Chapter 9

New Approaches for an Old Disease: Studies on Avian Malaria Parasites for the Twenty-First Century Challenges

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Abstract

Emerging infectious diseases (EIDs) impose a burden on economies and public health. Because EIDs on wildlife are mainly affected by environmental and ecological factors, the study of EIDs in wildlife provides valuable insights to improve our understanding on their causes and their impact on global health. Malaria is an EID that has increased its prevalence in the last few decades at an alarming rate. Avian malaria parasites are abundant, widespread and diverse, which turn these parasites into an excellent model for the study of EIDs. In the face of new health and environmental challenges in the twenty- irst century, studies on avian malaria will provide new approaches for this old disease. The identfiication of essential genes for the malaria invasion, the study of modification of host behaviour by malaria parasites in order to promote the parasite transmission, and the knowledge of factors contributing to the emergence of infectious diseases in wildlife are essential for understanding parasite epidemiology, local patterns of virulence and evolution of host resistance. In this chapter, we will review the results of some recent investigations on these topics that will be useful for predicting and preventing EIDs in wildlife, livestock and humans.

Keywords: avian malaria, emerging infectious diseases, *Haemoproteus*, haemosporidians, *Plasmodium*

1. Introduction

Malaria is one of the world's deadliest diseases, with 214 million cases and an estimated 1 million malaria deaths every year. Although the first human recording of malaria was in China in 2700 B.C., most probably this disease is older than humans. Fossil evidence shows that modern malaria was transmitted by mosquitoes at least 20 million years ago, and the recent analysis of the pre-historic origin of malaria has suggested that earlier forms of the disease, carried by biting midges, are at least 100 million years old and probably much older [1]. Hence, malaria not only infects humans. In fact, systematic parasitologists have erected more than 500 described species belonging to 15 genera within the order Haemosporidia (phylum Apicomplexa) that infect reptiles, birds and mammals, and use at least seven families of dipteran vectors for transmission [2, 3]. These parasites are widely distributed in every terrestrial habitat on all the warm continents. Within these parasites, avian malaria is the largest group of haemosporidians by the number of species. They are widespread, abundant and diverse, and are easily sampled without disrupting the host populations. Although the term 'malaria parasites' has been a controversial issue among parasitologists, ecologists and evolutionary researchers [4, 5], authors usually include genera *Plasmodium*, *Haemoproteu*s and *Leuocytozoon* among the malaria parasites [4].

Investigations on avian malaria have contributed significantly to the knowledge on biology and ecology of malaria parasites of other vertebrates, including human malaria [6]. Since the discovery of the mosquito transmission of malaria in birds by Sir Ronald Ross, studies on malaria parasites of birds have saved millions of human lives. For example, essential advances in medical parasitology such as the development of anti-malarial compounds (e.g. plasmochin, primaquine and atebrin), the study of the life cycle and cultivation in vitro were initially developed using bird haemosporidian models.

Also, during the 2000s, research on bird malaria was at the very peak because scientists recognised the benefits of using studies on avian malaria to answer ecological, behavioural and evolutionary questions. Nowadays, far to be outdated, investigations on avian malaria will be essential to face new health and environmental challenges in the twenty-first century. In this chapter, we will review the newest contributions on bird studies helping in the fight against malaria.

2. Emerging infectious diseases and wildlife studies

In the last century, advances in vaccines and antibiotics, as well as other improvements in food intake and sanitation, contributed to the fast development in demography and economic growth in many parts of the world [7]. These advances brought the erroneous idea of a possible world without the burden of pathogens, followed by a flawed policy of reducing investment in the research of infectious diseases [8]. Pathogenic microorganisms rapidly evolve using multiple genetic evolutionary mechanisms, thus steadily adapting to new environments and escaping host's defences. As a consequence, more than 300 events of emerging and re-emerging

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infectious diseases (EIDs) have killed millions of people since the 1940s and represent one of the major threats to human, livestock and wildlife in the twenty-first century [9]. These diseases are caused by pathogens from animals that now infect humans (HIV-1), or pathogens that have been probably presented in humans for centuries, but continue to appear in new locations (Lyme disease) or have evolved resistance to drugs (malaria resistance to chloroquine, mefloquine and artemisinin), or that reappear after apparent control or elimination (tuberculosis). Ironically, the health improvements and economic developments of the last century also contributed to the increase of these pathogenic diseases, as 'hidden costs' of this wellness. The economic and demographic growth led to millions of people live in crowded urban areas, thereby facilitating the spread of infections [10]. Also, the deforestation for logging and farming in tropical rainforests to meet the demands of growing population have provoked changes in the ecology and epidemiology of vector-borne diseases (e.g. malaria, leishmania and Chagas disease), thus favouring the spread of the disease [11].

