



Is Host Selection by Mosquitoes Driving Vector Specificity of Parasites? A Review on the Avian Malaria Model

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Parasites and hosts are in a complex evolutionary arm race where host compatibility represents a key obstacle for successful infections. The degree of parasite specialization on a host varies along a continuum: on one end, extreme specialist parasites may be restricted to a single host species, and on the other, generalist parasites are able to infect a diverse set of hosts. Multiple intrinsic factors associated to the host, such as their immune system and physiological condition, can contribute to the evolution of host specificity of parasites and have been well-studied and documented in vertebrates. In contrast, vector specificity of parasites has been largely overlooked, especially in natural conditions. While a few studies suggested that insect vectors do not play an important role in shaping the parasite community structure since they may feed widely from the bird community, current studies have demonstrated the importance of vector feeding behavior on transmission dynamics for several vector-borne pathogens. Here, we provide a review on the specialization of avian *Plasmodium* in vectors, emphasizing the necessity to study simultaneously the three players to further understand how host choice by the vectors might influence the distribution of parasites in the wild. In addition, we suggest specific research directions making use of both empirical data gathered in the field and controlled experiments on vector host-feeding preferences.

Keywords: avian *plasmodium*, feeding preference, insect-vector, ornithophilic, parasite specialization

INTRODUCTION

The degree of parasite specialization for a host varies along a continuum: on one end, extreme specialist parasites may be restricted to a single host species, and on the other, generalist parasites are able to infect a diverse set of hosts, with a large diversity of intermediate states (Vázquez et al., 2005; Poulin, 2007; Hellgren et al., 2009; McCoy et al., 2013). Both ecological and evolutionary mechanisms are currently acting to maintain this high diversity in the range of host specialization (Poiso et al., 2015). Understanding how parasite specialization has evolved and how different strategies can co-occur is challenging and remains a debated topic. It has been suggested first that

specialization represents an evolutionary “dead end,” which limits further evolution (Kelley and Farrell, 1998; Snyder and Loker, 2000; Nosi, 2002). However, several later studies have indicated that generalists can repeatedly evolve from specialist lineages, albeit with a relatively low frequency (Poulin et al., 2006; Johnson et al., 2009; Gomez et al., 2010).

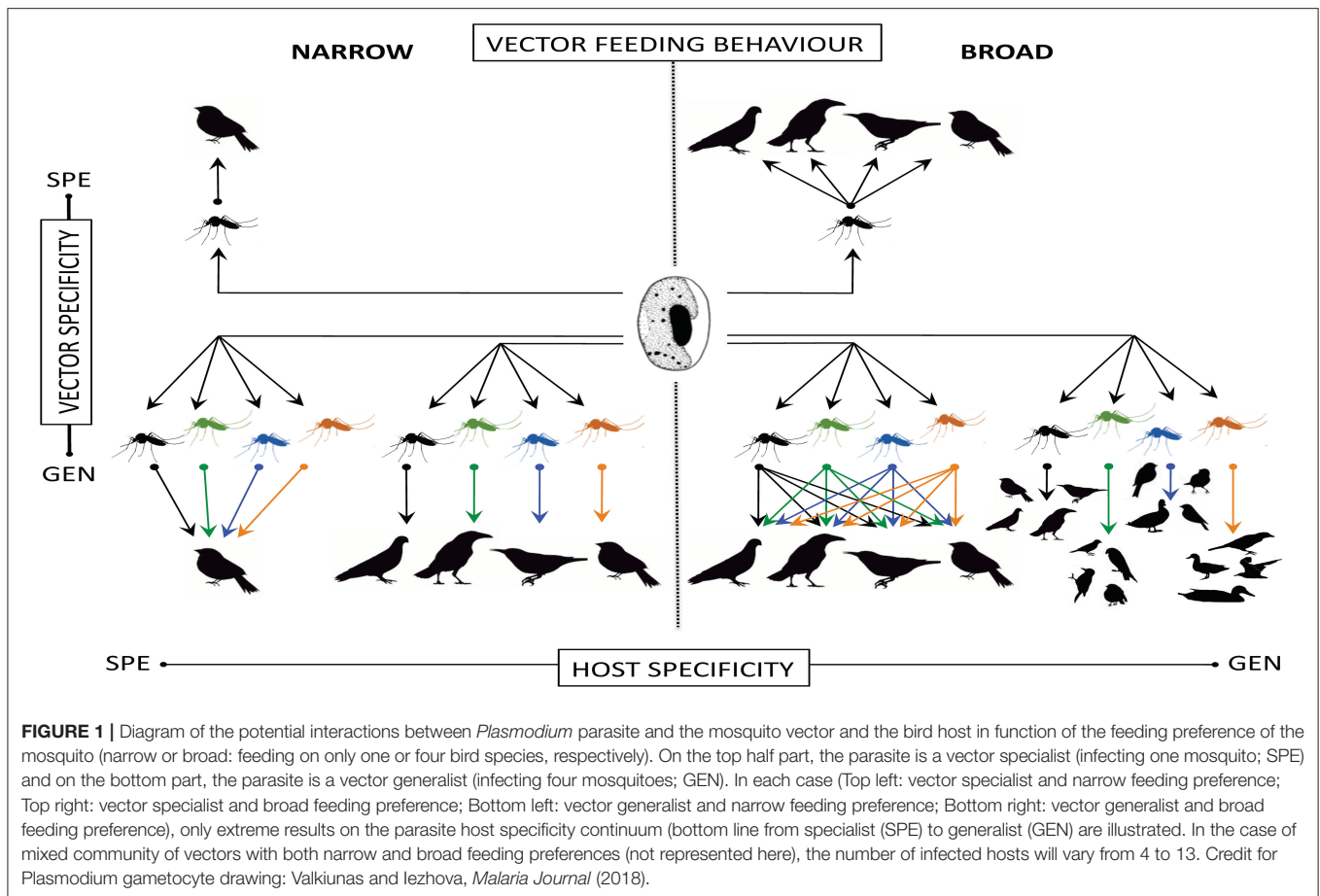
The probability for a parasite of infecting a suitable host depends on many factors, including the host-parasite compatibility, rate of encounter, the parasite life cycle, the population density (Combes, 1997) as well as host intrinsic factors such as its immune system, age, or sex (Loiseau et al., 2008; Bichet et al., 2014; Calero-Riestra and Garcia, 2016). For parasites such as avian *Plasmodium*, with a complex life cycle that involves two hosts, one vertebrate (bird) and one insect (mosquito; Valkiunas, 2005), additional parameters linked to the insect, such as its feeding behavior or immune system, may also influence parasite specialization (Billingsley and Sinden, 1997; Gutiérrez-López et al., 2020). Interactions with the insects, commonly called vectors (Wilson et al., 2017), are likely important for parasite evolution since mosquitoes are the definitive host, in which sexual reproduction occurs. Thus, as in the vertebrate hosts (hereafter the term “host” will be used), the parasite ingested in a mosquito blood meal must elude the immune system of the vector and complete all the developmental stages while the mosquito remains alive long enough to feed on another host (Marquardt et al., 2005).

