tested combination, although a slight attraction of mosquitoes towards IVM-treated rabbits was observed at DAI 14 and DAI 28 (Figure 3b).

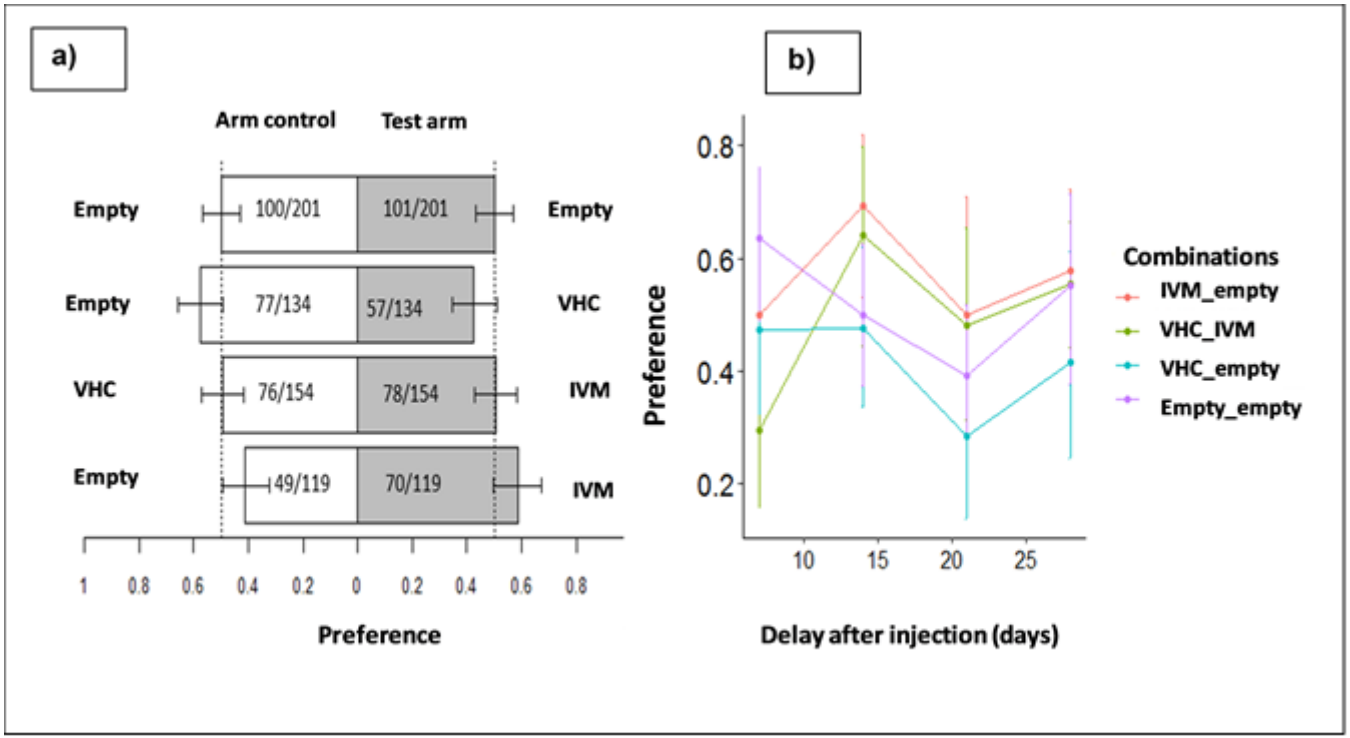

Figure 3. Preference of *An. coluzzii* according to a) the treatment and b) the DAI.

Table III. Effects of DAI and treatment on preference and odds ratios

Combinations	Effect of the DAI variable	Effect of the treatment variable	Odds ratios (OR)	Confidence interval (CI)
IVM *vs* empty	$\chi^2_2 = 2.9587$; p = 0.048	Z = 1.76; p = 0.088	OR= 1.43	[0.963; 2.13]
VHC *vs* IVM	$\chi^2_3 = 7.28$; p =0.063	Z = 0.161; p = 0.872	OR = 1.026	[0.74; 1.41]
VHC *vs* empty	$\chi^2_3 = 2.77$; p = 0.63	Z = 1.41; p = 0.167	OR = 0.74	[0.48; 1.12]
Empty *vs* empty	NA	Z = 0.07; p = 0.944	OR= 1,01	[0.76; 1.33]

DAI: Delay After Injection; IVM: Rabbit treated with slow-release ivermectin formulation; VHC: Rabbit treated with the adjuvant of the formulation.

Regardless of the combinations tested, the probabilities of female *An. coluzzii* heading towards the odor sources were not different. The effects of the DAI and treatments on mosquito preference are presented in Table II, with associated odds ratios and confidence intervals.

III. Discussion

Anopheles mosquitoes identify their hosts through various volatile organic compounds emitted by their hosts (24,25,36). The study of behavioral responses of *Anopheles* mosquitoes to control tools is critical as it provides valuable insights to guide strategies aimed at enhancing their efficacy. The objective of this study was to understand the effect of ivermectin on the attraction of *Anopheles* mosquitoes to treated hosts, in order to avoid potential repellent effects of treatments that could limit the effectiveness of this approach. In laboratory experiments, four odor combinations (VHC *vs* IVM, IVM *vs* empty, VHC *vs* empty, empty *vs* empty) were used to assess the activation and trophic preference of *An. coluzzii* using a dual-entry olfactometer. The results revealed that treating rabbits with ivermectin has no effect on their attraction to the malaria vector *An. coluzzii*. Combinations containing rabbit odors showed lower activation for mosquitoes than combinations with empty cages. Furthermore, *An. coluzzii* did not exhibit any significant preference for ivermectin-treated rabbits compared to the empty cage. This shows equal orientation between the different collection boxes, regardless of the type of odor introduced into the olfactometer.

The combination containing no rabbit odor (empty *vs* empty) showed an activation rate of around 13%, compared to 6%, 8%, and 7% for IVM *vs* empty, VHC *vs* IVM, and VHC *vs* empty, respectively. These activation rates are significantly lower than those obtained in previous studies using the same host species, which were around 30% using a Y-tube olfactometer (37). Other authors have reported activation rates of around 40% with *An. coluzzii* towards odors of cattle or humans using the same device (38). The low activation in combinations containing rabbit odors compared to the empty ones suggests that rabbits were less attractive to female *An. coluzzii*. Investigations into the trophic behavior of *Anopheles*, both in the laboratory and in semi-natural environments, have revealed an attraction of *Anopheles* towards certain vertebrate hosts such as humans and calves, depending on their status or physiological state (10,23,34,38). In the laboratory, female *An. coluzzii* showed similar attraction towards humans and calves compared to the outdoor

environment. However, in semi-natural settings, field mosquitoes exhibited higher activation towards the human odor source compared to that of the calf. Thus, cattle appear to be excellent hosts for further experiments. Nonetheless, the reduced attraction of treated rabbits highlighted in these preliminary experiments needs to be further characterized.

The results also showed a significant interaction between combination and mosquito release time. This significant difference could result from high activation scores coinciding with this time period, with an uneven distribution of tests of the empty *vs* empty combination compared to other periods, despite a random experimental design. The comparison of results between combinations containing IVM-treated rabbits and those that did not suggests that this molecule does not alter mosquito activation towards treated hosts. The trophic choice of *Anopheles* based on odor source showed no significant difference in all tested combinations. *Anopheles* mosquitoes were equally attracted to the collection boxes regardless of the odor source introduced into the device, which could be explained by the high anthropophilic level of this strain. A similar observation was reported with the same device when testing combinations: human-empty, calf-empty, and human-calf (34). The overall analysis of *Anopheles* preference for treated rabbits revealed that the number of days after injection (DAI) does not influence their choice. However, a slight preference of *Anopheles* towards rabbits treated with ivermectin formulation was noted at 14 days and 28 days after rabbit treatment. These observations require further investigation to understand the effect of ivermectin on *Anopheles* attraction. The significant effect observed only at 14 and 28 days after rabbit treatment could be attributable to the kinetics of ivermectin, which may not be uniformly released during the waiting period.

Conclusion and perspectives

This study indicated that administering ivermectin to rabbits does not influence their attraction to the malaria vector *An. coluzzii*. Combinations that contained rabbits, whether they were treated or not with ivermectin, exhibited reduced activation for mosquitoes compared to combinations with empty cages. Moreover, *An. coluzzii* displayed no notable preference for ivermectin-treated rabbits in comparison to the empty cages. These results represent a first step in assessing the relevance of ivermectin treatment to vertebrate hosts in the fight against

malaria vectors. Further field experiments using huts or trap tents on cattle would be required to draw definitive conclusions which are natural alternative hosts of *Anopheles* in the field. In addition, conducting field experiments using huts or trap tents with wild Anopheles mosquitoes will help.

Declarations

All authors declare no conflict of interest.

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Authors' contributions

LZ, SHP, TL, KM conceptualized the study and experiments. , LZ, SHP, BSP, DFSH, TL, KM developed the methodology. ZL, SHP, COWO, AMB were contributed to the data collection of the study. ZL, TL, BSP analyzed the data. ZL, SHP, ABS drafted the original manuscript. AP, AFS, KM, AMGB reviewed the manuscript. KRD, KM provided resources. All authors wrote, reviewed and edited the paper.

Ethics approval

The study received approval from the CIRDES ethics committee under letter no. 15/CE-CIRDES/16-10-2018.

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