Studies on wildlife may provide essential information in the fight against EIDs for several reasons. On the one hand, wildlife is an essential component in the epidemiology of many EIDs. In this sense, more than 60% of these diseases in humans are caused by pathogens spread from animals, and 71.8% of these zoonotic diseases events are provoked by pathogens with a wildlife origin [9]. On the other hand, socio-cultural and economic drivers (e.g. population density, economic growth), as well as ecological and environmental conditions (wildlife species richness, rainfall), may be major determinants of surge and spread of diseases in humans. In opposition to human studies on EIDs, wildlife studies are free of socio-economics and cultural confounding variables, thus providing reliable conclusions on the ecological drivers of the epidemiology.

2.1. Avian malaria and deforestation

Infections with vector-borne pathogens have become one of the main EIDs in the last years. Arthropods such as mosquitoes, ticks and bugs are responsible for transmission of viruses (dengue, chikungunya, Zika), bacteria (Lyme disease) and protozoans (malaria, Chagas). Anthropogenic deforestation and land use change have been proposed to cause the spread of vectors and the re-emergence of malaria in South America [12]. In this sense, it has been shown that the biting rate of *Anopheles darlingi* (primary human malaria vector in the Amazon) in deforested rainforest sites was more than 278 times higher than the rate determined for areas that were predominantly forested [13]. Also, it has been reported that deforestation can increase human malaria prevalence up to 50% [14]. However, as mentioned previously, the drivers favouring malaria outbreaks go beyond the basic biological elements and include ecological as well as socio-economic factors [15]. Because these puzzling effects are irrelevant in the context of wildlife malaria parasites, further studies (e.g. avian malaria studies) removing potential confounding variables are required to confirm whether anthropogenic land-use change is a key driver of disease emergence.

In recent years, several studies have analysed the effects of habitat fragmentation and deforestation on the prevalence of bird haemosporidian parasites in different continents. Bonneaud et al. [16] examined the prevalence of infection of bird malaria in both pristine and

disturbed forests from Cameroon, showing a higher prevalence of *Plasmodium* lineages in pristine as compared with disturbed forest sites. Also, Chasar et al. [17] analysed the diversity, prevalence and distribution of avian haemosporidian parasites (*Plasmodium*, *Haemoproteus* and *Leucocytozoon*) from nine-paired sites (disturbed vs. undisturbed habitats) in Southern Cameroon in two widespread species of African rainforest birds. They found that the prevalence of *Haemoproteus* and *Leucocytozoon* infections was significantly higher in undisturbed than in deforested habitats. They also showed that the prevalence of *Plasmodium megaglobularis* was higher in undisturbed areas, whereas the prevalence of infection of *P. lucens* was higher in deforested areas. Furthermore, Loiseau et al. [18] reported the variation of parasitaemia intensity and co-infections of avian haemosporidian parasites in two common African bird species at three sites with distinct habitat characteristics in Ghana. They detected a variation in infection prevalence and intensity of parasitaemia that differ in environmental factors; thus suggesting that spatial heterogeneity can impact the prevalence, frequency of co-infections, and chronic parasitaemia intensity of haemosporidian parasites.

In Hawaiian Islands, malaria is thought to be responsible of the population decline and even extinctions of many native bird species [19]. In addition, deforestation could also have contributed to the population decimation by altering the patterns of malaria transmission [20, 21]. In this sense, it has been suggested that deforestation of the Alaka'i Wilderness Preserve on Kaua'i Island could have changed the pattern of seasonal transmission of avian malaria to a pattern of continuous transmission through all the year [20], which could enormously increase the prevalence and pathogenic effects of avian malaria.