Avian malaria parasites are considered an excellent model for investigating parasite transmission dynamics in ecological and evolutionary studies (LaPointe et al., 2012; Rivero and Gandon, 2018). They have been studied extensively in birds because of their high diversity of hosts and nearly worldwide distribution (Valkiunas, 2005). To date, parasite specialization for their vertebrate hosts has been much more studied compared to their vector specificity. Studies have investigated host-parasite associations using phylogenetic analyses and indices of host specialization (e.g., Ishtiaq et al., 2008; Hellgren et al., 2009; Loiseau et al., 2012; Ricklefs et al., 2014; Lauron et al., 2015; Fecchio et al., 2019) and have revealed that several lineages of *Plasmodium* exhibit extreme host generalist parasitism strategies, whereas other lineages appear to have been constrained to certain host families or individual bird species (Ricklefs and Fallon, 2002; Ricklefs et al., 2004; Beadell et al., 2009). Interestingly, in the discussion of a large number of these publications, authors suggest a key role for vectors in the system, but very few studies are exploring this vector role. In fact, the number of publications using the bird-avian *Plasmodium* system has considerably increased with on average 25 articles published per year since the last 10 years, but the number of publications that integrates the vector in their study remains much lower (3.5 per year since 2010; see **Supplementary Figure 1**). A number of reasons are responsible for the fact that vector specificity of avian parasites has been largely overlooked, especially in natural conditions: (i) researchers studying avian malaria are often trained ornithologists with little or no entomological expertise, (ii) insect vectors are difficult to capture compared to birds, (iii) they are also more difficult to identify, especially in tropical countries, (iv) the parasite prevalence in mosquitoes is usually

low (10% on average with values ranging from 0.003 to 30%; Aruch et al., 2007; Glaizot et al., 2012; Lalubin et al., 2013; Zélé et al., 2014; Martínez-de la Puente et al., 2015, 2016, 2020) compared to birds where prevalence often reaches up to 80% (Bichet et al., 2014).

Different ecological and behavioral factors determine the co-evolution of avian *Plasmodium* and mosquitoes (Ferraguti et al., 2016). Among them, the vector feeding behavior is an important parameter that can affect the specialization of parasites both in the vector and the vertebrate host (**Figure 1**). A hypothesis on parasite vertebrate host specificity is that if the vector is not selective and feeds on a large variety of avian hosts, then the malaria parasite should have an advantage in being an avian host generalist, maintaining compatibility with a wide set of birds, even if some of them are not optimal hosts. This should increase its encounter rate with suitable avian hosts and, therefore, its overall prevalence in the community (Dobson, 2004; Hellgren et al., 2009). On the other hand, if the vector is selective and feeds on specific bird species (Kilpatrick et al., 2006; Hellgren et al., 2008; Rizzoli et al., 2015), the parasite should have an advantage in being host specialist and optimize its host compatibility, development and transmission efficiency. Interestingly, the host specificity of parasites may not reflect their vector specificity. As shown in **Figure 1**, a parasite that is a vector specialist (i.e., able to complete its sexual cycle in one mosquito species only) could present different host strategies, specialist or generalist, depending on the host selection by vectors. If the parasite is a vector generalist (i.e., able to complete its sexual cycle in various mosquito species), the diversity in the range of host specialization can be even more important i.e., from highly host specialist to extremely host generalist (**Figure 1**). Therefore, from a parasite perspective, it would seem more advantageous to be a vector generalist since this would enable a broader gradient of host specificity (considering always that those vectors are competent to transmit the parasite). On the other hand, being a vector or host generalist may come at the expense of optimal parasite compatibility with host or vector.

Here, we review the current knowledge on parameters that influence host selection by mosquitoes and its potential repercussions on vector-parasite co-evolution and vector specificity. Using the MalAvi database (Bensch et al., 2009), which currently comprises 1276 unique *Plasmodium* lineages found in around 1,200 bird species and 40 mosquito species and data from the literature, we aimed at (i) evaluating the feeding preference of those mosquito species that could be potential avian malaria vectors and (ii) exploring the phylogenetic relationships of avian malaria lineages and their vector and bird specificity. We selected mosquito species where *Plasmodium* lineages have been isolated from the head/thorax or from salivary glands as a proxy of competent vector. We excluded lineages found in whole mosquitoes since they may correspond to parasites that will experience abortive developments in the vector midgut (Valkiunas et al., 2013). Finally, we address various challenges and limitations when working with vectors and suggest lines of research for the future, both in the field and in laboratory conditions.



HOW DO MOSQUITOES SELECT THEIR HOSTS?

