

***Plasmodium* spp. (avian species)**

(protist: apicomplexan)

Overview

Protists are single-celled organisms with membrane-bound nuclei (eukaryotes). One protistan supergroup known as SAR comprises the Stramenopiles (with heterokont flagella), Alveolata (with cortical alveoli) and Rhizaria (with fine pseudopodia). Three major alveolate groups are recognized: ciliates, apicomplexans and dinoflagellates. Apicomplexan cells possess a distinctive apical complex of organelles, comprising a conoid, polar ring, rhoptries, micronemes and subpellicular microtubules, which facilitate entry into host cells as they are obligate intracellular parasites for most of their life-cycles. There are three main apicomplexan groups: gregarines, coccidia and haematozoa. Haematozoa are small blood-borne parasites which undergo merogony (= schizogony) and gamogony (gamete formation) in vertebrates and sporogony (sporozoite formation) in blood-sucking invertebrate vectors. Two main groups are recognised in terrestrial vertebrates: haemosporidia with insect vectors; and piroplasms with arachnid vectors. Haemosporidian parasites multiply in the tissues of vertebrates before forming gamonts in blood cells (*Plasmodium* spp. also undergo cyclic merogony in erythrocytes). Most species produce haemozoin pigment granules as a byproduct of haemoglobin metabolism. Gametes ingested by insect vectors undergo fertilization in the gut forming motile zygotes (ookinetes) which form oocysts and then thousands of sporozoites which invade the salivary glands. Infections by *Plasmodium* spp. are transmitted by mosquitoes and numerous species have been described in mammals, birds and reptiles; most causing no apparent harm, except those infecting humans causing one of the worst fever scourges of mankind, the disease malaria.

Classification:

Domain: Eukaryota (membrane-bound nucleus)

Supergroup: SAR (Stramenopiles + Alveolata + Rhizaria)

Group: Alveolata (with cortical alveoli)

Phylum: Apicomplexa (with apical complex, all parasitic, sexual development (gamogony))

Class: Aconoidasida (asexual stages without conoid)

Order: Haemosporida (pleomorphic stages in blood of vertebrates, insect vectors, motile zygote (ookinete))

Family: Plasmodiidae (schizogony in tissues then blood cells, gamonts in blood cells, haemozoin pigment)

Genus: *Plasmodium* (vector-borne haemosporidian parasites of vertebrates)

Species: various species cause infections in mammals/birds/reptiles

Parasite biodiversity and host range: Protists are unicellular eukaryotes that move using undulipodia (flagella or cilia), pseudopodia (false-feet) or a unique gliding motion. Cells with different modes of locomotion do not form separate monophyletic assemblages as previously thought, but rather are distributed across several disparate supergroups (as evidenced by recent molecular phylogenetic analyses). One protistan supergroup known as SAR comprises the Stramenopiles (with heterokont flagella), Alveolata (with cortical alveoli) and Rhizaria (with fine pseudopodia). Three diverse alveolate groups are recognized: Ciliophora (with cilia), Dinoflagellata (with flagella) and Apicomplexa (with gliding motion, some also with flagellated microgametes). Over 4,000 species of Apicomplexa have been described as obligate parasites from vertebrate and invertebrate hosts. At some stage in their development, these possess unique cytoskeletal and membrane-bound organelles (conoid, rhoptries, micronemes, subpellicular microtubules) forming an apical complex that facilitates host cell invasion. Apicomplexans undergo cyclic development involving up to three different divisional processes: asexual merogony (schizogony) either by fission (splitting of maternal cell) or endogony (internal formation of daughter cells); gamogony involving formation of gametes (macrogametes = female, microgametes = male) which undergo fertilization to recombine by fusion (syngamy) with or without paired alignment (syzygy); and sporogony (formation of infective sporozoites).