Moreover, Laurance et al. [22] investigated the effects of habitat fragmentation and ecological parameters on the prevalence of malaria parasites (genera *Plasmodium* and *Haemoproteus*) in bird communities of Australia. They analysed the prevalence and genetic diversity of haemosporidians across six study sites including large sites and continuous-forest sites, finding that the prevalence of the dominant haemosporidian infection (*Haemoproteus*) was significantly higher in continuous forest than in habitat fragments.

In Brazil, Belo et al. [23] examined the presence and genetic diversity of haemosporidian parasites in 676 wild birds from three different environmental regions (intact cerrado, disturbed cerrado and transition area Amazonian rainforest-cerrado) with the aim to determine whether different habitats are associated with differences in the prevalence and diversity of malaria infection. Surprisingly, they found that neither the prevalence nor the diversity of infection of *Plasmodium* spp. or *Haemoproteus* spp. differed significantly among the three habitats studied. More recently, Ricopa and Villa-Galarce [24] have studied the prevalence and genetic characterisation of avian malaria lineages in one disturbed and one preserved area of National Reserve Allpahuayo-Mishana in Peruvian Amazon. They found a higher prevalence and a higher diversity of malaria infection in birds from the deforested area when compared to birds from pristine forest.

2.2. Avian malaria parasites as emerging infectious diseases: the role in biological invasions

Alien, also called non-indigenous, exotic or non-native species, are defined as those species that colonise an area beyond their natural range, where they reproduce and establish a

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population. In addition to urbanisation, demographic growth and land-use change, the introduction of domestic and wildlife alien species can also provoke emerging diseases with tremendous costs in terms of loss of biodiversity, mortality and economic expenses [25]. In this sense, several studies have shown zoonosis linked to birds spreading diseases to humans. For example, it is thought that the West Nile virus, a bird pathogen but also causing mortality to humans, was introduced to New York by migratory or invasive bird species [26]. Also, the bird flu virus (H5N1), which has been registered, was transported by invasive bird species [27]. But despite these negative impacts of invasive species and the efforts from scientists to understand biological invasions, the mechanisms that allow one species to become invasive are still poorly understood.

Since the eighteenth century, more than 1400 human attempts to introduce 400 bird species have been recorded worldwide [28]. But not all of these introduced birds have resulted in established populations of invasive birds in the new regions. In fact, only 10% of introduced species are able to colonise new environments and become successful invaders [29]. In consequence, some life history traits and ecological attributes could allow some alien species to maintain high survival and reproductive success in new locations and to become successful invaders [28]. It has been proposed that parasites may play this role facilitating the successful colonisation of their bird hosts [30]. Hence, parasitic infections (or sometimes, their absence) may facilitate or limit invasions impacting native species via both direct and indirect effects. Three hypotheses (novel weapon hypothesis, enemy release hypothesis and biotic resistance hypothesis) have been proposed to explain the role of parasites in invasions in bird- parasite systems (**Table 1**). On the one hand, exotic bird species can act as a 'Trojan horse' because they can bring alien parasites and pathogens inside them, which could favour the dissemination in the new areas of their avian host species. In the history, pathogens have played a role bringing diseases in humans that become epidemic in susceptible native populations [39]. As example, in European conquest in the Americas smallpox spread rapidly killing an estimated 95% of the indigenous population far in advance of the European themselves [39]. Following this idea, the novel weapon hypotheses (NWH) states that invasive species gain advantages over native species by bringing their own parasites to the new environments against which the introduced species but not the natives have evolved defences [40, 41]. These co-introduced parasites may switch to native bird hosts and spread in the new communities, hence becoming themselves invasive parasites provoking serious damages to indigenous bird species. But the role of parasites in invasions may extend well beyond such direct effects, and hence some indirect effects may also be expected. In this sense, the enemy release hypothesis (ERH) states that non-native bird species could become invaders because they have lost their co-evolved malaria parasites during the process of colonisation, and thus they may increase their competitive ability and displace native species in the new areas. Conversely, the biotic resistance hypothesis states that native parasites in the indigenous species may reduce the fitness of the potential bird invader and prevent its spread and establishment. Next, we will focus on the role of avian malaria parasites co-introduced with their bird hosts.

Avian malaria parasites are among the most pathogenic species of poultry and wildlife birds, being responsible for economic losses, mass mortality, population declines and even extinc-

tions of many bird species worldwide after its introduction outside its native range [42]. For all these reasons, the International Union for Conservation of Nature (IUCN) classifies avian malaria to be among the 100 of the world's worst invasive alien species [43]. The spread of exotic avian malaria in Hawaiian Islands is the best documented example of the effects of invasive malaria on native bird communities. Since the discovery of Hawaiian Archipelago by the Captain Cook in 1774, more than a half of over 100 endemic bird taxa in Hawaii have been driven to extinction by a combination of habitat loss, introduced species and diseases [19, 44]. In 1826, the primary vector for avian malaria *Culex quinquesfasciatus* was accidentally introduced in Hawaii from shipping vessel HMS Wellington [19, 45]. The colonisation of this mosquito species, as well as the introduction of non-native bird species co-transporting avian malaria *Plasmodium relictum*, then provoked a wave of extinctions and endangerment among Hawaiian forest birds since the 1920s [21].

Novel weapon hypothesis (NWH)	**Reference**	**Observations**
Hawaii	van Ripper et al. [21]	
Hawaii	Atkinson et al. (2005) [46]	
Hawaii	Lapointe (2005) [47]	
Hawaii	Atkinson and Samuel (2010) [48]	
New Zealand	Doré (1920) [49]	
New Zealand	Tompkins and Gleeson [31]	
New Zealand	Barraclough et al. [32]	
New Zealand	Howe et al. [33]	
New Zealand	Ewen et al. (2012) [50]	
New Zealand	Schoener et al. (2014) [51]	
Galapagos Islands	Levin et al. [34]	
Galapagos Islands	Santiago-Alarcón et al. [35]	
Galapagos Islands	Levin et al. [36]	
Perú	Marzal et al. (2015) [52]	
Enemy release hypothesis (ERH)		
Southern Asia	Beadell et al. (2006) [53]	Mixed results with NWH
Seychelles Islands	Hutchings (2009) [54]	
Brazil	Lima et al. (2010) [55]	
6 continents (58 locations)	Marzal et al. [37]	
Biotic resistance hypothesis		
Lesser Antilles	Ricklefs et al. (2010) [56]	

*s*García-Longoria et al. [38].

Table 1. Main studies on the role of avian malaria parasites in the global spread of their bird hosts.

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Similar to Hawaii, recent investigations have detected avian malaria *Plasmodium* spp. in New Zealand birds, thus suggesting that avian malaria could be an emerging threat to New Zealand avifauna [32, 33]. For example, an outbreak of malaria has killed more than 90% of the population of the endemic Yellowheads (*Mohoua ochrocephala*) [46]. Also, Howe et al. [33] have reported the death of native and exotic bird species due to acute *Plasmodium* spp. infection. In addition, Baillie et al. [46] have documented three exotic *Plasmodium* species infecting the endemic New Zealand passerine Bellbird *Anthornis melanura*. Finally, it is known that four alien species of mosquitoes have been established and rapidly spread in New Zealand [31, 47] and are likely to be the vectors responsible for some avian malaria outbreaks in the New Zealand [48].

Malaria parasites were historically considered to be absent in Galápagos Islands, because studies based on microscopic and molecular screening of parasites failed to detect malaria parasites in Galápagos birds [49, 50], most probably due to the absence of competent vectors. However, in the last decade, several studies have showed malaria-infected birds in several islands in the archipelago, thus suggesting recent arrival of avian malaria parasites. In this sense, the only known competent vector for *Plasmodium* parasites present in the archipelago is the mosquito *Culex quinquesfasciatus*, which was described for the first time in Galápagos in 1989 and it was well established by 2003 [51]. Following the mosquito introduction, the first report of malaria-infected birds in the Galápagos Archipelago come from Levin et al. [34], identifying penguins as positives for *Plasmodium*. Later, Santiago-Alarcon et al. [35] showed haemosporidian parasites infecting the endemic Galápagos dove (*Zenaida galapagoensis*). More recently, Levin et al. [35] have found different genetic lineages of *Plasmodium* parasites infecting Galápagos birds. Some of these lineages seem to be transient infections of parasites not established on the archipelago, whereas other parasite lineages are thought to be established and regularly transmitted in the archipelago.

P. relictum is an avian malaria parasite with highly virulence, genetic diversity and markedly invasive nature [19, 45, 52]. Recent molecular studies on partial sequences of the cytochrome oxidase b gene on this parasite have revealed different genetic diversity of this parasite, with two main parasite lineages: *P. relictum* GRW4 and *P. relictum* SGS1. *P. relictum* GRW4 is the parasite lineage responsible for devastating epizooties reported in Hawaii and New Zealand, and has a broad geographical range including Africa, Asia and the Americas [37, 45]. Its sister lineage, *P. relictum* SGS1 is widespread and actively transmitted in Europe, Africa and Asia [37], but until very recently, this invasive lineage had not been reported in the mainland Americas [37, 45, 53–55].

Marzal et al. [56] have recently showed the first report of this invasive pathogen in the mainland Americas. They analysed more than 100 blood samples from native bird species from South America, showing the presence of *P. relictum* SGS1 in neotropical birds from two different areas of Peru. In this study, *P. relictum* SGS1 was also geographically spread, and the most generalist and prevalent parasite lineage found in the study, infecting 13 individuals from eight host species (39.40% of the total infections). We must be particularly aware on the presence of this invasive parasite in birds of South America because it may represent a serious risk to this avifauna and a potential threat to over one-third of all bird species in the world.

Would it be possible to eliminate emerging infectious diseases? We do not think so. Indeed, it seems unlikely that most emerging infectious diseases will be eradicated in a close future [57]. In the fight against emerging infectious diseases, we have to follow the advice of the Red Queen to Lewis Carroll's Alice in Wonderland: '…it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!' Therefore, this is a continuous process, where we have to keep on researching to avoid being out of step in the fight against malaria and other emerging infectious diseases. Studies on avian malaria research may play an essential role in these investigations to determine the key factors (e.g. deforestation and land-use change, biological invasions) contributing to the emergence of these diseases.

3. Identification of malaria genes

Approximately, 40% of the world population lives in areas where malaria is transmitted. In some areas, as sub-Saharan Africa, malaria may cause a rate of mortality in 5-year-old children around 90% [58]. An important tool in the fight against malaria parasites is the identification and sequencing of malaria genes that could give essential information about this harmful disease. Hence, in 1996, an international effort was launched to sequence the *Plasmodium falciparum* genome with the aim to open new paths for researching and for the development of new treatments and vaccines against malaria parasites. Some years later, the results were published showing that there was possible to sequence all the chromosomes of *P. falciparum* clone 3D7 [59–61]. The results showed that these chromosomes encode for 5300 genes and are the most (A + T)-rich genome sequence to date.

Moreover, these chromosomes possess a high number of genes related to immune evasion and host-parasite interactions and fewer enzymes and transporters. In the short term, however, it has been suggested that the genome sequence alone provides little information about malaria parasites. As Gardner et al. [59] claim 'much remains to be done'. These results might need to be accompanied by new methods of control, including new drugs and vaccines, improved diagnostics and effective vector control techniques. In this section, we will deal with some malaria genes that are essential for identification of malaria transmission areas and to develop strategies to avoid spread of the disease.

Also, we will show some recent studies on the identification of malaria genes that are crucial in the parasite life cycle, and could be used as a target for future vaccines or anti-malaria drugs.

3.1. Identification of merozoite surface protein gene 1 (MSP1) and malaria transmission areas

Malaria parasites have an important effect in populations where it is present affecting the survival of the community and la*y*ing out with facility [5]. Therefore, there is a general need to define populations at risk for appropriate resource allocation and to provide a robust framework for evaluation its global economic impact. The interest of mapping the global distribution of malaria parasite has increased in the last decade. Some authors have decided

http://dx.doi.org/10.5772/65347

to identify some essential genes with an enormous variability in order to distinguish different location of the malaria parasites [62]. A commonly used good candidate gene is merozoite surface protein 1 (msp1). This gene is one of the most variable genes found in the human malaria parasite *P. falciparum* [63]. It encodes a protein involved in the attachment of the malaria parasite to the host red blood cell [64]. Within *P. falciparum*, the msp1 gene encodes for a 190 kDa protein that is separated in four different polypeptides (p83, p42, p38 and p30). During the erythrocyte invasion, the polypeptide p42 is split in two more polypeptides (p19 and p33). However, at the end of the process the only polypeptide that remains into the erythrocyte is p19 [65]. This gene has been analysed in a wide number of studies with the aim to determine whether it is a good candidate for developing vaccines or anti-malaria drugs. In this sense, [66] showed that antibodies to the p19 peptide are found in populations with high malaria prevalence and can be associated with immunity to the malaria parasite.

In 2013, Hellgren et al. [67] identified this gene in *P. relictum* SGS1, GRW11 and GRW4 lineages. They found that, within msp1 gene, there are nine different alleles split into the three

P. relictum lineages: SGS1 (alleles Pr1, Pr2, Pr3 and Pr7), GRW4 (alleles Pr4, Pr5, Pr6, Pr8 and Pr9) and GRW11 (alleles Pr2, Pr3 and Pr7). Theses alleles have a specific distribution around the world affecting areas as South America, Europe, Asia or Africa [68]. Moreover, they suggested that due to its high variability, this gene could be used as a candidate to investigate how different host species cope with the infection. In this sense, Hellgren et al. [68] confirmed some transmission events by the lineages analysing resident bird species or juvenile individuals before migration. Therefore, some alleles are restricted to a specific area. For instance, the allele Pr1 is, to date, only present in sub-Sahara areas, while the Pr2 allele has been mainly detected in European areas. This strict allocation may suggest the existence of transmission barriers (e.g. vector communities or abiotic factors) limiting transmission between regions.

By barcoding the msp1 gene in SGS1 and GRW4, a recent study has determined whether haemosporidian transmission in house martins occurs at European sites by sampling juvenile birds house martins (a migratory species with a high fidelity to its area of hatching and nesting) [30].

Moreover, they analysed the msp1 alleles in both adult and juvenile house martins in order to identify their potential areas of transmission. Surprisingly, their results showed that some juvenile and adult house martins were infected by Pr2 allele of *P. relictum* SGS1, an allele thought to be exclusively transmitted in Europe. These results showed, for the first time, that juvenile house martins may become infected with *Plasmodium* parasites already before their first migration to Africa, thus confirming that active transmission of *Plasmodium* spp. to house martins also occur in Europe. These findings emphasise not only the importance of using multiple independent loci of avian *Plasmodium* parasites to understand transmission areas of blood parasites but also the use of birds as study model in parasite analyses.

3.2. New target to avoid completion of malaria life cycle: the chitinase gene (CHT1)

Malaria parasites (including human malaria) show a complex life cycle that requires mechanisms adapted to enable the parasite invasion into the different tissues from the vertebrate host

to the arthropod vector. Apparently, arthropods develop a protective peritrophic membrane (PM) against pathogens around their midgut after each blood meal. This PM blocks the penetration of blood parasites and avoids the spreading of the parasite to other organs. In turn, malaria parasites have developed a mechanism to overcome the PM barrier. Once the malaria parasite has complete its sexual stage in the mosquito stomach, the ookinete has the ability to cross the PM by secreting a chitinase that has catalytic and substrate-binding sites breaking down this layer. After crossing the PM, ookinetes finally transform into oocytes, which after maturing releases the sporozoites that move to the salivary glands where they are ready for infecting a new host [69]. Therefore, the role of the chitinase gene is essential in the life cycle of malaria parasites.

The chitinase gene has been study for years due to the variability of structures that it shows. In mammals, some *Plasmodium* parasites may present two different structures. For example, in human malaria (*Plasmodium vivax*), shared human and primate malaria (*Plasmodium knowlesi*) and in rodent malaria (*Plasmodium berghei*, *Plasmodium yoelii* and *Plasmodium chabaudi*) the chitinase gene presents a long structure and has a catalytic domain and a chitin-binding domain. However, the chitinase gene in human *P. falciparum* and in primate *Plasmodium reichenowi* presents a short structure and lacks the chitin-binding domain [70]. Concerning birds, it has been shown that *Plasmodium gallinaceum* has functional copies of both the long (PgCHT1) and the short (PgCHT2) chitinase gene suggesting that *P. gallinaceum* could be a common ancestor of the mammalian *Plasmodium* parasites that subsequently lost either the short or the long copy of this gene. However, the phylogenetic relationship among *Plasmodium* parasites infecting mammals and birds has been intensively debated over the past decades. On the one hand, some authors suggest that *P. falciparum* is closer phylogenetically to bird parasites than other mammalian malaria parasites [71]. On the other hand, several authors claim that mammalian parasites form a monophyletic clade [72]. Additionally, it has been suggested that *P. gallinaceum* is not the most prevalence parasite in birds and new studies would be needed in order to clarify this relationship. In this sense, Garcia-Longoria et al. [73] identified the chitinase gene in one of the most harmfulness and widespread avian malaria parasites, *P. relictum*. They demonstrated that *P. relictum* presents both copies encoding for chitinase (PrCHT1 and PrCHT2), thus supporting the hypothesis that avian malaria parasites could be the ancestor for the chitinase gene in malaria parasites of primates and rodents. Therefore, given the current phylogenetic hypothesis, it could be assumed that mammalian parasites evolved from an avian parasite that carried two copies of the chitinase gene. These findings are quite remarkable if we take into account that the evolutionary pathway of the malaria parasites is being decoded day-by-day, and the ancestors of human malaria parasites may give essential gene information that could be used for development of new anti-malaria treatment.

4. Malaria parasites and escape behaviour

Behavioural traits are an important factor in the life cycle of all live organisms. Behaviour may determine whether an individual ends up as a survivor or as a prey [74] or it can even acts as a defence against some parasites. For example, some organisms modified their behaviour by

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plastically changing their life history in order to evade parasite or to minimise the impact of infection [75]. A good example of behaviour as a defence mechanism to avoid is displayed in *Drosophila melanogaster*. Since small larvae are better protected from parasites, this fly can reduce the size of their larvae in habitats with high concentration of pathogens [76]. Ants also can modify their behaviour as a defence against parasites, as they reallocate their nests more often in areas where parasites are common [77]. All these examples suggest that behaviour is an essential key in the survival of individuals.

Anti-predator behaviour is a specific kind of behaviour that is consistent in the presence of a predator across time and contexts [78] and imposes an important selection pressure on preys [79]. Thus, when a predator stalks a prey, the first mean of avoidance of predation is escaping from the predator. However, when the prey is already captured by the predator, the behaviour displayed by the prey can be much more specific: the escape behaviour. Among others, escape behaviour includes several behavioural traits such as (i) the intensity with which a captured individual wriggles to escape, (ii) biting or attacking the predator,(iii) whether it loses feathers, limbs, or a tail and thereby manages to escape, (iv) fear screaming and (v) akin behaviour to feigning death [80]. These variables are closely related to the probabilities that one individual has to escape; thus, the more intense this escape behaviour in one individual is, the more probabilities would have this individual to escape from the predator. For example, a prey individual may emit a loud fear scream that can either warn co-specifics or to attract secondary predators, thus facilitating the escape [81]. Additionally, in 2011, Møller et al. [82] showed that birds with high levels of predation wriggled more when captured by a human, hence increasing their probabilities to escape from the predator, showing that intense escape behaviour is related with high levels of predation.

In addition to predation, parasite represents another major cause of mortality in birds. Some studies demonstrated that the presence of parasites and predators may provoke stress to animals and reduce the immune function in one individual suggesting a relationship between malaria parasites and predation [83]. Later, Møller and Nielsen [81] showed that individuals infected with blood parasites showed lower intense of escape behaviour. Both studies reveal an underlying mechanism that links predation to prevalence of blood parasites. Recently, this underlying mechanism has been analysing. In this sense, Garcia-Longoria et al. [84] tested whether species with higher prevalence of *Haemoproteu*s, *Plasmodium* or *Leucocytozoon* infection differed in escape behaviour from species with lower prevalence. They found that some escape behaviours are positively related with the prevalence of these blood parasites, where bird species with an intense escape behaviour showed higher parasitaemia of blood parasites. The observed correlation between blood parasite infections and escape behaviour may suggest a correlation between host behaviour and parasite infection, where individuals showing brave behaviours (e.g. exploratory behaviours or escape behaviours) could increase their likelihood of become infected by increasing the chances of co-specific encounters, injuries or vector bites. Alternatively, this correlation may also show a possible manipulation by the parasite of the behaviour of its host to enhance its chances of transmission.

Regarding to this latter hypothesis, the behavioural manipulation hypothesis posits that manipulation of host behaviour by parasites may confer fitness benefits to the parasite, usually

increasing transmission success to the parasite [85]. There are some studies supporting this hypothesis. One of the most well-known examples is the manipulation displayed by *Toxoplasma gondii*, a blood parasite that may infect rodent and other mammals. A mice infected with *T. gondii* lose its fear against feline predators (the definitive host of *T. gondii*), thus increasing the likelihoods of transmission of the parasite to its final host [86]. Concerning malaria parasites, little is known about whether malaria parasites can manipulate the behaviour of their avian host. Malaria parasites show a complex life cycle with both vertebrate (e.g. birds, reptiles and mammals) and invertebrate host (e.g. mosquitoes). In 2013, Cornet et al. [87] demonstrated that infected birds attract more vectors than uninfected ones suggesting that malaria parasites may modify the behaviour of their vector in order to increase their own transmission. However, whether malaria parasites may manipulate escape behaviour of their vertebrate host has been poorly analysed. To date, only one study has explored the association between avian malaria parasites and behaviour in the vertebrate host [88]. Garcia-Longoria et al. [88] experimentally tested whether malaria parasites could manipulate the escape behaviour of their bird hosts. They experimentally infected house sparrows with *P. relictum* and measured the escape behaviour of sparrows before and after the malaria infection. They showed that experimentally infected individuals increased the intensity of their escape behaviour after the parasite inoculation, hence demonstrating that *P. relictum* may modify the escape behaviour of their avian hosts. These results agree with the behavioural manipulation hypothesis, because the facility to escape from predators would indirectly increase the transmission of the parasite, as well as enhance the survival of the hosts. One remaining question concerns the identification of the mechanisms that malaria parasites may use to boost the escape behaviour of their avian hosts. In this sense, some parasites are known to modify the behaviour of their host by secreting substances capable of altering the neuronal activity of the host. For example, the trematode *Schistosoma mansoni* secretes opioid peptides that change the function in the brain of its hosts by producing cystic fibrosis causing the necrosis of some brain areas. Other parasites, like helminths, can alter the concentration of serotonin or dopamine in the host, thus altering some neurological mechanism in their host. Hence, the mechanisms that *P. relictum* might use in order to modify the escape behaviour of its avian host it remains unknown. Future studies on avian malaria research should go deeper with the aim to identifying the mechanisms underlying the behaviour alterations of their bird hosts after malaria infection.

5. Conclusions

Malaria parasites and other emerging infectious diseases are one of the major challenges for global health in the twenty-first century. Despite the efforts made by scientist and health care providers, malaria parasites are becoming drug-resistant, as well as they are boosting their mortality rate in some regions and increasing their areas of transmission. These risings can be provoked by some anthropogenic alterations as deforestation or biological invasions, thus provoking changes in the ecology and epidemiology of vector-borne diseases and outbreaks in human, livestock and wildlife emerging infectious diseases. Moreover, in human malaria studies, it is very difficult to assess if the changes in parasite prevalence are due to socio-

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ecological factors or to the effects of environmental alterations. These facts emphasise the importance of the study of malaria parasites in wild animals, free from social and economic factors, to fight against this pathogen. Here, we have also focused our attention in the identification of new avian malaria genes that could help in the detection of malaria transmission areas around the world. In addition, the identification of malaria genes with high genetic variability will supply essential information in the evolution of both human and avian malaria pathogens and would provide scientists with new tools for the development of anti-malaria drugs. Our current knowledge about malaria and EIDs is still limited. Further investigation and exploration are needed in order to gain a better understanding of the malaria distribution and the global economic and health impact of malaria. Moreover, it is important to increase awareness of the consequences of introducing non-native species in different habitats and to increase the control in biosecurity borders for avoiding the introduction of alien pathogens such as malaria parasites. Finally, we should be fully aware that there is no ending in the fight against EIDs, where 'it will take all the running (*researching*) you can do, to keep in the same place'.

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