Large Variation in Feeding Preferences

The transmission dynamics of avian *Plasmodium* is going to be strongly influenced by the contact rates between mosquitoes and susceptible hosts (Takken and Verhulst, 2013). Under natural conditions, mosquitoes show different innate feeding preferences at different levels. First, while some species feed mostly on mammals (i.e., mammophilic species), others prefer to feed on birds (i.e., ornithophilic species), or amphibians and reptiles, while yet other species show a real opportunistic behavior (Molaei et al., 2007; Burkett-Cadena et al., 2008; Viana et al., 2010; Muñoz et al., 2012; Martínez-de la Puente et al., 2015). Second, in addition to this broad tendency for particular host groups, mosquitoes may feed on certain host species at higher rates than expected from their abundance (Hamer et al., 2009; Lura et al., 2012). For instance, in Europe, *Cx. pipiens* seems to show a preference for blackbirds (*Turdus merula*) compared to European starlings (*Sturnus vulgaris*; Rizzoli et al., 2015). These two levels (group/species) of selection by the mosquito could be altered by the availability of preferred hosts that depends on seasonality and habitat (Wekesa et al., 1997; Kilpatrick et al., 2006; Thiemann et al., 2011). As an example,

Culex pipiens and *Culex tarsalis*, known to be predominantly ornithophilic, shift their diet to include more mammals when the availability of certain bird species decreases at the end of the summer (Kilpatrick et al., 2006). Seasonality in temperate regions affects also mosquito abundance and in consequence parasite prevalence, with a typical peak in August or early autumn (Ferraguti et al., 2013; Lalubin et al., 2013). In addition, more or less effective host anti-mosquito behavior and other intrinsic host factors, developed below, influence feeding patterns of mosquitoes (Takken and Verhulst, 2013).

Host Characteristics Influencing Feeding Preferences

Female mosquitoes detect their vertebrate hosts by a combination of different cues [e.g., visual cues (body size), carbon dioxide (CO₂), temperature, moisture, and/or body odor], which influence the attractiveness of individuals to vectors (Eiras and Jepson, 1994; Lehane, 2005). Some individuals (males or females) depending on their physiological state (e.g., hormone levels), age-class groups (young or older individuals) or infectious status (infected vs. non-infected) may be more attractive than others. Those individuals are therefore more likely to receive more mosquito bites (Dye and Hasibeder, 1986; Liebman

et al., 2014) and acquire new infections from vectors, but also to pass on parasites to subsequent vectors with whom they come in contact. These super-receivers and super-spreaders increase the contact rates between hosts and vectors, and may influence the vector specificity of parasites. Both empirical studies and theoretical models (Woolhouse et al., 1997; Perkins et al., 2013) showed that inter-individual heterogeneity has considerable implications for the epidemiology of mosquito-borne parasites.

First, larger hosts may receive more mosquito bites (Yan et al., 2017), probably due to (i) the higher amounts of cues (e.g., CO₂) released by larger individuals or (ii) the greater skin surface available for mosquito bite (Kleiber, 1947; Yan et al., 2017). Different studies have reported a positive relationship between the host body mass and the feeding rate of different blood-searching insect vector (Martínez-de la Puente et al., 2010; Schönenberger et al., 2016). In addition, Yan et al. (2017) found that *Cx. pipiens* fed more frequently on birds with a longer tarsus, suggesting that larger areas of exposed skin are important in determining feeding patterns. However, experimental studies have observed contrasting results. While Simpson et al. (2009) found differences in *Cx. pipiens* attraction among bird species, with American robins (*Turdus migratorius*) being more attractive than house sparrows (*Passer domesticus*), Gutiérrez-López et al. (2019) found no difference in attraction between jackdaws (*Coloeus monedula*) and house sparrows. Furthermore, in both studies, differences in body mass between individuals of the same species did not determine mosquito attraction, suggesting that, at short distances (as happens in an experimental setup), other signals such as heat, humidity or odor could be more important than intraspecific differences in body mass (Raji and DeGennaro, 2017).

Sex-associated characteristics could also cause differences in the mosquito attraction (Zuk et al., 1990). Sex-biased individual attraction could explain why several studies found that male birds present usually a higher prevalence of blood parasites than females (Skorping and Jensen, 2004; Zuk and Stoehr, 2010; Calero-Riestra and Garcia, 2016). As an example, Burkett-Cadena et al. (2014) found that mosquitoes had a higher feeding preference for male birds, but this result was observed mainly in mammophilic mosquitoes. On the other hand, several studies failed to find any significant sex-biased feeding pattern in ornithophilic mosquitoes (Simpson et al., 2009; Yan et al., 2018; Cozzarolo et al., 2019; Díez-Fernández et al., 2019; Gutiérrez-López et al., 2019). It has also been suggested that the composition of volatile substances from the uropygial gland secretions, which differ between male and female birds (Jacob et al., 1979; Amo et al., 2012), could affect the attraction of blood-sucking insects (Russell and Hunter, 2005; Martínez-de la Puente et al., 2011). However, Díez-Fernández et al. (2020) found no difference between feeding pattern in *Culex pipiens* and the sex of the birds. Therefore, other factors such as the degradation of the uropygial secretions by the microbiome present in the feathers could act as an attractive to mosquitoes (Allan et al., 2006; Díez-Fernández et al., 2020).

Parasite Manipulation and Vector Adaptive Avoidance

According to the parasite manipulation hypothesis (Poulin, 2000), the infection with the parasite should increase the incidence of feeding by mosquitoes (Cornet et al., 2013), either by modifying its defense behavior or increasing its attractiveness (Heil, 2016). It could also modify the behavior of the mosquito, making it more aggressive. These parasite manipulations should increase the contact rates between the host and the vector and, therefore, favor the parasite transmission (Hurd, 2003; Lefèvre and Thomas, 2008).