Three main apicomplexan groups are recognized: haematozoa, gregarines, and coccidia. Haematozoa are small blood-borne parasites in vertebrates which complete their development in blood-sucking invertebrate vectors; with pleomorphic haemosporidia being transmitted by insects and pear-shaped piroplasms being transmitted by ticks. Gregarines are lumen-dwelling parasites that form large extracellular (sometimes septate) gamonts with an anterior holdfast organelle (mucron or epimerite) used to attach to the gut or body cavity of invertebrates. Coccidia are tissue-invading parasites that form small intracellular gamonts (lacking a mucron or epimerite) and most species undergo sexual reproduction by anisogamous fusion without syzygy forming non-motile resistant spores (oocysts) containing infective sporozoites usually confined within secondary spores (sporocysts). Three groups of coccidia are recognized: coelotrophiid coccidia in marine annelids; adeleid coccidia in marine and terrestrial animals (including blood parasites paradoxically known as 'haemogregarines' in reptiles and amphibians with leech or arthropod vectors); and eimeriid coccidia in vertebrates. Many eimeriid coccidia are monoxenous gut parasites undergoing faecal-oral transmission, but some are heteroxenous alternating between enteric stages in predators and encysted stages in prey (there are also a few enigmatic 'haemococcidia' in the blood of reptiles and birds).

Higher taxonomy	Family	Genera	Hosts	Site	Transmission*	
Class: Aconoidasida (asexual stages without conoid)						
Subclass: Haematozoa (clade of vector-borne spore-forming haemo-protozoa)						
Order: Haemosporida (pleomorphic blood stages, insect vectors, motile ookinete)	Plasmodiidae (schizogony in tissues then blood cells, haemozoin pigment)	<i>Plasmodium</i>	mammals, birds, reptiles	liver, erythrocytes	indirect (v-b)	
	Haemoproteidae (schizogony in tissues, haemozoin pigment)	<i>Haemoproteus</i>	birds	endothelia, erythrocytes	indirect (v-b)	
	Leucocytozoidae (schizogony in tissues, no haemozoin pigment)	<i>Leucocytozoon (Akiba)</i>	birds	tissues, leucocytes	indirect (v-b)	
Order: Piroplasmida (pear-shaped blood stages, tick vectors)	Babesiidae (merogony in erythrocytes, trans-stadial + trans-ovarian transmission)	<i>Babesia</i>	mammals	erythrocytes	indirect (v-b)	
	Theileriidae (merogony in leucocytes, trans-stadial transmission in ticks)	<i>Theileria</i>	ruminants	leucocytes, erythrocytes	indirect (v-b)	
Class: Coccidiomorpha [Conoidasida] (with conoid)						
Subclass: Coccidia [Coccidiasina] (small intracellular gamonts)						
Order: Eucoccidiorida (cyclic merogony (schizogony), gamogony, sporogony)						
Suborder: Adeleina (syzygy, 1-4 microgametes)	Haemogregarinidae (ookinete, gamonts in blood cells, invertebrate vectors)	<i>Haemogregarina</i>	reptiles, amphibia, fish	tissues, blood	indirect (v-b)	
		<i>Hepatozoon</i>	mammals, reptiles	tissues, blood	indirect (v-b)	
	Klossiellidae (sporocysts)	<i>Klossiella</i>	mammals	kidney	direct (f-o)	
Suborder: Eimeriorina (no syzygy, >4 microgametes)	Eimeriidae (monoxenous, endogenous merogony and gamogony, exogenous sporogony)	<i>Caryospora</i>	birds, reptiles	gut	direct (f-o)	
		<i>Cyclospora</i>	mammals, reptiles	gut	direct (f-o)	
		<i>Isospora</i>	birds, reptiles	gut	direct (f-o)	
		<i>Eimeria</i>	vertebrates	gut, tissues	direct (f-o)	
		<i>Epieimeria</i>	fish	gut	direct (f-o)	
		<i>Goussia</i>	fish	gut	direct (f-o)	
	Sarcocystidae (heteroxenous, 1:2:4 oocyst:sporocyst:sporozoite configuration)					
	subfamily Cystoisosporinae (monozoic cysts)	<i>Cystoisospora</i> (no Stieda bodies)	carnivores, omnivores	gut, tissues	direct (f-o), indirect (p-p)	
	subfamily: Sarcocystinae (thick-walls, metrocytes)	<i>Sarcocystis (Frenkelia)</i>	mammals, birds, reptiles	gut, muscles	indirect (p-p)	
	subfamily: Toxoplasmatinae (thin-walled cysts without metrocytes)	<i>Besnoita</i>	mammals, reptiles	gut, tissues	indirect (p-p)	
<i>Hammondia</i>		mammals	gut, tissues	indirect (p-p)		
<i>Neospora</i>		herbivores, dogs	gut, tissues	indirect (p-p)		
	<i>Toxoplasma</i>	vertebrates, cats	gut, tissues	indirect (p-p)		
Class: Gregarinomorpha (gregarines, trophonts with specialized attachment epimerite or mucron, syzygy)						
Subclass: Cryptogregarina (epicellular parasites of vertebrates with feeder organelle but lacking apicoplast)						
	Cryptosporidiidae (naked sporozoites)	<i>Cryptosporidium</i>	vertebrates	gut, lungs	direct (f-o)	

* f-o = faecal-oral transmission; p-p = predator-prey transmission; v-b = vector-borne transmission.

Haemosporida are spore-forming apicomplexan parasites with heteroxenous life-cycles, with merogony in cells of fixed tissues and in the blood of vertebrate (intermediate) hosts and sporogony in haematophagous invertebrate vectors (definitive hosts). In vertebrate blood cells, haemosporidia develop intracellularly forming sexually dimorphic gametocytes: macrogametocytes (female) with compact nuclei and dark-stained cytoplasm (plentiful ribosomes for protein synthesis), and microgametocytes (male) with larger diffuse nuclei (ready for microgamete production) and pale-staining cytoplasm [a simple mnemonic often used is “blue for girls, pink for boys”]. Gametocytes develop independently (without syzygy) and each microgamont produces about eight flagellated microgametes. Haemozoin granules (residual pigment formed due to incomplete haemoglobin digestion) may or may not be produced in infected erythrocytes. In the vector, the zygote is motile (ookinete) and ultimately forms numerous naked sporozoites (without sporocysts). Around 590 species belonging to some 19 haemosporidian genera have been described from a wide range of mammalian, avian and reptilian hosts around the world.

Four haemosporidian families are recognized mainly on the basis of their developmental cycles and whether haemozoin pigment is produced: namely, Plasmodiidae (merogony in tissues then cyclic in erythrocytes, pigment present); Haemoproteidae (merogony in tissues only, pigment present); Leucocytozoidae (merogony in tissues, pigment absent) and Garniidae (merogony in leucocytes, pigment absent). Vertebrates act as intermediate hosts in which the parasites undergo asexual multiplication within tissues and/or blood cells. Even though parasites begin gamete formation in vertebrates, sexual multiplication is not completed until after they are transmitted to their haematophagous invertebrate vectors, which therefore act as definitive hosts. Some 11 genera are recognized in the family Plasmodiidae on the basis of multiple biological characters (including morphology, development, host specificity and range): *Plasmodium* in mammals, birds and reptiles; *Hepatocystis*, *Polychromophilus*, *Nycteria*, *Biguetiella*, *Bioccala* and *Dionisia* in bats, *Rayella* in flying squirrels, *Billbraya* and *Haemocystidium* (including *Simondia*) in reptiles, and *Mesnilium* in fish.

Haemosporidian genera	No. spp.	Site* of development in vertebrate		Vertebrate hosts	Invertebrate vector
		meronts	gamonts		
Family: Plasmodiidae (merogony in tissues and erythrocytes, haemozoin pigment present)					
<i>Plasmodium</i>	225	liver, rbc	rbc	mammals, birds, reptiles	diptera
<i>Hepatocystis</i>	25	liver	rbc	primates/bats	midges
<i>Polychromophilus</i>	5	viscera	rbc	bats	nycterids
<i>Nycteria</i>	7	liver	rbc	bats	
<i>Biguetiella</i>	1	liver	rbc	bats	
<i>Bioccala</i>	2	RE cells	rbc	bats	
<i>Dionisia</i>	1	liver	rbc	bats	
<i>Rayella</i>	3	liver	rbc	flying squirrels	
<i>Billbraya</i>	1	rbc	rbc	lizards	
<i>Mesnilium</i>	1	RE cells, rbc	rbc	fish	leeches/insects
<i>Haemocystidium (Simondia)</i>	33	RE cells	rbc	lizards/tortoises	arthropods
Family: Haemoproteidae (merogony in tissues (not in blood cells), haemozoin pigment present in gametocytes)					
<i>Haemoproteus (Halteridium)</i>	6	RE cells	rbc	birds	louse flies
<i>Haemoproteus (Parahaemoproteus)</i>	150	RE cells	rbc	birds	midges
<i>Johnsprentia</i>	1	RE cells	rbc	flying foxes	
<i>Sprattiella</i>	1	RE cells	rbc	bats	
Family: Leucocytozoidae (merogony in tissues (not in blood cells), haemozoin pigment absent)					
<i>Leucocytozoon (Akiba)</i>	100	RE cells	blood cells	birds	black flies
<i>Sauocytozoon</i>	3	viscera	leucocytes	lizards	mosquitoes
Family: Garniidae (merogony in leucocytes, haemozoin pigment absent)					
<i>Fallisia</i>	12	leucocytes	leucocytes	lizards	arthropods
<i>Garnia</i>	10	leucocytes	leucocytes	lizards	arthropods
<i>Progarnia</i>	1	leucocytes	blood cells	crocodiles	

*rbc = red blood cells (erythrocytes); RE = reticuloendothelial cells

Many molecular phylogenetic studies using nuclear, mitochondrial and apicoplast gene sequences have demonstrated a clear relationship between haemosporidian genera not only with their vertebrate hosts but also their invertebrate vectors. There were clear groupings of *Leucocytozoon* from birds, *Haemoproteus (Haemoproteus)* from birds, *Haemoproteus (Parahaemoproteus)* from birds, *Plasmodium* from birds and reptiles, *Plasmodium* from rodents and primates, and *Hepatocystis* from bats. These groups were clearly associated with different vectors; namely, simuliids (black-flies), hippoboscids (louse-flies), ceratopogonids (midges), culicine mosquitoes, anopheline mosquitoes, and midges, respectively. There appears to have been a transition from haemosporidia which do not form haemozoin pigment (*Leucocytozoon* in white blood cells) to genera that do form pigment indicating haemoglobin digestion by parasites in red blood cells (*Haemoproteus*, *Plasmodium* and *Hepatocystis*). This was followed by a transition from haemosporidia which undergo schizogony exclusively in host tissues (*Leucocytozoon* and *Haemoproteus*) to those that undergo schizogony in blood cells (*Plasmodium*). While there appears to be a general shift in haemosporidian genera from birds and reptiles to mammals (from nucleated to non-nucleated blood cells), each genus is associated with a particular vector group: black-flies transmitting *Leucocytozoon* to birds; louse-flies transmitting *Haemoproteus (Haemoproteus)* to birds; midges transmitting *Haemoproteus (Parahaemoproteus)* to birds; culicine mosquitoes transmitting *Plasmodium* to birds and lizards; and anopheline mosquitoes transmitting *Plasmodium* to mammals. The exception to this general trend was *Hepatocystis* which does not undergo blood schizogony and is transmitted to bats by midges.

Over 225 *Plasmodium* species have been classified in 14 subgenera on the basis of parasite morphology, development and host occurrence. Three subgenera contain species in mammals, five subgenera contain those in birds, and six contain those in reptiles:

- *P. (Plasmodium)*, with large erythrocytic schizonts and round gametocytes, in primates;
- *P. (Lavernia)*, with large erythrocytic schizonts and crescentic gametocytes, in primates;
- *P. (Vinckeia)*, with small erythrocytic schizonts and round gametocytes, in antelopes, rodents and other mammals (except primates);

- *P. (Haemamoeba)*, with large erythrocytic schizonts and round gametocytes, in birds;
- *P. (Bennettinia)*, with small erythrocytic schizonts and round gametocytes, in birds;
- *P. (Huffia)*, with large schizonts and elongate gametocytes mostly in immature erythrocytes, in birds;
- *P. (Giovannolaia)*, with large erythrocytic schizonts and elongate gametocytes, in birds;
- *P. (Novyella*)*, with small erythrocytic schizonts and elongate-oval gametocytes, in birds;

- *P. (Sauramoeba)*, with large erythrocytic schizonts and large gametocytes, in lizards;
- *P. (Lacertamoeba)*, with medium erythrocytic schizonts and medium gametocytes, in lizards;
- *P. (Paraplasmodium)*, with medium erythrocytic schizonts and large gametocytes, in lizards;
- *P. (Carinamoeba)*, with small erythrocytic schizonts and small gametocytes, in lizards;
- *P. (Asiamoeba)*, with small erythrocytic schizonts and large gametocytes, in lizards; and
- *P. (Ophidiella)*, with large erythrocytic meronts and small elongate gametocytes, in snakes.

*A novel subgenus, *P. (Papernaia)*, was proposed for species in the subgenus *P. (Novyella)* which did not possess refractory 'vitreous' globules in erythrocytic developmental stages. However, morphological and molecular studies have shown that the presence/absence of these globules varied for the species *P. ashfordi* when passaged between different hosts, thereby not providing support for this character to be used to split the subgenus *P. (Novyella)*.

In contrast to the narrow host specificities of most mammalian *Plasmodium* spp., avian species often demonstrate broader host specificities, capable of infecting many bird species belonging to different families, and even orders, and being transmitted by multiple genera of Culicidae (*Aedes*, *Anopheles*, *Coquillettidia*, *Culisetta*, *Culex*, *Mansonia*, *Psorophora*, *Theobaldia* and *Wyeomyia* mosquitoes). The developmental cycles of avian *Plasmodium* spp. are similar to those of mammalian species, yet subtle differences may be involved. Exo-erythrocytic merogony occurs mostly in cells of the reticulo-endothelial system (haemopoietic system for the subgenus *Huffia*) rather than in hepatocytes, erythrocytic merozoites (of many species) may induce secondary tissue merogony in birds contributing to ischaemic pathology, and oocysts may be pedunculated (subgenus *Bennettinia*) with leg-like outgrowths attaching them to the mosquito midgut wall. Development in their vectors appears to occur faster and at lower temperatures, which may accommodate rapid transmission to birds undertaking annual seasonal migrations between continents. These features may explain the wide geographic distribution of avian malaria species in all landscape regions (from mountains to shores), often spanning multiple zoogeographic regions: species richness (biodiversity) being greatest in Nearctic (North America), Palearctic (Europe and Asia = Eurasia), Ethiopian/African (sub-Saharan Africa) and Oriental (India, South-East Asia, Western Indonesia) regions, and poorest in Australasian (Australia, Eastern Indonesia, New Guinea, New Zealand) and Neotropical (South America) regions. Survey records indicate species richness to be greatest in Passeriformes, Galliformes, Columbiformes, Coraciiformes and Piciformes, medium in Ciconiiformes, Anseriformes, Falconiformes, Gruiformes, Charadriiformes and Strigiformes, and poorest in relatively old groups such as Sphenisciformes, Struthioniformes, Tinamiformes, Pelecaniformes, Turniciformes, Musophagiformes, Coliiformes and Trogoniformes. While the vast majority of avian *Plasmodium* spp. have been recorded in birds in tropical or subtropical countries or in Holarctic migrants overwintering in warmer regions, several species have become widespread in many bird species throughout the world (notably, *P. (Ha.) cathemerium*, *P. (Ha.) relictum*, *P. (Hu.) elongatum*, *P. (G.) circumflexum*, *P. (N.) nucleophilum* and *P. (N.) vaughani*).

Plasmodium species	Avian intermediate hosts (IH)	Periodicity (pathogenicity)	Definitive hosts (DH) (vectors)	Zoogeographic distribution
Subgenus: <i>Haemamoeba</i> (large erythrocytic schizonts, round gametocytes, in birds)				
<i>P. (Ha.) caloti</i>	Passeriformes: alaudid (skylarks)			Palaearctic
<i>P. (Ha.) cathemerium</i> (syn. <i>centropi p.p.</i>)	Passeriformes: cardinalid (cardinals, grosbeaks), corvid (crows, jays, magpies), emberizid (buntings), fringillid (canaries, finches, redpolls), hirudinid (swallows), icterid (cowbirds, grackles, meadowlarks), laniid (shrikes), mimid (mockingbirds, thrashers), monarchid (monarchs), motacillid (pipits, wagtails), muscicapid (redstarts, robins), parid (tits), parulid (warblers), passerid (sparrows), passerellid (juncos), ploceid (weavers), sturnid (starlings), thraupid (grassquit, tanagers), timaliid (babbler), troglodytid (wrens), turdid (blackbirds, chats, thrushes), tyrannid (flycatchers); Apodiformes: apodid (swifts); Caprimulgiformes: caprimulgid (nightjars); Columbiformes: columbid (pigeons, doves); Gruiformes: rallid (rails); Piciformes: ramphistid (toucans); Sphenisciformes: spheniscid (penguins); Strigiformes: strigid (fish owls)	24 hrs (pathogenic, anaemia, ischaemia)	Diptera: culicid (<i>Aedes aegypti, cantator, geniculatus, sollicitans, Anopheles norestensis, quadrimaculatus, strodei, Culex bitaeniorhynchus, fuscus, pipiens, quinquefasciatus, salinarius, stigmatostoma, tarsalis, territans, tritaeniorhynchus, Culiseta melaneum, morsitans, Psorophora ferox</i>)	Holarctic, Neotropical, Ethiopian, Oriental
<i>P. (Ha.) coturnixi</i>	Galliformes: phasianid (quail)	24 hrs		Oriental (Pakistan)
<i>P. (Ha.) gallinaceum</i> (syn. <i>metastaticum</i>)	Galliformes: phasianid (chickens, junglefowl, grey partridge); Passeriformes: corvid (house crow)	36 hrs (pathogenic, anaemia, ischaemia)	Diptera: culicid (<i>Aedes aegypti, albolateralis, albipictus, atropalpus, campestris, canadensis, cantator, chrysolineatus, geniculatus, jamesi, japonicus, lepidus, pallirostris, pseudoalbopictus, pseudotaeniatus, scutellaris, stimulans, stokesi, togoi, triseriatus, trivittatus, unilineatus, vexans, vittatus, Anopheles freeborni, pulcherrimus, quadrimaculatus, sacharovi, Armigeres annulipalpis, aureolineatus, kuchingensis, magnus, obturbans, subalbus, Culex mimuloides, pipiens, salinarius, tarsalis, Culiseta inornata, Mansonia albimanus, crassipes, erturbans</i>)	Oriental
<i>P. (Ha.) giovannolai</i>	Passeriformes: fringillid (canaries), turdid (thrushes)	24 hrs (death in canaries)	Diptera: culicid (<i>Culex pipiens</i>)	Palaearctic (Italy)

<i>P. (Ha.) griffithsi</i>	Galliformes: phasianid (turkeys)			Oriental (Burma)
<i>P. (Ha.) lutzii</i>	Gruiformes: rallid (rails)	asynchronous		Neotropical
<i>P. (Ha.) maior</i>	Passeriformes: passerid (sparrows)			Palaearctic
<i>P. (Ha.) matutinum</i>	Passeriformes: passerid (sparrows), turdid (thrushes); Columbiformes: columbid (doves, pigeons)	24 hrs (organ congestion)	Diptera: culicid (<i>Culex pipiens, stigmatosoma, tarsalis</i>)	Holarctic, Oriental
<i>P. (Ha.) parvulum</i>	Passeriformes: vangid (vangas)			Madagascar
<i>P. (Ha.) relictum</i> [type species] [incl. subsp. <i>relictum, matutinum</i>] (syn. <i>paddae, alaudae p.p., biziurae, passeris, major, bioccai, grassii, muniae, majoris p.p., inconstans, pericrocati, capistrani, placeii, spheniscidae, chloropsidis, ginsburgi, dorsti, coluzzii</i> , and <i>Haemoproteus mcleani</i> ?)	Passeriformes: alaudid (larks, skylarks), callaeid (saddlebacks), campephagid (minivets), cardinalid (cardinals), cisticolid (tailorbirds), corvid (choughs, crows, ravens, jays, magpies), dicaeid (flowerpeckers), dicurid (drongos), emberizid (buntings), estrildid (mannikins, pytilias), eulacestomatid (ploughbills), fringillid (crossbills, euphonias, finches, grosbeaks, honeycreepers, siskins), hirudinid (swallows), icterid (caciques, grackles, marshbirds, meadowlarks), laniid (shrikes), locustellid (grassbirds), mimid (thrashers), monarchid (monarchs, flycatchers), motacillid (pipits, wagtails), muscicapid (batis, chats, nightingales, robins, shamas, wheatears), oriolid (orioles), nectariniid (sunbird), paradoxornithid (parrotbills), parulid (tits, warblers), passerellid (snowbird), passerid (sparrows), ploceid (weavers), polioptilid (gnatcatchers), ptilonorhynchid (catbirds), pycnonotid (bulbuls), rhipidurid (fantails), sturnid (starlings, mynas), thamnophilid (antbirds), thraupid (grassquits, saltators, tanagers), timaliid (babblers), troglodytid (wrens), turdid (blackbirds, thrushes), tyrannid (tyrannulets), vireonid (vireos), zosteropid (white-eyes); Accipitriformes: accipitrid (buzzards); Anseriformes: anatid (ducks, eiders, geese); Apodiformes: apodid (swifts); Charadriiformes: alcid (auks, puffins), charadriid (plovers), larid (gulls), scolopacid (snipes); Coraciiformes: coraciid (rollers), meropid (bee-eaters); Cuculiformes: cuculid (cuckoos, koels); Columbiformes: columbid (doves, pigeons); Falconiformes: falconid (falcons, hawks); Galliformes: phasianid (chickens, grouse, partridges, pheasant, quail), numidid (guineafowl); Gruiformes: rallid (bush-hens, coots, rails); Otidiformes: otidid (bustards); Suliformes: sulid (gannets); Piciformes: bucconid (puffbirds),	30-36 hrs (pathogenic, lesions in tissues)	Diptera: culicid (<i>Aedes aegypti, communis, concolor, dorsalis, mariae, vexans, Anopheles albimanus, crucians, freeborni, quadrimaculatus, subpictus, Culex apicalis, bitaeniorhynchus, fatigans, fuscianus, gelidus, hortensis, pipiens, quinquefasciatus, salinarius, stigmatosoma, tarsalis, territans, theileri, whitmorei, Culiseta annulata, longiareolata</i>)	cosmopolitan (except Antarctic)

	<p>picid (woodpeckers); Procellariiformes: diomedeid (albatross); Psittaciformes: psittaculid (parrots); Sphenisciformes: spheniscid (penguins); Strigiformes: strigid (owls)</p>			
<i>P. (Ha.) subpraecox</i> (syn. <i>wasielewskii</i>)	Strigiformes: strigid (little owl, red-chested owl, snowy owl, screech owl); Passeriformes: alaudid (skylark), passerid (sparrow)	24 hrs	Diptera: culicid (<i>Culex pipiens</i>)	Holarctic
<i>P. (Ha.) tejerai</i>	Galliformes: phasianid (turkeys, quail), numidid (guineafowl); Anseriformes: anatid (ducks, geese)	? (death in exptl infections)		Neotropical
Subgenus: <i>Bennettinia</i> (small erythrocytic schizonts, round gametocytes, in birds)				
<i>P. (B.) juxtannucleare</i> (syn. <i>japonicum</i>) [type species]	Galliformes: phasianid (chickens, partridges, peafowl, turkeys); Sphenisciformes: spheniscid (penguins)	24 hrs (mildly pathogenic, tissue lesions)	Diptera: culicid (<i>Culex annulus, gelidus, pipiens, pseudovishnui, sitiens, tritaeniorhynchus</i>)	Neotropical, Ethiopian, Oriental
Subgenus: <i>Huffia</i> (large erythrocytic schizonts, elongate gametocytes mostly in immature erythrocytes, in birds)				
<i>P. (Hu.) elongatum</i> (incl. <i>alloeelongatum</i>) [type species]	Passeriformes: fringillid (canaries), meliphagid (bellbirds), sylviid (warblers), thraupid (honeycreepers); Anseriformes: anatid (ducks); Falconiformes: falconid (eagles, hawks); Accipitriformes: accipitrid (sparrowhawks); Galliformes: phasianid (quail); Sphenisciformes: spheniscid (penguins); Strigiformes: strigid (owls)	24 hrs (pathogenic in captive penguins due to tissue lesions)	Diptera: culicid (<i>Culex pipiens, restuans, nigripalpus, salinarius, tarsalis, territans</i>)	Holarctic, Neotropical, Ethiopian, Oriental
<i>P. (Hu.) hermani</i>	Galliformes: phasianid (turkeys, quail); Charadriiformes: scolopacid (knots)		Diptera: culicid (<i>Culex nigripalpus, restuans, salinarius, Wyeomyia vanduzeei</i>)	Nearctic
<i>P. (Hu.) huffi</i>	Piciformes: ramphastid (toucans)	48 hrs (moderately pathogenic)		Neotropical
<i>P. (Hu.) polymorphum</i>	Passeriformes: alaudid (skylark)			Palaearctic
Subgenus: <i>Giovannolaia</i> (large erythrocytic schizonts, elongate gametocytes, in birds)				
<i>P. (G.) anasum</i>	Anseriformes: anatid (ducks)			Oriental
<i>P. (G.) bigueti</i> (species inquirenda)	Passeriformes: passerid (sparrows)			Palaearctic
<i>P. (G.) buteonis</i> (species inquirenda)	Accipitriformes: accipitrid (buzzards)			Palaearctic
<i>P. (G.) circumflexum</i> (incl. <i>homocircumflexum</i>) (syn. <i>heroni</i>) [type species]	Passeriformes: cardinalid (cardinals), corvid (jays), fringillid (canaries), mimid (thrashers), parulid (warblers), passerid (sparrows), ptilonorhynchid (catbirds), sturnid (starlings), turdid (blackbirds, robins, thrushes); Anseriformes: anatid (ducks, swans); Columbiformes: columbid (pigeons); Coraciiformes: alcedinid (kingfishers); Charadriiformes: glareolid (waders); Falconiformes: falconid (hawks); Galliformes: phasianid (chickens, partridges, pheasant, quail, turkeys), numidid	24 or 48 hrs (anaemia and ischaemia)	Diptera: culicid (<i>Culiseta longiareolata, melaneura, morsitans, Mansonia crassipes, Theobaldia annulata</i>)	cosmopolitan (except Antarctic)

	(guineafowl); Strigiformes: strigid (owls)			
<i>P. (G.) durae</i>	Galliformes: phasianid (francolins, turkeys, peafowl), numidid (guineafowl)	24 hrs (convulsions and anemia in turkeys)	Diptera: culicid (<i>Culex antennatus, pipiens, univittatus</i>)	Ethiopian
<i>P. (G.) fallax</i>	Strigiformes: strigid (eagles, hawks, owls); Accipitriformes: accipitrid (vultures); Galliformes: phasianid (guineafowl); Passeriformes: emberizid (buntings) parulid (warblers)	asynchronous (ischaemia in exptl. infections)	Diptera: culicid (<i>Aedes aegypti, albopictus, atropalpus, triseriatus, Anopheles quadrimaculatus, Culex quinquefasciatus, tarsalis</i>)	Ethiopian, Oriental, