



Does *Plasmodium* Infection Affect Mosquito Attraction?

Diego Santiago-Alarcon^{1*} and Francisco C. Ferreira^{2,3*}

¹ Red de Biología y Conservación de Vertebrados, Instituto de Ecología, Xalapa, Mexico, ² Center for Conservation Genomics, Smithsonian Conservation Biology Institute, Washington, DC, United States, ³ Center for Vector Biology, Rutgers University, New Brunswick, NJ, United States

OPEN ACCESS

Edited by:

Laura Gangoso,
Consejo Superior de Investigaciones
Científicas (CSIC), Spain

Reviewed by:

Rafael Gutiérrez López,
University of Porto, Portugal
Leanne Grieves,
McMaster University, Canada
Jiyue Yan,
University of Illinois
at Urbana-Champaign, United States

*Correspondence:

Diego Santiago-Alarcon
diego.santiago@inecol.mx;
onca77@gmail.com
Francisco C. Ferreira
franciscocarlosfj@gmail.com

Specialty section:

This article was submitted to
Behavioral and Evolutionary Ecology,
a section of the journal
Frontiers in Ecology and Evolution

Received: 13 July 2020

Accepted: 21 October 2020

Published: 09 November 2020

Citation:

Santiago-Alarcon D and
Ferreira FC (2020) Does *Plasmodium*
Infection Affect Mosquito Attraction?
Front. Ecol. Evol. 8:582943.
doi: 10.3389/fevo.2020.582943

Vector-host interactions play a central role in the transmission of vector-borne diseases. Determining the factors that affect vector attraction to vertebrate hosts is critical to understand disease ecological dynamics. Using malaria as the primary model, we reviewed studies that examined whether pathogen infection and host traits affect mosquito attraction. We found contradictory results examining mosquito attraction to birds infected with *Plasmodium* parasites, presumably because of widely variable experimental approaches. We summarize current experimental findings and propose standardized experimental approaches for future studies.

Keywords: behavioral manipulation, vector attraction, experimental parasitology, arboviruses, avian malaria, Culicidae, Diptera

INTRODUCTION

Insect vectors have often been considered passive vessels that carry pathogens without exerting much selection. However, vectors may suffer high pathogen-related mortalities (Valkiūnas et al., 2014; Gutiérrez-López et al., 2019a,b), and vectors selection of vertebrate hosts to obtain blood meals is not random or solely based on host availability, they follow general and specific host cues such as carbon dioxide and volatile body chemicals (Takken and Verhulst, 2013). Interestingly, both host choice and host attractiveness may be manipulated by the parasite in order to increase its transmission success (i.e., manipulation hypothesis; Heil, 2016).

The process by which pathogens manipulate vectors' behavior can be indirect during the development in a vertebrate host (e.g., increased attractiveness of infected hosts to uninfected vectors), and/or direct during the cycle inside the vectors (e.g., increase in attraction or feeding rates toward uninfected hosts; Gandon, 2018). These changes have profound implications for pathogen transmission. For instance, uninfected vectors highly attracted toward infected hosts would initially increase transmission in local populations (Gandon, 2018). Generalist mosquito species feeding on birds and mammals (depending on host availability; Abella-Medrano et al., 2018) play important roles in the transmission of zoonotic pathogens (e.g., *Culex pipiens* transmitting West Nile virus (WNV) and Usutu (USUV) virus among birds, equids, and humans; Brugman et al., 2018; Rochlin et al., 2019). Thus, investigating drivers of mosquito host selection is essential to understand the dynamics of vertebrate-vector-pathogen systems.

In recent years avian haemosporidian parasites have received attention as model systems to understand the ecology and evolution of vector-borne parasites (Rivero and Gandon, 2018). In particular because they are widespread, infect a large proportion of bird species worldwide, and affect bird fitness and survival (Atkinson and Van Riper, 1991; Valkiūnas, 2005;

Palinauskas et al., 2020). Thus, by focusing on avian malaria, here we provide an overview of the factors affecting host selection by mosquitoes concentrating on *Culex* mosquitoes, which transmit human pathogens, bird pathogens, and zoonotic pathogens that use birds as reservoirs (WNV, USUV). Although *Culex* mosquitoes have a broad range of hosts, some are predominantly mammophilic and others are ornithophilic (e.g., *Culex theileri* vs. *Cx. pipiens*), yet their feeding behaviors depend on the species and population of origin, which also affects the parasites they transmit (Santa-Ana et al., 2006; Farajollahi et al., 2011; Rochlin et al., 2019).

Birds are used as models to analyze factors within species that affect host attractiveness to mosquitoes, which include mosquito and bird pathogen infection status, differences in the production of natural chemicals by birds (urophygial gland secretion and volatile compounds), host sex, and interactions among some of these factors (Table 1). We took advantage of studies on human and mice malaria systems that also addressed some of these factors to suggest next steps for studies on bird attractiveness to mosquitoes. We found discrepancies among studies, which may be due to differences in study design (Table 1). Therefore, we propose standardized experimental approaches to help identify generalities and contingencies in pathogen-vector-host interactions using avian malaria as a model (Figure 1).

CURRENT EXPERIMENTAL APPROACHES

In general, laboratory experiments assess mosquito attraction using dual-choice olfactometers, or they assess feeding choice by placing mosquitoes inside cages containing target host groups. Olfactometers expose mosquitoes to olfactory host cues (CO₂ and volatile compounds) and prevent mosquitoes from using visual cues or differences in body temperature for host detection (Lalubin et al., 2012; De Moraes et al., 2014; Díez-Fernández et al., 2020a). This approach is useful for studies using chemical stimuli collected from hosts and has the advantage to protect hosts from being bitten by mosquitoes. Host attractiveness in single-choice system can be measured as the number of mosquitoes approaching a host in one end of an enclosure or in a tunnel in relation to the number of mosquitoes released at the opposite end (Cator et al., 2013; Batista et al., 2014).

Feeding rates can be measured by comparing the proportion of mosquitoes taking a blood meal from single-housed (Cornet et al., 2019) or pair-housed hosts. In the latter, two hosts from different groups (e.g., control vs. experimental group) are placed inside the same cage where mosquitoes are released and host choice is assessed via microsatellite testing (Yan et al., 2018b) or by molecular sexing methods (Cornet et al., 2013a; Yan et al., 2018a) using engorged mosquitoes to determine blood source. Overall, studies varied in duration and type (attraction assays using olfactometers vs. feeding choice inside cages), with feeding experiments used either immobilized or non-immobilized birds (Table 1). These differences, therefore, may explain discrepancies in the general findings.

INDIRECT AND DIRECT MANIPULATION OF VECTOR'S BEHAVIOR BY PATHOGENS

Pathogens can modify conditions within vertebrate hosts or within vectors to increase transmission rates from infected to uninfected hosts. These indirect and direct vector manipulations, respectively, may affect host-seeking behaviors, feeding behaviors, or both (Gandon, 2018).

Infected Hosts and Mosquito Attraction

Most studies tested whether hosts infected with *Plasmodium* parasites are more attractive to uninfected mosquitoes or whether uninfected mosquitoes feed more on infected hosts (indirect vector manipulation). Some of these studies also tested whether hosts with higher number of circulating gametocytes (sexual parasite stage that is infective to mosquitoes) were more attractive to mosquitoes even when compared with hosts with low levels of gametocytes (Table 1).

Avian Malaria

Cornet et al. (2013a,b) found that laboratory-reared *Cx. pipiens* fed more on domestic canaries (*Serinus canaria*) infected with a laboratory strain of *Plasmodium relictum* (SGS1) when compared to uninfected birds. This effect was detected in birds undergoing chronic infections (24–26 days post infection – dpi), but not in birds undergoing the acute phase of the infection (10 dpi; Cornet et al., 2013b). Mosquitoes fed more on birds with a higher hematocrit, a measure that can be interpreted as a higher blood quality (Cornet et al., 2013a).

Four avian malaria studies used wild caught *Cx. pipiens* and free-living birds infected with *Plasmodium* spp. and uninfected birds to assess vector manipulation in more natural systems (Table 1). One set of experiments conducted by Yan et al. (2018b) compared infected birds with their counterparts treated with primaquine to reduce parasitemia (the number of circulating parasites). They found mosquitoes fed more on infected birds than on treated birds, which provided experimental support for the vector manipulation hypothesis. Similarly, mosquitoes were more attracted to body odors isolated from infected birds when compared to uninfected birds (Díez-Fernández et al., 2020b). However, this effect was not observed when using uropygial gland secretion collected from the same bird groups. Other experiments found that mosquitoes were either more attracted to uninfected birds (Lalubin et al., 2012) or that infection status did not change mosquito feeding rates when compared to control groups (Yan et al., 2018b; Gutiérrez-López et al., 2019a).

From the discussed studies, two used dual-choice olfactometers to assess mosquito attraction to birds or to chemical compounds collected from birds, while three studies released mosquitoes inside cages containing single birds or pairs of infected and uninfected birds that were immobilized in most cases (except Yan et al., 2018b; Table 1). Observed contrasting results addressing the host manipulation hypothesis may be the result of differences in host, vector and parasites used and/or due to differences in experimental settings.

TABLE 1 | Studies conducted on mosquito attraction toward bird, humans and mice.

<i>Plasmodium</i> Infections						
Indirect manipulation						
Host sp.	Vector sp.*	Parasite species	Factor	Main Results	Experimental details	Source**
Avian hosts						
Great tit – <i>Parus major</i>	<i>Culex pipiens</i> (wild caught). Not tested for pipiens and molestus forms and hybrids.	<i>Plasmodium</i> sp. – natural infections	Mosquito attraction as a function of bird infection.	Infected birds less attractive than uninfected birds. Females more attractive to mosquitoes than males.	Dual-choice olfactometer. Twenty-eight paired experiments combining six infected and five uninfected birds. Birds kept out of sight of the mosquitoes. Parasitemia not assessed. Experiments lasted 15 min.	Lalubin et al. (2012) ¹
Domestic canary – <i>Serinus canaria</i>	<i>Cx. pipiens</i> (S-LAB strain)	<i>Plasmodium relictum</i> (SGS1) – experimental infection	Feeding choice as a function of bird infection and infection stage (acute or chronic).	Mosquitoes fed more on chronically infected birds than on either uninfected or acutely infected birds. Mosquito preference for birds with higher hematocrit. No difference between uninfected birds and birds during acute infection.	Paired birds in 25 independent cages with 70 mosquitoes each. Feeding experiments lasted 2 h. Birds were immobilized.	Cornet et al. (2013b) ²
House sparrow – <i>Passer domesticus</i>	<i>Cx. pipiens</i> – wild caught. Not tested for pipiens and molestus forms and hybrids.	<i>Plasmodium</i> sp. – natural infections	Feeding choice as a function of bird infection.	No difference in feeding rates between infected and uninfected birds.	Twenty pairs of infected and uninfected birds exposed to mosquitoes. Birds were not immobilized. Experiments lasted 12 h.	Yan et al. (2018b) ³
House sparrow – <i>Passer domesticus</i>	<i>Cx. pipiens</i> – wild caught. Not tested for pipiens and molestus forms and hybrids.	<i>Plasmodium</i> sp. – natural infections	Feeding choice as a function of parasite levels.	Higher feeding rates on non-treated (higher parasite levels) than on treated birds. Higher feeding rates on females.	Parasitemia reduced via primaquine treatment. Nineteen pairs of infected non-treated birds and infected treated birds exposed to an average of 151 mosquitoes. Birds were not immobilized. Experiments lasted 12 h.	Yan et al. (2018b) ⁴
Jackdaw – <i>Corvus monedula</i> , and house sparrow – <i>Passer domesticus</i>	Wild caught <i>Ochlerotatus (Aedes) caspius</i> and <i>Cx. pipiens</i> (not tested for pipiens and molestus forms and hybrids).	<i>Plasmodium</i> sp. – natural infections	Feeding choice as a function of bird infection, sex and body mass	No difference in feeding rates for both mosquito species according to <i>Plasmodium</i> infection status and body mass for both bird species. <i>Ochlerotatus caspius</i> fed more on female than on male jackdaws.	Birds single-housed. Parasitemia not assessed. Experiments lasted 30 min. Birds were immobilized.	Gutiérrez-López et al. (2019a) ⁵

(Continued)

TABLE 1 | Continued

<i>Plasmodium</i> Infections						
Indirect manipulation						
Host sp.	Vector sp.*	Parasite species	Factor	Main Results	Experimental details	Source**
Mammal hosts						
Mice – <i>Mus musculus</i>	<i>Anopheles stephensi</i>	<i>Plasmodium chabaudi</i> – clones CR and ER	Feeding choice as a function of host infection.	Higher rates of mosquito feeding on infected hosts when compared to uninfected hosts. Positive relationship between parasitemia and feeding rates.	Groups of six mice uninfected, infected with either CR or ER or infected with a 1:1 mix of both <i>Plasmodium</i> clones. Mosquito exposure at 14 dpi. Asexual stages and gametocyte ratios calculated by microscopy. Anesthetized single-house mice exposed to 20–40 mosquitoes. Experiments lasted 20 min.	Ferguson et al. (2003)
Mice – <i>Mus musculus</i>	<i>Anopheles stephensi</i>	<i>Plasmodium chabaudi</i> – clone AS	Mosquito attraction as a function of host infection and infection stage.	Gametocyte-positive mice after acute stage more attractive (vs. negative and vs. chronically infected gametocyte-negative mice). Attractiveness associated to changes in volatile profiles due to infection.	Dual-choice assay in wind tunnel. Six pairs of infected and uninfected mice exposed to 20 mosquitoes for 15 min.	De Moraes et al. (2014)
Humans – <i>Homo sapiens</i> (children)	<i>Anopheles gambiae</i> – ICIPE lab strain	<i>Plasmodium falciparum</i> – natural infections	Mosquito attraction as a function of infection and gametocyte presence.	Children harboring gametocytes more attractive when compared to uninfected and to infected children harboring asexual parasite stages only. No difference in attractiveness after antimalarial treatment.	Children divided into three categories: uninfected, infected presenting asexual parasite forms only, and infected presenting gametocytes. One hundred mosquitoes released at the central chamber of three-way olfactometers in 12 experiments containing one child of each category. Experiments lasted 30 min.	Lacroix et al. (2005)
Humans – <i>Homo sapiens</i> (adults)	<i>Anopheles darlingi</i>	<i>Plasmodium vivax</i> – natural infections	Mosquito attraction as a function of gametocyte presence in infected humans.	Patients harboring gametocytes more attractive when compared to patients with no visible gametocytes and when compared to patients during and after antimalarial treatment.	One foot of <i>P. vivax</i> -infected patients exposed to 10 F ₁ mosquitoes in single-choice olfactometers (three replicates each time) for 10 min. A subset of these patients were exposed to mosquitoes during and after antimalarial therapy (7 and 14 days after diagnosis, respectively). Gametocyte presence evaluated by microscopy only.	Batista et al. (2014)

(Continued)

TABLE 1 | Continued

<i>Plasmodium</i> Infections						
Indirect manipulation						
Host sp.	Vector sp.*	Parasite species	Factor	Main Results	Experimental details	Source**
Mammal hosts						
Humans – <i>Homo sapiens</i> (children)	<i>Anopheles gambiae</i> – Mbita strain	<i>Plasmodium falciparum</i> – natural infections	Mosquito attraction as a function of gametocyte presence and intensity in infected humans.	Children with gametocytes detected by microscopy (higher intensity) more attractive than the other three groups (parasite free, asexual stages only and submicroscopic gametocyte levels). Similar attractiveness among all groups after treatment.	Children divided into four groups: Uninfected, asexual parasite stage only, gametocyte detected by qPCR only, and gametocyte detected by microscopy and by qPCR. One hundred mosquitoes in a dual-choice system. Experiments lasted 30 min and were repeated 3 weeks after antimalarial treatment.	Busula et al. (2017)
Humans – <i>Homo sapiens</i> (adults)	<i>Anopheles coluzzii</i> – lab colony	<i>Plasmodium falciparum</i> NF54 strain – experimental infections	Mosquito attraction as a function of host infection.	Odor samples from infected individuals less attractive when compared to treated and to uninfected individuals in one trial. No difference observed in the second trial.	Groups of 30 mosquitoes exposed to cotton pads with odor from infected humans and with ammonia (negative control) in a dual-choice system for 15 min. Odor samples from infected humans collected before, during (6–8 dpi) and after (34 dpi) treatment with antimalarial.	de Boer et al. (2017)
Humans – <i>Homo sapiens</i> (children – body odor)	<i>Anopheles gambiae</i> – Mbita strain	<i>Plasmodium falciparum</i> – natural infection	Mosquito attractiveness of foot odor as a function of host infection.	Odors from infected children more attractive when compared to odor from the same children after parasite clearance with antimalarials. No effect of gametocyte presence or absence.	Groups of 10 mosquitoes placed in a dual-choice system containing socks worn by the same child before and after antimalarial treatment (six replicates). A total 23 children presented circulating gametocytes (qPCR testing), 10 did not present circulating gametocytes (microscopy testing) and 12 were not infected (qPCR testing). Experiments lasted 15 min.	Robinson et al. (2018)
Direct manipulation						
Host sp.	Vector sp.*	Parasite species	Factor	Main Results	Experimental details	Source**
Avian hosts						
Domestic canary – <i>Serinus canaria</i>	<i>Cx. pipiens</i> (S-LAB strain)	<i>Plasmodium relictum</i> (SGS1) – experimental infection	Feeding rate of sporozoite-infected and uninfected mosquitoes as function of bird infection	Both infective and uninfected mosquitoes feed more on chronically infected birds when compared with uninfected birds. Positive correlation between hematocrit level and feeding rate in infected birds for both infected and uninfected mosquitoes	Birds from different groups exposed to mosquitoes in different cages. Ten cages with uninfected birds and 10 cages with infected birds exposed to 40 infected and 40 uninfected mosquitoes each. Behavioral assay at peak of sporozoite presence in mosquitoes, 12–14 dpbm. Behavioral assay 53–55 dpi of bird host. Immobilized birds. Feeding experiment lasted 2 h.	Cornet et al. (2013a) ⁶
Domestic canary – <i>Serinus canaria</i>	<i>Cx. pipiens</i> (S-LAB strain)	<i>Plasmodium relictum</i> (SGS1) – experimental infection	Feeding rate as a function of mosquito infectivity (harboring sporozoites).	No difference in feeding rate between infective and uninfected mosquitoes at the end of the experiments (3 h). Uninfected mosquitoes feed faster than infective mosquitoes.	Six cages, each with an uninfected bird exposed to 45 uninfected and 45 sporozoite-infected mosquitoes (13 dpbm). Immobilized birds.	Cornet et al. (2019) ⁷

(Continued)

TABLE 1 | Continued

<i>Plasmodium</i> Infections						
Direct manipulation						
Host sp.	Vector sp.*	Parasite species	Factor	Main Results	Experimental details	Source**
Mammal hosts						
Humans – <i>Homo sapiens</i> (adults)	<i>Anopheles stephensi</i> (NIH strain)	<i>Plasmodium yoelii</i> (clone 17XNL)	Host choice as a function of mosquito infection, parasite stage and immune challenge.	Mosquitoes feeding on infected blood less likely to fly toward a human during oocyst stage and more likely to fly toward a human during sporozoites stage when compared to negative controls. Same changes were observed in mosquitoes infected with heat-killed <i>E. coli</i> .	Host-seeking was tested at short and long ranges. Behavioral challenges in mosquitoes injected with heat-killed <i>E. coli</i> . Trials conducted over a 1 h period.	Cator et al. (2013)
Human – <i>Homo sapiens</i> (odor)	<i>Anopheles gambiae</i> – Ngousso strain	<i>P. falciparum</i> – NF54 strain	Landing behavior in matrixes with human odor as a function of sporozoite infection in mosquitoes.	Infective mosquitoes more attracted to human odor when compared to uninfected mosquitoes.	Twenty mosquitoes of each group were provided with a choice of matrixes with and without human odor. Average landing rate calculated for each matrix group over 3 min.	Smallegange et al. (2013)
Humans – <i>Homo sapiens</i>	<i>Anopheles gambiae</i> and <i>An. coluzzii</i> – lab colonies replenished with wild-caught mosquitoes. <i>An. arabiensis</i> – wild-caught.	<i>Plasmodium falciparum</i> – natural infections.	Host choice as a factor of mosquito infection and parasite developmental stages (non-infectious vs. infectious).	No difference in host choice between infected and uninfected mosquitoes and between mosquitoes harboring either oocysts or sporozoites.	Mosquitoes fed on blood containing active and inactivated gametocytes from the same human host. Mosquito host-seeking tested in dual-choice system using humans, calf and outdoor air (control) lasting 30 min. Twenty infected and 20 uninfected mosquitoes tested simultaneously. Eight experimental replicates using 9 different gametocyte carriers.	Nguyen et al. (2017)
Arboviruses infections						
Host sp.	Vector sp.	Virus	Factor	Main Results	Experimental details	Source
House sparrow – <i>Passer domesticus</i>	<i>Culex quinquefasciatus</i> and <i>Culex tarsalis</i> (lab colony)	St. Louis encephalitis virus and Western equine encephalitis virus – laboratory strains	Mosquito attraction as a function of Arbovirus infection in birds	No difference in <i>C. quinquefasciatus</i> attraction toward SLEV-infected birds. No difference in <i>C. tarsalis</i> attraction toward WEEV-infected birds. <i>Culex quinquefasciatus</i> more attracted to adults than to nestlings.	Host attractiveness measured with 10 mosquitoes in each trial in a 50 cm single-choice vertical olfactometer (birds placed at the bottom) for 10 min.	Scott et al. (1990) ^B
Human – <i>Homo sapiens</i> and chicken – <i>Gallus gallus domesticus</i> (odors)	<i>Cx. pipiens</i> form pipiens (wild caught).	West Nile virus lineage 2 (originated from Greece)	Host-seeking response and host choice as a function of mosquito infection	WNV-infected mosquitoes had lower host-seeking response when compared to controls. No changes in flight duration and blood-feeding propensity.	Host-seeking response measured in an olfactometer. Between 53 and 57 mosquitoes from each group exposed to human and chicken odors for 7 min.	Vogels et al. (2017)

(Continued)

TABLE 1 | Continued

Uropygial secretion, volatile compounds and other attributes					
Host sp.	Vector sp.	Factor	Main Results	Experimental details	Source
Crow – <i>Corvus brachyrhynchus</i>	<i>Cx. pipiens</i> / <i>Cx. restuans</i> and <i>Aedes vexans</i> (experiment performed in the wild)	Mosquito attraction toward CO ₂ baited traps as a function of trap height and presence of uropygial gland secretion.	<i>Cx. pipiens</i> / <i>Cx. restuans</i> more attracted to traps at 5 m high with uropygial gland secretion and dry ice (source of CO ₂) when compared to traps with dry ice only (control group). No difference when traps were placed at 1.5 m high and in the attraction of <i>Ae. vexans</i> at both heights.	Study performed in Ontario, Canada. Uropygial secretion from frozen glands applied to cotton swabs. Swabs with and without uropygial gland secretion were attached to CDC traps baited with dry ice. Traps run at heights of 1.5 and 5 m in a total of 280 trap catches.	Russell and Hunter (2005)
American robin – <i>Turdus migratorius</i>	Several species observed during filming, including <i>Cx. pipiens</i> , <i>Cx. restuans</i> , and <i>Aedes albopictus</i> as the most common	Mosquito landing rates on either adults or nestlings of American robins at nests.	Mosquitoes land more frequently on nesting adults than on nestlings, and parental brooding activities reduces mosquitos landing rates on nestlings.	Natural experiment using direct observations via filming.	Griffing et al. (2007)
Blue birds – <i>Sialia sialis</i>	<i>Culex quinquefasciatus</i> (wild caught)	Feeding choice as a function of bird's age (mother vs. nestlings).	No feeding preference between mother and nestlings. Feeding upon mothers decreased as age of the nestlings increased.	Mosquitoes introduced into nest boxes containing mother and nestlings. Around 22 mosquitoes per nest box. Exposure run overnight.	Burkett-Cadena et al. (2010)
Zebra finch – <i>Taeniopygia guttata</i>	<i>Culex quinquefasciatus</i> – laboratory colony	Feeding choice as a function of corticosterone level in birds	Higher feeding rates on birds with artificially elevated levels of corticosterone.	Birds received one or two implants of corticosterone and were assigned to CORT+ and CORT++ groups, respectively. Negative control and birds from both CORT groups exposed simultaneously to 50 mosquitoes for 13 h. Birds were not immobilized.	Gervasi et al. (2016) ¹¹
House sparrows – <i>Passer domesticus</i>	<i>Cx. pipiens</i> (Laboratory colony)	Mosquito attraction toward chemicals from uropygial gland secretions as a function of bird sex and age	Mosquitoes more attracted to uropygial gland secretions from adults over nestlings. No preference for adults over fledglings. No difference in preference for adults, nestlings or fledglings when using semi-volatile components isolated from secretions.	Use of dual olfactometer. Thirty mosquitoes for each trial, which lasted 45 min.	Garvin et al. (2018a)
House sparrow – <i>Passer domesticus</i> European starling – <i>Sturnus vulgaris</i> American robin – <i>Turdus migratorius</i>	<i>Cx. pipiens</i> (laboratory colony)	Mosquito attraction to chemicals from uropygial gland secretions as a function of bird species.	Chemical composition of robins' uropygial gland secretions was different to those of sparrows and starlings. No differences on <i>Cx. pipiens</i> preference for secretions of robins over those of sparrows. However, <i>Cx. pipiens</i> more attracted to live starlings and starlings secretions than to either live robins or their secretions.	Adult House sparrows, European starlings and American robins. Thirty mosquitoes for each trials, which lasted 2 h.	Garvin et al. (2018b)

(Continued)

TABLE 1 | Continued

Uropygial secretion, volatile compounds and other attributes					
Host sp.	Vector sp.	Factor	Main Results	Experimental details	Source
House sparrow – <i>Passer domesticus</i>	<i>Cx. pipiens</i> – wild caught (not distinguished for pipiens and molestus forms).	Feeding choice as a function of bird metabolic rate.	Mosquito feeding rate similar between control and treatment group. Negative association between mosquito feeding preference and bird resting metabolic rate. Positive association between mosquito feeding preference and bird body mass.	Use of 2,4-dinitrophenol to induce higher metabolic rate. Thirty juvenile House sparrows, 21 males and nine females. Trials included a pair of birds exposed to an average of 190 mosquitoes for 12 h. Birds were not immobilized.	Yan et al. (2018a) ¹²
Great tit – <i>Parus major</i>	<i>Cx. pipiens</i> (laboratory colony established with local mosquitoes)	Feeding choice as a function of host sex.	No difference in host choice due to nestling sex	Eighteen independent cages with a pair of 14 days old siblings, one male and one female. Twenty-five uninfected mosquitoes in each cage allowed to feed for 1 h. Host sex determined by PCR.	Cozzarolo et al. (2019)
House sparrow – <i>Passer domesticus</i> (juveniles)	Wild caught <i>Ochlerotatus (Aedes) caspius</i> and <i>Cx. pipiens</i> (not tested for pipiens and molestus forms and hybrids)	Mosquito attraction toward uropygial gland secretion.	No difference in mosquito attraction between uropygial gland secretion and negative controls.	Dual choice (Y-shaped) olfactometer. Negative controls consisted on air flow with no stimuli. Each trial run with 20 mosquitoes (6–15 days old) for 15 min. <i>Cx. pipiens</i> assayed in 21 trials and <i>O. caspius</i> assayed in 20 trials.	Díez-Fernández et al. (2020a) ¹⁰
House sparrow – <i>Passer domesticus</i> (juveniles)	<i>Cx. pipiens</i> – wild caught. Not tested for pipiens and molestus forms and hybrids.	Mosquito attraction toward uropygial gland secretions and whole-body odor as a function of <i>Plasmodium</i> infection.	Mosquitoes more attracted to whole-body odors of infected sparrows regardless of sex. No effect when using uropygial secretions. The volatile lipophilic fraction of the uropygial secretion was not different between infected and uninfected sparrows.	Dual choice (Y-shaped) olfactometer. Experimental pairs were always of the same sex. Each trial run with 20 mosquitoes (6–15 days old) for 15 min in complete darkness. Analyzed whether <i>Plasmodium</i> spp. infections alter chemical composition of uropygial secretions.	Díez-Fernández et al. (2020b) ⁹
Chicken (<i>Gallus gallus domesticus</i>), pigeon (<i>Columba livia</i>), and magpie (<i>Pica pica</i>)	<i>Culex quinquefasciatus</i> (Thai strain) and <i>Cx. pipiens molestus</i> (laboratory colony)	Mosquito attraction toward whole-body odor in the presence or absence of an extra source of CO ₂ .	<i>Cx. quinquefasciatus</i> more attracted to both chicken sexes and to female pigeons. No difference toward male pigeons and magpies. Addition of CO ₂ increased attraction toward chickens and pigeons, but not toward magpies. <i>Culex p. molestus</i> more attracted only to chickens (both sexes). No effect on the addition of CO ₂ .	Single-choice and dual choice olfactometers used for <i>Cx. quinquefasciatus</i> and for <i>Cx. p. molestus</i> , respectively. Bird sex determined only for chickens and pigeons. Ten trials performed with 30 mosquitoes lasting 4 min for <i>Cx. quinquefasciatus</i> and 2 min for <i>Cx. p. molestus</i> .	Spanoudis et al. (2020)

* *Cx. pipiens* for Diptera taxonomists is still under debate, and sometimes is used as a synonym of *Cx. quinquefasciatus*. Some authors even write it as *Cx. pipiens quinquefasciatus*.

** Superscript numbers, whenever present, are related to the experiments described in **Figure 1**.

From the perspective of the vector, here we consider an indirect manipulation when the parasite is infecting the vertebrate host (i.e., the parasitic infection changes some trait of the host that makes it more attractive to the vector), and a direct manipulation when the parasite is inside the vector.

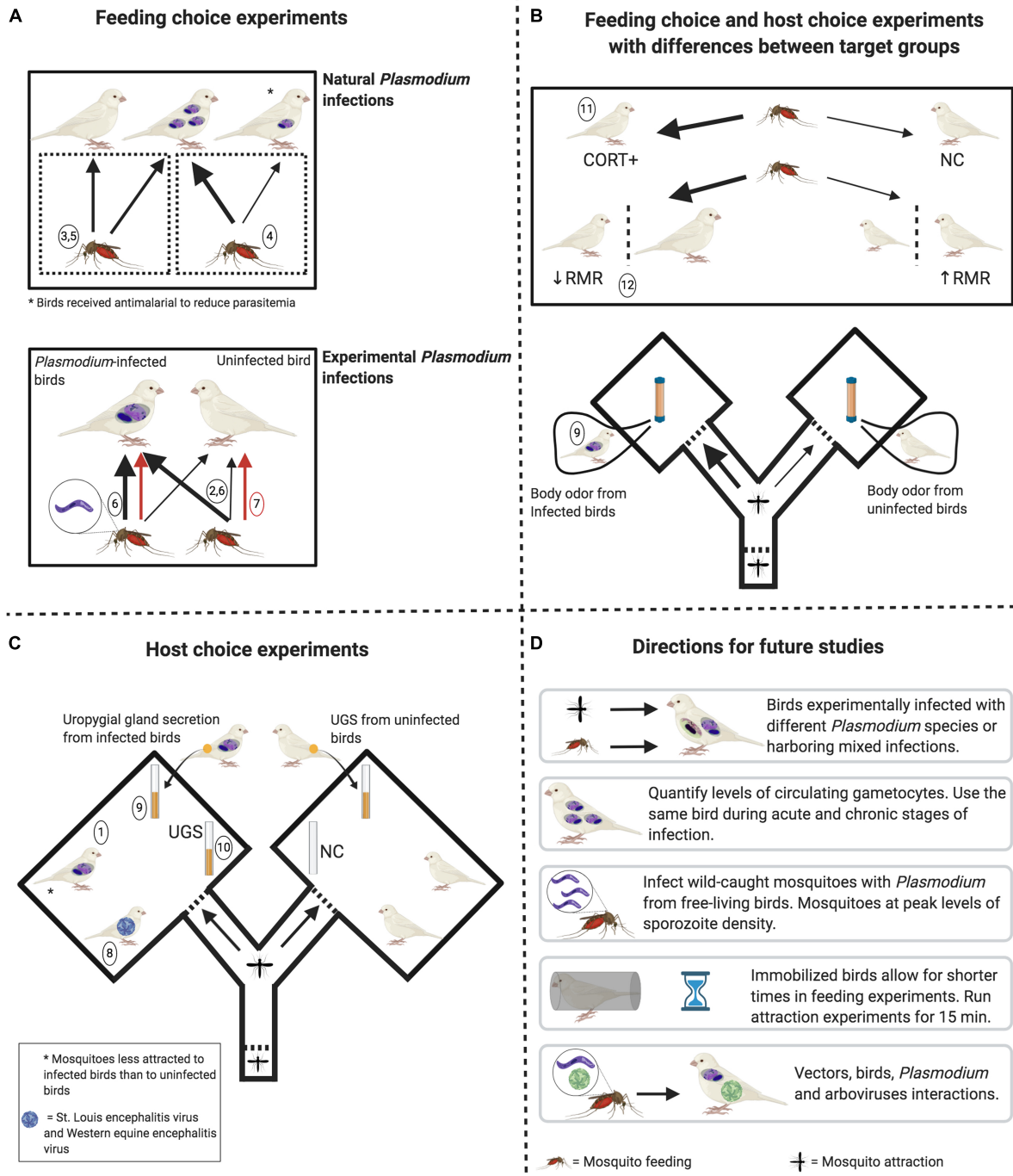


FIGURE 1 | Experimental designs to determine the factors potentially affecting mosquito feeding behavior and attraction toward birds. **(A) Upper** pane: mosquitoes do not feed more on naturally infected birds than on uninfected birds. However, feeding rates are higher on birds with higher levels of circulating parasites (thick black arrow) when compared to birds with reduced levels of parasites after antimalarial treatment (thin black arrow). **Lower** pane: uninfected mosquitoes feed more on birds experimentally infected with *Plasmodium relictum* (thick black arrow) when compared to uninfected birds. Infective mosquitoes (harboring sporozoites) may (thick black arrow) or may not (red arrows) feed more on infected birds than on uninfected ones. **(B) Upper** pane: Mosquitoes feed more (thick black arrows) on birds with higher levels of corticosterone (CORT+) and feed more on birds with lower resting metabolic rate (RMR) and with higher body mass. **Lower** pane: Mosquitoes are more attracted toward whole-body odor from birds naturally infected with *Plasmodium* parasites. **(C)** No mosquito preference in relation to bird arboviral infection and to uropygial gland secretion (UGS) from *Plasmodium*-infected birds when compared to UGS from uninfected birds. No mosquito preference toward UGS when compared to vials containing no stimuli. Mosquitoes were less attracted to birds naturally infected with *Plasmodium*. **(D)** Open questions that can be addressed in future studies, always keeping in mind to standardize bird and mosquito cohorts in terms of age and sex. Numbers in circles refer to specific studies indicated in **Table 1** (see Source column). Figure created with BioRender.com.

Human and Mice Malaria

Most studies on human malaria found that natural *Plasmodium* infections are associated with higher host attractiveness to vectors. Three out of four studies found that *Anopheles* mosquitoes were more attracted to humans harboring microscopically detectable gametocytes when compared to uninfected people and to people with only asexual stages detectable in the blood stream (Lacroix et al., 2005; Batista et al., 2014; Busula et al., 2017). The fourth study showed that socks worn by children parasitized by *Plasmodium falciparum* were more attractive to mosquitoes when compared with socks worn by the same children after the completion of antimalarial treatment (Robinson et al., 2018). A study during its first trial using feet odors found that samples from individuals infected with *P. falciparum* were less attractive to mosquitoes when compared to cotton pads from the same individuals after antimalarial treatment and compared to odors from uninfected people; the second trial did not find any difference in mosquito attraction (de Boer et al., 2017).

Two studies using mice malaria found that *Plasmodium chabaudi* infection increased *Anopheles stephensi* feeding rates (Ferguson et al., 2003) and attraction (De Moraes et al., 2014) when compared to uninfected hosts. This latter study found this effect only during the initial chronic stage, which was associated to microscopically observable levels of circulating gametocytes. These studies on mammals also show contrasting results, precluding generalizations and strengthening the fact of having a standard initial experimental design.

Infected Mosquitoes and Host-Feeding

Pathogens can influence host-seeking and feeding behaviors during their development inside mosquitoes. Because mosquitoes only become infective a few days or even weeks after blood feeding on an *Plasmodium*-infected host (i.e., once sporozoites are found in salivary glands; Valkiūnas et al., 2013; Palinauskas et al., 2016), changes in host-seeking and feeding behaviors may be displayed differentially according to vector infective stage rather than infection status only.

When mosquitoes were simultaneously exposed to both *Plasmodium*-infected and uninfected birds, both infective and uninfected mosquitoes fed more frequently on *Plasmodium*-infected birds (Cornet et al., 2013a). When exposed to uninfected birds, uninfected mosquitoes fed faster than infective mosquitoes, but the final feeding rate after the 3 h the experiment lasted was identical between both groups (Cornet et al., 2019). This demonstrates that experiment duration can affect results, because the authors would have observed higher feeding rates of uninfected mosquitoes if experiments had lasted only 1 h.

Mosquitoes that fed on *Plasmodium yoelii*-infected mice were less attracted to hosts during the oocyst stage (non-infective) than during the sporozoite stage, when they engaged in higher rates of host-seeking behavior when compared to negative controls (Cator et al., 2013). However, these changes were also observed in mosquitoes that were not infected after feeding on infected mice. Therefore, the observed behavioral changes may be due to

Plasmodium infections and to unspecific immune stimuli in the challenged mosquitoes.

Laboratory reared *Anopheles gambiae* harboring sporozoites of a laboratory strain of *P. falciparum* were more attracted to human odor when compared to infective mosquitoes exposed to negative-controls (Smallegange et al., 2013). In contrast, three different species of wild caught *Anopheles* infected with *P. falciparum* from natural infections had similar attraction rates to humans when compared with uninfected mosquitoes (Nguyen et al., 2017).

CHEMICAL COMPOUNDS STUDIED IN RELATION TO VECTOR ATTRACTION

Differences in mosquito attraction are related to dissimilarities in chemical volatiles produced by each host, which can be modified by pathogen infections. Díez-Fernández et al. (2020b) were the first to show that whole-body odor from *Plasmodium*-infected birds are more attractive to mosquitoes when compared to uninfected birds. De Moraes et al. (2014) demonstrated that mice displayed different odor profiles when infected with *Plasmodium chabaudi* and became more attractive to mosquitoes after the acute phase of infection. Mice produced fewer volatile chemicals during the acute phase of infection and attracted less mosquitoes. In humans, increased mosquito attraction toward *Plasmodium*-infected children was associated to changes in skin odor profile driven by increases in the production of aldehydes (Robinson et al., 2018). Children infected with *P. falciparum* in Malawi produced a different chemical breath composition than uninfected children (Schaber et al., 2018), which mosquitoes can use as a cue to find their hosts (Kelly et al., 2015). Thus, the chemical volatiles emitted by hosts and how they change during infection likely constitute the most important factor determining vector attraction.

Birds' uropygial (or preen) gland produces some antimicrobial and antifungal chemicals that protect the plumage and skin of birds; they also provide defense against ectoparasites and haemosporidian infection (Salibian and Montalti, 2009; Magallanes et al., 2016). Some studies suggest that uropygial gland secretions can attract vectors (Russell and Hunter, 2005), but others suggest no increased attraction toward such secretions (Díez-Fernández et al., 2020a) or toward common chemicals from uropygial glands (Allan et al., 2006) when compared to negative controls (no stimuli). The amount of volatile compounds of uropygial glands differ among adult, fledging and nestling house sparrows (*Passer domesticus*), but these differences did not modify mosquito attraction in dual-choice olfactometer assays (Garvin et al., 2018a). *Plasmodium* infection did not change the composition of the volatile fraction of uropygial gland secretion in house sparrows when compared to the uninfected group, and this may explain the similar mosquito attraction toward the secretion from both bird groups (Díez-Fernández et al., 2020b). However, other study showed that exposure to *Plasmodium* altered the wax ester composition of the secretion in song sparrows (*Melospiza melodia*), regardless of whether infections were cleared or not (Grieves et al., 2018).

Therefore, more research is needed to cover the whole array of chemicals produced by the uropygial gland and their effect on different vector species and families (Martínez-de la Puente et al., 2020). Particularly considering that parasites from different Haemosporida genera (e.g., *Haemoproteus*, *Leucocytozoon*) are transmitted by different Diptera families, which have both different life cycles and ecologies (Ibáñez-Bernal et al., 2020).

STUDIES FOCUSED ON OTHER HOST ATTRIBUTES

Physiological differences (e.g., hormones) and differential exposure between males and females due to sex-specific physiology (e.g., immunosuppression due to breeding activities), behavior (e.g., nesting), morphology (e.g., body size), and pathogen infections can influence mosquito attraction (Darbro et al., 2007; Cozzarolo et al., 2019). For instance, *Cx. pipiens* were more attracted to female Great tits (*Parus major*; Lalubin et al., 2012). *Ochlerotatus caspius* fed more on female than on male jackdaws (*Corvus monedula*), but no difference was observed when using *Cx. pipiens*. In addition, these two mosquito species did not show sex-biased feeding preference toward house sparrows (Gutiérrez-López et al., 2019a). Cozzarolo et al. (2019) did not find any mosquito feeding preference between sexes, but they used nestlings instead of adults (see also Simpson et al., 2009). Higher feeding rate on female birds by wild-caught *Culex restuans* has been reported during the nesting period, suggesting the role of seasonality in this process (Egizi et al., 2014), but this has yet to be investigated under laboratory conditions. Yan et al. (2018a) found that mosquitoes fed less on birds with higher resting metabolic rate, which authors interpreted as related to bird activity, where birds with higher metabolic rates are more active and thus display more defensive behaviors than more lethargic individuals. Finally, elevated levels of corticosterone increased bird attractiveness to mosquitoes despite the fact that these birds displayed increased anti-mosquito behaviors when compared to the control group (Gervasi et al., 2016). Increases in corticosterone levels may lead to *Plasmodium* resurgence in the blood stream in chronically infected birds with an increase in parasitemia (Applegate and Beaudoin, 1970). Therefore, the interaction between elevated stress hormone levels and parasitemia may synergistically increase bird attractiveness to mosquitoes, but this has yet to be tested. Different results across studies may be due to differences in life history traits of bird species, which may in turn influence exposure to vectors and species-specific physiological trade-offs. Hence, we suggest that fair comparisons and generalizations must be done across species (both hosts and vectors) with similar life history traits.

SUMMARY OF CURRENT EVIDENCE AND IMPLICATIONS FOR FUTURE STUDIES

We found that fewer studies assessed direct effects of avian and mammalian *Plasmodium* on mosquito host choice (infective

mosquitoes) when compared to the number of studies on indirect effects on mosquitoes (infected vertebrate hosts). Rearing mosquitoes under laboratory conditions over many generations may alter some genetic traits involved in their responsiveness to host cues (Takken and Verhulst, 2013), but nothing is known about whether genetic bottlenecks would change as a function of host-vector-parasite lineage assemblages (Gutiérrez-López et al., 2020). Although using hosts (birds and mice), mosquitoes and pathogens maintained in laboratories has provided fundamental tests of hypothesis related to the vector manipulation by pathogens, experiments mimicking natural conditions using wild caught mosquitoes are essential to fill in gaps for real world situations.

Free-living birds are infected with genetic lineages that vary in their pathological effects as a function of host species and parasite lineage (Palinauskas et al., 2011; Himmel et al., 2020). Assays using experimental infections have focused on domestic canaries infected with a *P. relictum* strain (SGS1) kept in the laboratory over dozens of passages, while assays using free-living birds have used three avian species naturally infected with a high diversity of parasites. In Gutiérrez-López et al. (2019a), 21 of 23 jackdaws exposed to wild-caught *Cx. pipiens* were naturally infected with *P. relictum* (SGS1), and yet these authors did not find differences in mosquito feeding rates between infected and uninfected birds. On the other hand, laboratory-reared mosquitoes fed more on canaries experimentally infected with a laboratory strain of *P. relictum* SGS1 (Cornet et al., 2013a,b).

The use of naturally infected birds has the limitation of confounding the bird's infection stage during mosquito exposure. This is because in birds the *Plasmodium* acute stage of infection usually finishes within a month post infection. After this period surviving birds enter the chronic stage of infection, in which they display low parasitemia for long periods or even for their entire life (Valkiūnas, 2005). In many of the studies, free-living birds were undergoing chronic infections when exposed to mosquitoes and parasitemia was not evaluated. Interestingly, mosquitoes were more attracted to chronically infected birds when compared to acute infection stages in experimental settings (Cornet et al., 2013b), which may be interpreted as a parasite avoidance strategy because high parasitemia in the host is associated to high vector mortality (Gutiérrez-López et al., 2019b).

Birds and mosquitoes can be co-infected by different genetically related or unrelated parasites (e.g., co-infection between *Plasmodium* parasites and WNV; Hughes et al., 2010; Medeiros et al., 2014). Co-infections by different *Plasmodium* spp. and other related haemosporidians are often found in wild birds (e.g., Valkiūnas et al., 2006). Yet, evidence for the effects of multiple infections on vector feeding behavior and on fitness of both bird hosts (e.g., Marzal et al., 2008) and vectors (e.g., Gutiérrez-López et al., 2020) is still very limited (see Martínez-de la Puente et al., 2020). To complicate matters further, if mosquitoes are more attracted to birds co-infected with *Plasmodium* and arboviruses than to birds infected with arboviruses only, avian malaria may indirectly increase the transmission of zoonotic pathogens. Future studies, therefore, should perform feeding or attraction assays using birds

experimentally infected with strains of different *Plasmodium* species with as few laboratory passages as possible, and also using different parasite groups (e.g., malaria and arbovirus). In addition, stage of infection (acute vs. chronic) and gametocyte levels (parasitemia) should be taken into consideration in studies using both natural and experimental infections. Furthermore, mosquitoes captured from the wild should be favored over populations kept in the laboratory for many generations. This would provide more real settings to understand host attractiveness to free-moving mosquitoes in nature.

Important issues to consider when planning experiments are:

(1) will birds be free or immobilized? Free birds may reflect natural conditions, but immobilized birds will increase vector sample size and reduce vector mortality by birds' behavioral defenses. (2) Will birds be visible to vectors or just odor cues will be investigated? Our opinion is that light levels should reflect those from the natural conditions during which vector activity peaks, which depends on vector species. (3) What would be the duration of the experiment? Immobilizing birds allows for shorter feeding experiments (1–3 h), while 15 min seems to be a common and reasonable time for attraction experiments. Ideally, researchers must know the natural feeding ecology of the studied vector in order to make an informed decision on the duration of experiments. Finally, (4) co-infections by different *Plasmodium* lineages or different parasite genera (e.g., *Plasmodium/Haemoproteus*) that are ubiquitous in nature, or even by Haemosporidians and arboviruses (e.g., WNV and USUV) should be considered. Understanding factors that change mosquito attraction to birds may have implications for human health as well, since highly ornithophilic mosquitoes such as *Cx. pipiens*, *Cx. perexiguus*, and *Cx. restuans* are vectors of some arboviruses

that may affect humans, such as WNV and USUV (e.g., Kilpatrick et al., 2006; Vázquez et al., 2011; Brugman et al., 2018). Thus, further studies are necessary to understand the range of effects that multiple infections may have on host-vector contact rates and, hence, on the dynamics of parasite transmission. Our review highlights the need to design and implement general standard experimental procedures to obtain comparable results, which can help to generalize findings across studies and to identify contingencies (**Figure 1**) that later will allow drawing generalizations by, for instance, conducting meta-analyses.

AUTHOR CONTRIBUTIONS

Both authors have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

DS-A has been supported by Consejo Nacional de Ciencia y Tecnología (CONACYT, project number Ciencia Básica 2011-01-168524 and project number Problemas Nacionales 2015-01-1628). FCF was supported by National Science Foundation grant 1717498 as part of the joint NSF-NIH-USDA Ecology and Evolution of Infectious Diseases program.

ACKNOWLEDGMENTS

We thank Sergio Ibáñez-Bernal, Daniela A. Dutra, Dina M. Fonseca, the editor Laura Gangoso and the three reviewers for their comments that highly improved the quality of this review.

REFERENCES

- Abella-Medrano, C. A., Ibáñez-Bernal, S., Carbó-Ramírez, P., and Santiago-Alarcon, D. (2018). Blood-meal preferences and avian malaria detection in mosquitoes (Diptera: Culicidae) captured at different land use types within a neotropical montane cloud forest matrix. *Parasitol. Int.* 67, 313–320. doi: 10.1016/j.parint.2018.01.006
- Allan, S. A., Bernier, U. R., and Kline, D. L. (2006). Laboratory evaluation of avian odors for mosquito (Diptera: Culicidae) attraction. *J. Med. Entomol.* 43, 225–231. doi: 10.1093/jmedent/43.2.225
- Applegate, J. E., and Beaudoin, R. L. (1970). Mechanism of spring relapse in avian malaria: effect of gonadotropin and corticosterone. *J. Wildl. Dis.* 6, 443–447. doi: 10.7589/0090-3558-6.4.443
- Atkinson, C. T., and Van Riper, I. I. C. (1991). "Pathogenicity and epizootiology of avian haematozoa: *Plasmodium*, *Leucocytozoon* and *Haemoproteus*," in *Bird-Parasite Interactions*, eds J. E. Loye and M. Zuk (Oxford: Oxford University Press), 19–48.
- Batista, E. P., Costa, E. F., and Silva, A. A. (2014). *Anopheles darlingi* (Diptera: Culicidae) displays increased attractiveness to infected individuals with *Plasmodium vivax* gametocytes. *Parasit. Vector.* 7:251. doi: 10.1186/1756-3305-7-251
- Brugman, V. A., Hernández-Triana, L. M., Medlock, J. M., Fooks, A. R., Carpenter, S., and Johnson, N. (2018). The role of *Culex pipiens* L. (Diptera: Culicidae) in virus transmission in Europe. *Int. J. Environ. Res. Public Health* 15:389. doi: 10.3390/ijerph15020389
- Burkett-Cadena, N. D., Ligon, R. A., Liu, M., Hassan, H. K., Hill, G. E., Eubanks, M. D., et al. (2010). Vector-host interactions in avian nests: do mosquitoes prefer nestlings over adults? *Am. J. Trop. Med. Hyg.* 83, 395–399. doi: 10.4269/ajtmh.2010.10-0048
- Busula, A. O., Bousema, T., Mweresa, C. K., Masiga, D., Logan, J. G., Sauerwein, R. W., et al. (2017). Gametocytemia and attractiveness of *Plasmodium falciparum*-infected kenyan children to *Anopheles gambiae* mosquitoes. *J. Infect. Dis.* 216, 291–295. doi: 10.1093/infdis/jix214
- Cator, L. J., George, J., Blanford, S., Murdock, C. C., Baker, T. C., Read, A. F., et al. (2013). 'Manipulation' without the parasite: altered feeding behaviour of mosquitoes is not dependent on infection with malaria parasites. *Proc. R. Soc. B* 280:20130711. doi: 10.1098/rspb.2013.0711
- Cornet, S., Nicot, A., Rivero, A., and Gandon, S. (2013a). Both infected and uninfected mosquitoes are attracted toward malaria infected birds. *Malar. J.* 12:179. doi: 10.1186/1475-2875-12-179
- Cornet, S., Nicot, A., Rivero, A., and Gandon, S. (2013b). Malaria infection increases bird attractiveness to uninfected mosquitoes. *Ecol. Lett.* 16, 323–329. doi: 10.1111/ele.12041
- Cornet, S., Nicot, A., Rivero, A., and Gandon, S. (2019). Avian malaria alters the dynamics of blood feeding in *Culex pipiens* mosquitoes. *Malar. J.* 18, 82. doi: 10.1186/s12936-019-2690-5
- Cozzarolo, C.-S., Sironi, N., Glaizot, O., Pigeault, R., and Christe, P. (2019). Sex-biased parasitism in vector-borne disease: vector preference? *PLoS One* 14:e0216360. doi: 10.1371/journal.pone.0216360
- Darbro, J. M., Dhondt, A. A., Vermeylen, F. M., and Harrington, L. C. (2007). *Mycoplasma gallisepticum* infection in house finches (*Carpodacus mexicanus*)

- affects mosquito blood feeding patterns. *Am. J. Trop. Med. Hyg.* 77, 488–494. doi: 10.4269/ajtmh.2007.77.488
- de Boer, J. G., Robinson, A., Powers, S. J., Burgers, S. L. G. E., Caulfield, J. C., Birkett, M. A., et al. (2017). Odours of *Plasmodium falciparum*-infected participants influence mosquito-host interactions. *Sci. Rep.* 7:9283. doi: 10.1038/s41598-017-08978-9
- De Moraes, C. M., Stanczyk, N. M., Betz, H. S., Pulido, H., Sim, D. G., Read, A. F., et al. (2014). Malaria-induced changes in host odors enhance mosquito attraction. *Proc. Natl. Acad. Sci. U.S.A.* 111, 11079–11084. doi: 10.1073/pnas.1405617111
- Díez-Fernández, A., Martínez-de la Puente, J., Gangoso, L., Ferraguti, M., Soriguer, R., and Figuerola, J. (2020a). House sparrow uropygial gland secretions do not attract ornithophilic nor mammophilic mosquitoes. *Med. Vet. Entomol.* 2020:12401. doi: 10.1111/mve.12401
- Díez-Fernández, A., Martínez-de la Puente, J., Gangoso, L., López, P., Soriguer, R., Martín, J., et al. (2020b). Mosquitoes are attracted by the odour of *Plasmodium*-infected birds. *Int. J. Parasitol.* 50, 569–575. doi: 10.1016/j.ijpara.2020.03.013
- Egizi, A. M., Farajollahi, A., and Fonseca, D. M. (2014). Diverse host feeding on nesting birds may limit early-season West Nile virus amplification. *Vector Borne Zoonotic Dis.* 14, 447–453. doi: 10.1089/vbz.2013.1536
- Farajollahi, A., Fonseca, D. M., Kramer, L. D., and Marm Kilpatrick, A. (2011). “Bird biting” mosquitoes and human disease: a review of the role of *Culex pipiens* complex mosquitoes in epidemiology. *Infect. Genet. Evol.* 11, 1577–1585. doi: 10.1016/j.meegid.2011.08.013
- Ferguson, H. M., Rivero, A., and Read, A. F. (2003). The influence of malaria parasite genetic diversity and anaemia on mosquito feeding and fecundity. *Parasitology* 127, 9–19. doi: 10.1017/s0031182003003287
- Gandon, S. (2018). Evolution and manipulation of vector host choice. *Am. Nat.* 192, 23–34. doi: 10.1086/697575
- Garvin, M. C., Austin, A., Boyer, K., Gefke, M., Wright, C., Pryor, Y., et al. (2018a). Attraction of *Culex pipiens* to house sparrows is influenced by host age but not uropygial gland secretions. *Insects* 9:127. doi: 10.3390/insects9040127
- Garvin, M. C., Austin, A. L., Stracker, N. H., Slowinski, S. P., Rutter, J. E., Butler, M., et al. (2018b). Attraction of *Culex pipiens* to uropygial gland secretions does not explain feeding preference for American robins. *J. Vect. Ecol.* 43, 110–116. doi: 10.1111/jvec.12290
- Gervasi, S. S., Burkett-Cadena, N., Burgan, S. C., Schrey, A. W., Hassan, H. K., Unnasch, T. R., et al. (2016). Host stress hormones alter vector feeding preferences, success, and productivity. *Proc. R. Soc. B* 283:20161278. doi: 10.1098/rspb.2016.1278
- Griesves, L. A., Kelly, T. R., Bernards, M. A., and MacDougall-Shackleton, E. A. (2018). Malarial infection alters wax ester composition of preen oil in songbirds: results of an experimental study. *Auk: Ornithol. Adv.* 135, 767–776. doi: 10.1642/AUK-17-242.1
- Griffing, S. M., Kilpatrick, A. M., Clark, L., and Marra, P. P. (2007). Mosquito landing rates on nesting American robins (*Turdus migratorius*). *Vect. Borne Zoonot. Dis.* 7, 437–443. doi: 10.1089/vbz.2006.0560
- Gutiérrez-López, R., Martínez-de la Puente, J., Gangoso, L., Soriguer, R., and Figuerola, J. (2019a). Effects of host sex, body mass and infection by avian *Plasmodium* on the biting rate of two mosquito species with different feeding preferences. *Parasit. Vect.* 12:87. doi: 10.1186/s13071-019-3342-x
- Gutiérrez-López, R., Martínez-de la Puente, J., Gangoso, L., Yan, J., Soriguer, R., and Figuerola, J. (2019b). Experimental reduction of host *Plasmodium* infection load affects mosquito survival. *Sci. Rep.* 9:8782. doi: 10.1038/s41598-019-45143-w
- Gutiérrez-López, R., Martínez-de la Puente, J., Gangoso, L., Soriguer, R., and Figuerola, J. (2020). *Plasmodium* transmission differs between mosquito species and parasite lineages. *Parasitology* 147, 441–447. doi: 10.1017/S0031182020000062
- Heil, M. (2016). Host manipulation by parasites: cases, patterns and remaining doubts. *Front. Ecol. Evol.* 4:80. doi: 10.3389/fevo.2016.00080
- Himmel, T., Harl, J., Pfanner, S., Nedorost, N., Nowotny, N., and Weissenböck, H. (2020). Haemosporidiosis in wild Eurasian blackbirds (*Turdus merula*) and song thrushes (*T. philomelos*): an in situ hybridization study with emphasis on exo-erythrocytic parasite burden. *Malar. J.* 19:69. doi: 10.1186/s12936-020-3147-6
- Hughes, T., Irwin, P., Hofmeister, E., and Paskewitz, S. M. (2010). Occurrence of avian *Plasmodium* and West Nile virus in *Culex* species in Wisconsin. *J. Am. Mosq. Control Assoc.* 26, 24–31. doi: 10.2987/09-5893.1
- Ibáñez-Bernal, S., Rivera-García, K. D., and Abella-Medrano, C. A. (2020). “Introduction to the taxonomy and general biology of Diptera (Insecta) involved in the transmission of avian haemosporida,” in *Avian Malaria and Related Parasites in the Tropics - Ecology, Evolution and Systematics*, eds D. Santiago-Alarcon and A. Marzal (Cham: Springer).
- Kelly, M., Su, C.-Y., Schaber, C., Crowley, J. R., Hsu, F.-F., Carlson, J. R., et al. (2015). Malaria parasites produce volatile mosquito attractants. *mBio* 6:e00235-15.
- Kilpatrick, A. M., Kramer, L. D., Jones, M. J., Marra, P. P., and Daszak, P. (2006). West Nile virus epidemics in North America are driven by shifts in mosquito feeding behavior. *PLoS Biol.* 4:e82. doi: 10.1371/journal.pbio.0040082
- Lacroix, R., Mukabana, W. R., Gouagna, L. C., and Koella, J. C. (2005). Malaria infection increases attractiveness of humans to mosquitoes. *PLoS Biol.* 3:e298. doi: 10.1371/journal.pbio.0030298
- Lalubin, F., Bize, P., van Rooyen, J., Christe, P., and Glaizot, O. (2012). Potential evidence of parasite avoidance in an avian malarial vector. *Anim. Behav.* 84, 539–545. doi: 10.1016/j.anbehav.2012.06.004
- Magallanes, S., Møller, A. P., García-Longoria, L., de Lope, F., and Marzal, A. (2016). Volume and antimicrobial activity of secretions of the uropygial gland are correlated with malaria infection in house sparrows. *Parasit. Vect.* 9:232. doi: 10.1186/s13071-016-1512-1517
- Martínez-de la Puente, J., Díez-Fernández, A., Soriguer, R., Rambozzi, L., Peano, A., Meneguz, P., et al. (2020). Are malaria-infected birds more attractive to mosquito vectors. *Ardeola* 68, 251–264. doi: 10.13157/arla.68.1.2021.fo1
- Marzal, A., Bensch, S., Reviriego, M., Balbontin, J., and De Lope, F. (2008). Effects of malaria double infection in birds: one plus one is not two. *J. Evol. Biol.* 21, 979–987. doi: 10.1111/j.1420-9101.2008.01545.x
- Medeiros, M. C. I., Anderson, T. K., Higashiguchi, J. M., Kitron, U. D., Walker, E. D., Brown, J. D., et al. (2014). An inverse association between West Nile virus serostatus and avian malaria infection status. *Parasit. Vect.* 7:415. doi: 10.1186/1756-3305-7-415
- Nguyen, P. L., Vantaux, A., Hien, D. F., Dabiré, K. R., Yameogo, B. K., Gouagna, L.-C., et al. (2017). No evidence for manipulation of *Anopheles gambiae*, *An. coluzzii* and *An. arabiensis* host preference by *Plasmodium falciparum*. *Sci. Rep.* 7:9415. doi: 10.1038/s41598-017-09821-x
- Palinauskas, V., Martínez-de la Puente, J., Hernández-Soto, R. S., and Marzal, A. (2020). “Experimental Parasitology and Ecoimmunology: concepts and opportunities in avian Haemosporidian studies,” *Avian Malaria and Related Parasites in the Tropics*, eds D. Santiago-Alarcon and A. Marzal (Cham: Springer).
- Palinauskas, V., Valkiūnas, G., Bolshakov, C. V., and Bensch, S. (2011). *Plasmodium relictum* (lineage SGS1) and *Plasmodium ashfordi* (lineage GRW2): the effects of the co-infection on experimentally infected passerine birds. *Exp. Parasitol.* 127, 527–533. doi: 10.1016/j.exppara.2010.10.007
- Palinauskas, V., Žiegytė, R., Iezhova, T. A., Ilgūnas, M., Bernotienė, R., and Valkiūnas, G. (2016). Description, molecular characterisation, diagnostics and life cycle of *Plasmodium elongatum* (lineage pERIRUB01), the virulent avian malaria parasite. *Int. J. Parasitol.* 46, 697–707. doi: 10.1016/j.ijpara.2016.05.005
- Rivero, A., and Gandon, S. (2018). Evolutionary ecology of avian malaria: past to present. *Trends Parasitol.* 34, 712–726. doi: 10.1016/j.pt.2018.06.002
- Robinson, A., Busula, A. O., Voets, M. A., Beshir, K. B., Caulfield, J. C., Powers, S. J., et al. (2018). Plasmodium-associated changes in human odor attract mosquitoes. *Proc. Natl. Acad. Sci. U.S.A.* 115, E4209–E4218. doi: 10.1073/pnas.1721610115
- Rochlin, I., Faraji, A., Healy, K., and Andreadis, T. G. (2019). West Nile virus mosquito vectors in North America. *J. Med. Entomol.* 56, 1475–1490. doi: 10.1093/jme/tjz146
- Russell, C. B., and Hunter, F. F. (2005). Attraction of *Culex pipiens/restuans* (Diptera: Culicidae) mosquitoes to bird Uropygial gland odors at two elevations in the niagara region of Ontario. *J. Med. Entomol.* 42, 301–305. doi: 10.1093/jmedent/42.3.301
- Salibian, A., and Montalti, D. (2009). Physiological and biochemical aspects of the avian uropygial gland. *Braz. J. Biol.* 69, 437–446. doi: 10.1590/s1519-69842009000200029

- Santa-Ana, M., Khadem, M., and Capela, R. (2006). Natural infection of *Culex theileri* (Diptera: Culicidae) with *Dirofilaria immitis* (Nematoda: Filarioidea) on Madeira Island. *Portugal J. Med. Entomol.* 43, 104–106. doi: 10.1093/jmedent/43.1.104
- Schaber, C. L., Katta, N., Bollinger, L. B., Mwale, M., Mlotha-Mitole, R., Trehan, I., et al. (2018). Breathprinting reveals malaria-associated biomarkers and mosquito attractants. *J. Infect. Dis.* 217, 1553–1560. doi: 10.1093/infdis/jiy072
- Scott, T. W., Lorenz, L. H., and Edman, J. D. (1990). Effects of house sparrow age and arbovirus infection on attraction of mosquitoes. *J. Med. Entomol.* 27, 856–863. doi: 10.1093/jmedent/27.5.856
- Simpson, J. E., Folsom-O'Keefe, C. M., Childs, J. E., Simons, L. E., Andreadis, T. G., and Diuk-Wasser, M. A. (2009). Avian host-selection by *Culex pipiens* in experimental trials. *PLoS One* 4:e7861. doi: 10.1371/journal.pone.0007861
- Smallegange, R. C., van Gemert, G. J., van de Vegte-Bolmer, M., Gezan, S., Takken, W., Sauerwein, R. W., et al. (2013). Malaria infected mosquitoes express enhanced attraction to human odor. *PLoS One* 8:e63602. doi: 10.1371/journal.pone.0063602
- Spanoudis, C. G., Andreadis, S. S., Bray, D. P., Savopoulou-Soultani, M., and Ignell, R. (2020). Behavioural response of the house mosquitoes *Culex quinquefasciatus* and *Culex pipiens molestus* to avian odours and its reliance on carbon dioxide. *Med. Vet. Entomol.* 34, 129–137. doi: 10.1111/mve.12429
- Takken, W., and Verhulst, N. O. (2013). Host preferences of blood-feeding mosquitoes. *Annu. Rev. Entomol.* 58, 433–453. doi: 10.1146/annurev-ento-120811-153618
- Valkiūnas, G. (2005). *Avian Malaria Parasites and Other Haemosporidia*, 1st Edn, Boca Raton, FL: CRC Press.
- Valkiūnas, G., Bensch, S., Iezhova, T. A., Križanauskienė, A., Hellgren, O., and Bolshakov, C. V. (2006). Nested cytochrome b polymerase chain reaction diagnostics underestimate mixed infections of avian blood haemosporidian parasites: microscopy is still essential. *J. Parasitol.* 92, 418–422. doi: 10.1645/je-3547rn.1
- Valkiūnas, G., Kazlauskienė, R., Bernotienė, R., Bukauskaitė, D., Palinauskas, V., and Iezhova, T. A. (2014). *Haemoproteus* infections (Haemosporida, Haemoproteidae) kill bird-biting mosquitoes. *Parasitol. Res.* 113, 1011–1018. doi: 10.1007/s00436-013-3733-4
- Valkiūnas, G., Kazlauskienė, R., Bernotienė, R., Palinauskas, V., and Iezhova, T. A. (2013). Abortive long-lasting sporogony of two *Haemoproteus* species (Haemosporida, Haemoproteidae) in the mosquito *Ochlerotatus cantans*, with perspectives on haemosporidian vector research. *Parasitol. Res.* 112, 2159–2169. doi: 10.1007/s00436-013-3375-6
- Vázquez, A., Ruiz, S., Herrero, L., Moreno, J., Molero, F., Magallanes, A., et al. (2011). West Nile and Usutu viruses in mosquitoes in Spain, 2008–2009. *Am. J. Trop. Med. Hyg.* 85, 178–181. doi: 10.4269/ajtmh.2011.11-0042
- Vogels, C. B. F., Fros, J. J., Pijlman, G. P., van Loon, J. J. A., Gort, G., and Koenraadt, C. J. M. (2017). Virus interferes with host-seeking behaviour of mosquito. *J. Exp. Biol.* 220, 3598–3603. doi: 10.1242/jeb.164186
- Yan, J., Broggi, J., Martínez-de la Puente, J., Gutiérrez-López, R., Gangoso, L., Soriguer, R., et al. (2018a). Does bird metabolic rate influence mosquito feeding preference? *Parasit. Vector.* 11:110. doi: 10.1186/s13071-018-2708-9
- Yan, J., Martínez-de la Puente, J., Gangoso, L., Gutiérrez-López, R., Soriguer, R., and Figuerola, J. (2018b). Avian malaria infection intensity influences mosquito feeding patterns. *Int. J. Parasitol.* 48, 257–264. doi: 10.1016/j.ijpara.2017.09.005

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Santiago-Alarcon and Ferreira. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.