To date, experimental tests of this hypothesis using the *Plasmodium relictum*—*Cx. pipiens* system have obtained contradictory results. While some studies found that mosquitoes were attracted to, or fed on chronically infected birds at a higher rate than uninfected hosts (Cornet et al., 2013; Díez-Fernández et al., 2020), other studies have reported the opposite pattern (Lalubin et al., 2012) or an absence of significant differences between infected and uninfected birds (Yan et al., 2018; Gutiérrez-López et al., 2019). This discrepancy may come from the different experimental procedures used (e.g., either dual-choice olfactometer or direct contact with immobilized hosts) and therefore further studies are required to clarify how the infection status may influence the feeding behavior of mosquitoes.

The parasite load in the vertebrate (i.e., parasitemia) may also play an important role on the mosquito feeding patterns. According to the vector adaptive avoidance (Lalubin et al., 2012), mosquitoes should avoid highly infected individuals due to the costs induced by parasite in the vectors. However, Yan et al. (2018) found the opposite with mosquitoes feeding with a higher rate on those individuals that had a higher *Plasmodium* parasite load, suggesting a pre-eminence of parasite manipulation over vector avoidance. Comprehensive studies controlling for multiple factors are needed to better understand the interplay between these two opposite factors in the host selection by vectors.

WHAT ARE THE FEEDING PREFERENCES OF MOSQUITOES TRANSMITTING AVIAN MALARIA?

To illustrate the diversity of mosquito feeding preference patterns, we used the MalAvi database and a set of publications to gather information on blood meals for all the vectors collected in the field with avian *Plasmodium* in their head/thorax or salivary glands ($N_{\text{vector}} = 22$ and $N_{\text{lineage}} = 58$; **Figure 2** and see **Supplementary Materials, Table S1**). We classified the diet, using the percentage of blood meals derived from birds, in three categories as (i) mammophilic (from 0 to 33%), (ii) opportunistic (from 33 to 66%), or (iii) ornithophilic (more than 66%).

According to the literature, *Cx. pipiens* was the most studied mosquito species for avian malaria and was found to feed on more than 74 different bird species. In fact, 82% of the blood meals found in *Cx. pipiens* were from birds, confirming its ornithophilic feeding preference (Kilpatrick et al., 2006;

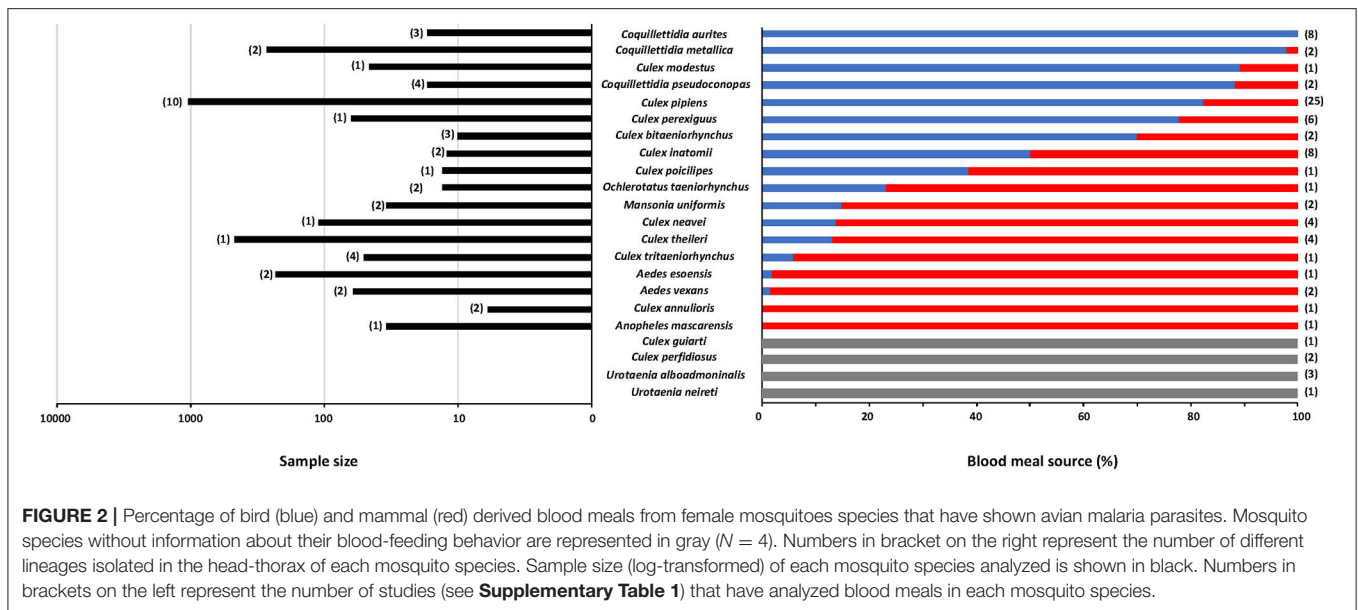


FIGURE 2 | Percentage of bird (blue) and mammal (red) derived blood meals from female mosquitoes species that have shown avian malaria parasites. Mosquito species without information about their blood-feeding behavior are represented in gray ($N = 4$). Numbers in bracket on the right represent the number of different lineages isolated in the head-thorax of each mosquito species. Sample size (log-transformed) of each mosquito species analyzed is shown in black. Numbers in brackets on the left represent the number of studies (see **Supplementary Table 1**) that have analyzed blood meals in each mosquito species.

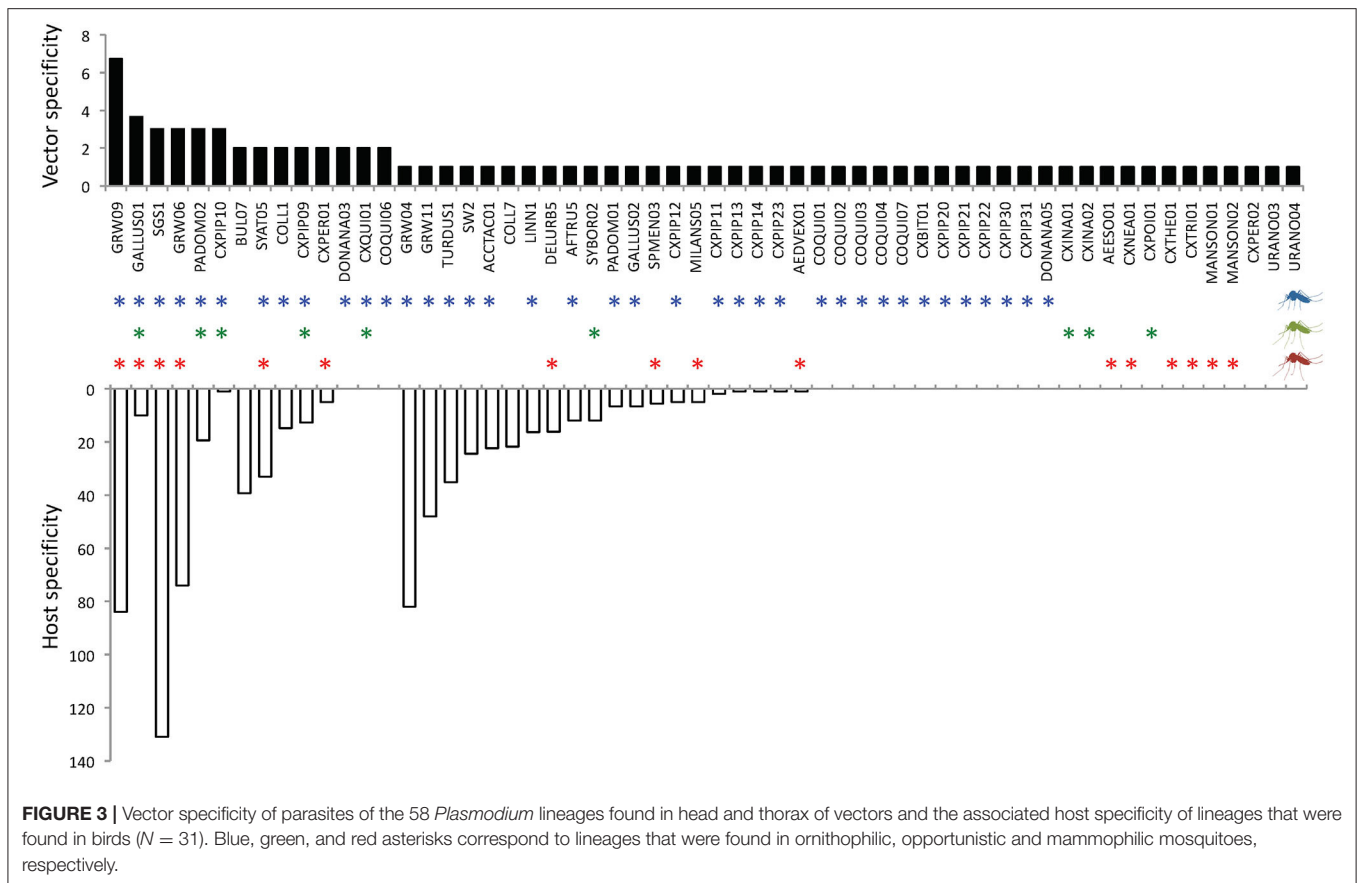
Hamer et al., 2008; **Figure 2**). It also harbors the highest number of avian *Plasmodium* lineages in the head/thorax ($N = 25$; **Supplementary Figure 2**). Therefore, its feeding preference together with its wide distribution around the world, its ecology (Farajollahi et al., 2011) and the diversity of lineages harbored, make this mosquito species one of the main vectors of avian *Plasmodium*. Among other vector species known to harbor avian *Plasmodium*, we found species that exhibit mammophilic ($N = 9$; e.g., *Culex theileri* and *Culex neavei*), opportunistic ($N = 2$; *Cx. inatamii*, *Cx. poicilipes*), and ornithophilic preferences ($N = 7$; **Figure 2**). We therefore observe a large variation in mosquito behavior that should lead to different vector specificity strategies and parasite transmission efficiency. For instance, avian *Plasmodium* lineages should enter in contact at higher rate with ornithophilic mosquito species, which preferentially feed on birds, than with opportunistic or mammophilic mosquito species. This in turn should cause avian *Plasmodium* lineages to become better adapted to ornithophilic mosquitoes and develop specificity for this vector type.

WHAT DO WE KNOW ABOUT VECTOR SPECIFICITY OF AVIAN *PLASMODIUM*?

Ten years ago, some studies began to use molecular markers and phylogenetic analyses to examine the distribution of avian blood parasite lineages in wild-caught arthropod vectors. One of the first studies showed that different parasite lineages found in different mosquito genera were sharing a common vertebrate host (Gager et al., 2008). Their data imply that the co-occurrence of two parasite lineages in the same vertebrate host is not necessarily explained by access being provided by a shared mosquito. Other studies showed that different mosquito species could harbor and share closely related or identical parasite lineages (Ishtiaq et al., 2008; Kimura et al.,

2010; Inci et al., 2012), suggesting that these lineages did not have high vector specificity. However, these studies identified lineages from whole mosquitoes or head-thorax and discussed the fact that without salivary gland dissection or experimental demonstration of the transmission cycle, it was not possible to establish the vector competence of mosquitoes for parasite lineages and therefore to fully assess the vector specificity. Indeed, an important percentage of parasite DNA amplification could come from abortive stages of parasite and not from infective stages (i.e., sporozoites; Valkiunas, 2011; Valkiunas et al., 2013). More recently, researchers performed experimental work to identify competent vector species for different avian *Plasmodium* lineages by studying sporogonic development in salivary glands or saliva (Valkiunas, 2005; Kazlauskienė et al., 2013; Palinauskas et al., 2016; Carlson et al., 2018; Gutiérrez-López et al., 2020). These studies highlighted variation in the mosquito ability to transmit different avian *Plasmodium* lineages, with some mosquito species being completely refractory to some parasite lineages or some being able to transmit different parasite lineages and/or species.

These experimental results combined with empirical data from field surveys demonstrate that avian *Plasmodium* lineages, which show extensive variation in host range (from one to more than 100 bird species) and specialization (host specificity index calculated as in Hellgren et al., 2009; **Figure 3**), also show variation in vector specificity (from one to 6 mosquito species; **Figure 3**). It is worth noting that the most host generalist parasite (*Plasmodium relictum* SGS1) that has been found to infect around 120 bird species is not the lineage that has been found in the most vector species so far (**Figure 3**). Some host specialist lineages (e.g., CXPIP10) or with an intermediate host range (e.g., PADOM02) were found in the same number of vectors as *Plasmodium* SGS1 (**Figure 3**), reflecting differential host and vector specificity for a given parasite lineage. Overall however, the parasite host specificity was positively correlated to



its vector specificity (Pearson coefficient $R = 0.47$; $P = 0.008$; see **Supplementary Figure 3**).

In order to explore the phylogenetic relationships of *Plasmodium* lineages and their associations with mosquito species, we performed Bayesian phylogenetic analyses with 58 *Plasmodium* lineages plus another 16 morphospecies described and deposited in MalAvi (**Figure 4**; see methods in **Supplemental Materials**). In the tree, we were able to determine 12 clades that correspond to groups of lineages closely related (Clades A to L; represented by a triangular tip with a node support higher than 0.85), most of them including a known morphospecies. First, we observe that most lineages found in the same mosquito species were not necessarily closely related but rather were found all across the phylogenetic tree, suggesting no evidence for strong coevolutionary relationships between these lineages and their vectors. At the lineage level, it appears that around 75% of the lineages were found in only one vector species, which probably does not always reflect strict vector specificity but rather a sampling effort bias. The other lineages were found in two to six different mosquito species sometimes from different genus (e.g., *Plasmodium elongatum* GRW06, *Plasmodium gallinaceum* GALLUS1, *Plasmodium* GRW09). These three lineages are most likely vector generalists since they shared different mosquito genus that also had different feeding preferences (**Figure 4**). Interestingly, at the clade level, we found more variation in vector specificity. If we consider a gradient of

specialization, from generalist to specialist, we could discern: (i) clades associated with two or three mosquito genera (2–6 species; clades B, D, E, H, J, and L) with different feeding preferences (i.e., vector generalists), (ii) clades associated with only one genus (*Culex*) but 2–4 different species with different feeding preferences as well (i.e., intermediate vector specificity; clades C, F, and I), and (iii) clades associated with only one or two ornithophilic mosquito species (i.e., vector specialists; Clades A, G, and K).

DOES HOST SELECTION BY THE MOSQUITO INFLUENCE PARASITE VECTOR SPECIFICITY?

Depending on the feeding preference of the vectors, parasites should have different strategies of transmission and specificity. We predicted that avian *Plasmodium* lineages found in ornithophilic vectors should be more numerous and on average more vector specialists than lineages found in opportunistic or mammophilic mosquitoes since they have a higher chance of ending up in avian hosts. First, we found that ornithophilic mosquitoes harbor more *Plasmodium* lineages ($N = 38$) than opportunistic or mammophilic vectors as predicted (9 and 16 lineages, respectively; **Figure 3**). In addition, all the clades were associated with at least one ornithophilic mosquito, which

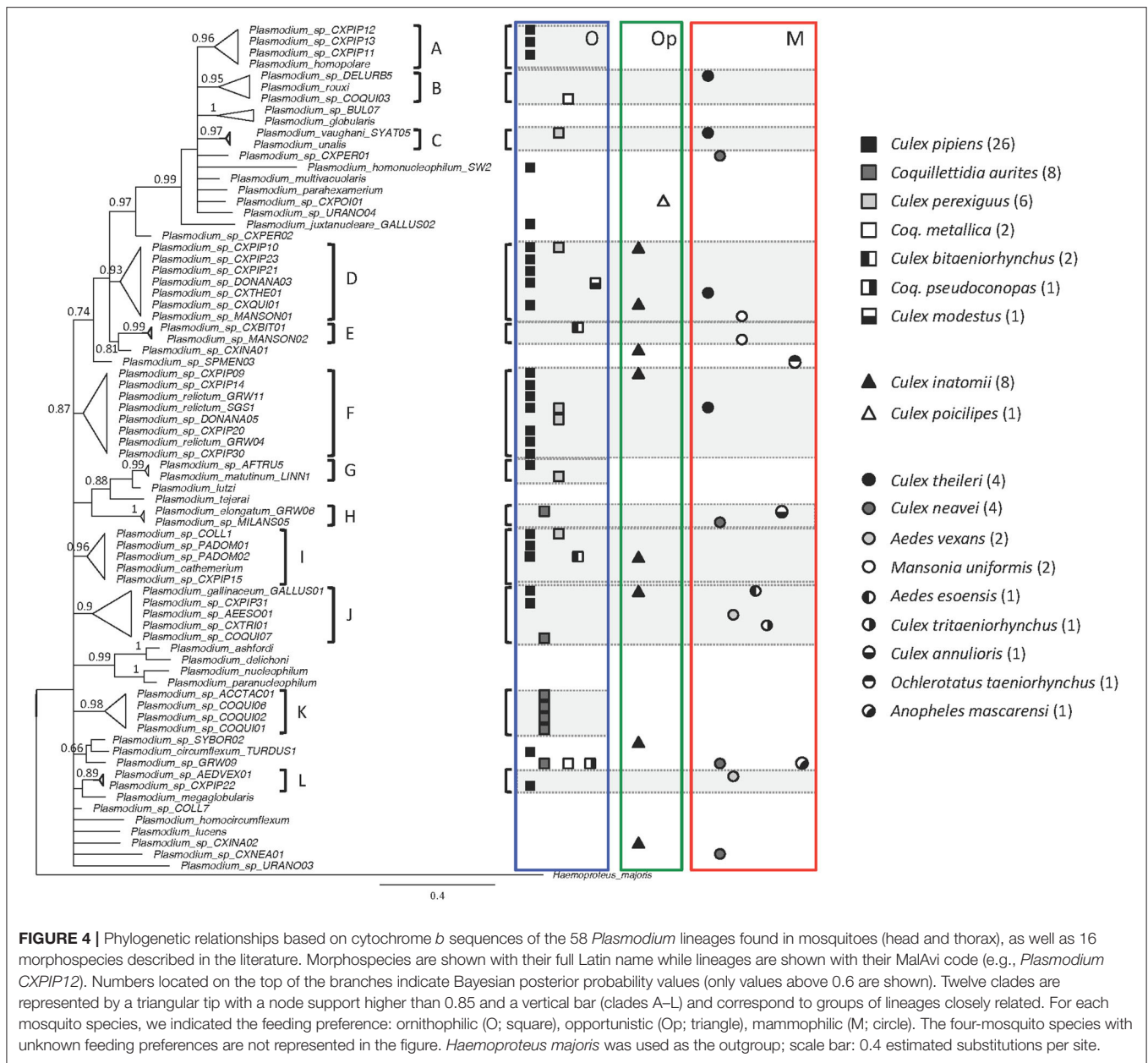


FIGURE 4 | Phylogenetic relationships based on cytochrome *b* sequences of the 58 *Plasmodium* lineages found in mosquitoes (head and thorax), as well as 16 morphospecies described in the literature. Morphospecies are shown with their full Latin name while lineages are shown with their MalAvi code (e.g., *Plasmodium CXPIP12*). Numbers located on the top of the branches indicate Bayesian posterior probability values (only values above 0.6 are shown). Twelve clades are represented by a triangular tip with a node support higher than 0.85 and a vertical bar (clades A–L) and correspond to groups of lineages closely related. For each mosquito species, we indicated the feeding preference: ornithophilic (O; square), opportunistic (Op; triangle), mammophilic (M; circle). The four-mosquito species with unknown feeding preferences are not represented in the figure. *Haemoproteus majoris* was used as the outgroup; scale bar: 0.4 estimated substitutions per site.

was not the case for opportunistic or mammophilic species. However, the feeding preference of each mosquito species (i.e., the percentage of blood meal from birds, ranging from 0 to 100%; **Figure 2**) was not significantly associated with the number of *Plasmodium* lineages that they carried (Pearson coefficient $R = 0.39$; $P = 0.11$; see **Supplementary Figure 4**). We also failed to find statistical associations between the vector specificity index and feeding preference, either at the lineage level ($F_{2,62} = 0.64$; $P = 0.53$) or clade level ($F_{2,22} = 1.83$; $P = 0.18$; see **Supplementary Figure 5**). However, this could be due to insufficient data being available from scarce studies on mosquito-parasite interactions. Most of the lineages are probably transmitted by different mosquito species and therefore the vector specificity of *Plasmodium* lineages calculated here does not

reflect the true parasite specialization. Therefore, it seems difficult to have a clear answer to our question at present since we cannot decipher if host selection is driving or not the vector specificity of avian *Plasmodium*. Nonetheless, some of these limitations can be addressed by doing extensive mosquito surveys and experimental work in the field that could fill the current knowledge gaps.

HOW CAN WE DETERMINE THE VECTOR SPECIFICITY OF AVIAN PLASMODIUM? CHALLENGES AND FUTURE RESEARCH

Experimental studies have provided essential information about the vector competence of different mosquito species for

avian *Plasmodium* (Santiago-Alarcon et al., 2012; Palinauskas et al., 2016; Gutiérrez-López et al., 2020). Nonetheless, it also seems essential to carry out more holistic studies in natural conditions to allow a better understanding of all the potential interactions between avian *Plasmodium*, their vectors and their vertebrate hosts. Today, molecular techniques greatly facilitate the identification of blood meal origin in mosquitoes (Alcaide et al., 2009), as well as the presence of blood parasites in different parts of the mosquito body (Njabo et al., 2011; Gutiérrez-López et al., 2016; Palinauskas et al., 2016). However, the number of studies combining both the feeding behavior of mosquitoes and the transmission of avian *Plasmodium* are still very rare (Ejiri et al., 2011; Ferraguti et al., 2013; Martínez-de la Puente et al., 2016), mainly due to the difficult task of capturing engorged mosquitoes during short field seasons. Other vector-parasite systems suffer from the same fieldwork limitations, and to date, very few studies investigated the vector specificity in closely related haemosporidian parasites (Leucocytozoon: Hellgren et al., 2008; Haemoproteus: Martínez-de la Puente et al., 2011) or other blood parasites (e.g., Trypanosoma: Bennett, 1961; Svobodová et al., 2017). More efforts should be put on regular and constant surveys using various resting boxes to increase resting insects' collections and blood fed females (Panella et al., 2011) even though it is particularly time consuming. One unusual but appealing solution to overcome this field work limitation and to perform more efficient research is to foster multidisciplinary collaborations between research teams and centers for diseases control to (i) mutualize material and human resources, and (ii) answer different questions using the same specimens. More collaborative work would avoid double laborious field surveys while greatly enhancing the results since one mosquito can be used by different researchers and be screened for a great variety of parasites. For example, the feeding behavior of mosquitoes has been extensively studied in North America. However, due to the spread of West Nile Virus [CDC (Centers for Disease Control and Prevention) (2019)], studies mainly focused on arboviruses (Savage et al., 2007; Farajollahi et al., 2011) while to our knowledge very few studies have investigated avian malaria in vectors (Kimura et al., 2010; Carlson et al., 2018). Something similar can be observed in Central Africa for example, where the main entomological studies have been based on anthropophilic mosquitoes and human malaria or other zoonotic diseases of medical importance (Kamgang et al., 2012; Mayi et al., 2020), while the role of mosquito species in the transmission of avian *Plasmodium* is practically unknown (Njabo et al., 2009, 2011). If researchers with different research interests but working in the same region or localities were willing to combine their sampling effort, material and data, it would be beneficial for everyone and likely add value to everybody's data. One obvious advantage would be to determine natural co-infection rates in mosquito species and their consequences on pathogen transmission. Although this idea may seem utopian in the ever more specialized research world, it would be a very interesting prospect to greatly increase mosquitoes sampling size from field surveys while exploring mosquito-avian parasite interactions in more details.

To date, *Cx. pipiens* has been considered as the main vector of avian malaria in temperate regions. This mosquito species has a wide geographical distribution and is certainly the easiest ornithophilic species to catch and raise in laboratory, which makes it a perfect study model for experimental work. Studies have shown so far that 12 morphospecies of avian *Plasmodium* are able to develop sporozoites in *Cx. pipiens* (Santiago-Alarcon et al., 2012; Palinauskas et al., 2016; Gutiérrez-López et al., 2020). However, other less abundant species that share habitats with *Cx. pipiens*, such as *Cx. perexiguus*, *Cx. restuans*, or *Cx. inatomii*, among others, may play an important secondary role as vectors of avian malaria parasites. Further research work should therefore focus on less studied mosquitoes that present different feeding behaviors or restricted geographical distribution compared to *Cx. pipiens*, although some other potential vectors may be difficult to raise and study. For example, opportunistic mosquitoes might feed on a smaller number of bird species, and thus, come into contact with a smaller number of avian *Plasmodium* parasites, leading to different co-evolutionary processes between mosquito and avian *Plasmodium*. In addition, according to the MalAvi database, studies that have identified *Plasmodium* lineages in insects have been carried out in 20 countries only, mostly in Europe. Thus, future research projects could be conducted in geographical areas that are poorly studied up until now, such as tropical regions and migratory bird wintering areas in Africa, that may present very distinct host selection patterns and vector specificity due to the highly diverse communities of hosts and vectors. Undoubtedly, the development of field surveys and experimental studies on vector competence of poorly sampled or little-known mosquito species is essential to better understand the vector specificity and transmission dynamics of avian *Plasmodium*.

Lastly, detection of avian *Plasmodium* DNA in mosquito's head and thorax, where the salivary glands are located, provides valuable information on interactions between parasites and potential vectors. However, this does not fully guarantee the vector competence for avian malaria since DNA amplification could come from abortive stages of the parasite (Valkiunas, 2011; Valkiunas et al., 2013). To determine the transmission capacity of avian *Plasmodium* by the mosquito, visualization of sporozoites in the salivary glands or the extraction of saliva from the mosquito are more reliable methods (Valkiunas, 2005; Gutiérrez-López et al., 2016; Palinauskas et al., 2016). In order to dissect the salivary glands or obtain a saliva sample, the mosquito must be fresh or alive, and must not have been previously frozen. However, mosquito dissection is not always compatible with field conditions and the number of engorged mosquitoes that fed on infected birds that show parasites in their salivary glands or saliva is usually very low (between 1 and 5%; Alves, 2012; Gutiérrez-López et al., 2020). In addition to fieldwork, experimental studies in laboratory conditions seem therefore essential to evaluate the competent mosquito species for avian *Plasmodium* lineages, even if it requires complex logistics to (i) test several lineages at the same time, and (ii) keep mosquitoes in colonies and birds in captivity. Among many lines of research that could improve our understanding of vector specificity, future projects should focus on (i) questioning the parasite

transmission capacity of mammophilic mosquitoes since, so far, *Plasmodium* lineages have been found in head/thorax only and not in salivary glands, (ii) testing the vector competence of mosquitoes that share the same habitat as *Cx. pipiens* but are present in lower abundance, (iii) determining if the infection status of the mosquitoes influences their host selection, using a wide range of mammals and bird species, or, (iv) evaluating if lineages with different host specialization strategies (specialists vs. generalists) are transmitted equally by mosquitoes.

CONCLUSION

Research projects based on a global approach to host-parasite relationships that integrates the pivotal role of vectors in avian malaria transmission are still very rare, but essential to understand the evolutionary strategies of parasites. Although molecular ecology tools helped make great strides, there is still a long way to go to understand parasite-vector-host relationships, especially given the high diversity of known parasites and potential vectors. To date, data from the literature suggest that avian *Plasmodium* lineages present a gradient of host specificity from highly specialist to highly generalist, and relatively high vector specificity (i.e., each lineage uses only a few vectors). However, true vector specificity of avian *Plasmodium* needs to be clarified by obtaining larger datasets about vector-parasite interactions in the field and by demonstrating vector competence. Among factors that could influence interactions between vectors and their hosts and parasites, the feeding behavior of mosquitoes may be a key factor that influences vector specialization, although this remains to be proven. Multidisciplinary teams, including ecologists, ornithologists, parasitologists and entomologists, should work hand in hand to understand fully the range of parasite evolutionary strategies in both hosts and vectors.

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DATA AVAILABILITY STATEMENT

The raw data of this article will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

RG-L and CL conceived the idea for this study, extracted the data from MalAvi, and wrote the first draft. CL carried out the statistical analyses. VB commented on the setup and assisted during the writing of the paper and revisions. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fevo.2020.569230/full#supplementary-material>

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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.

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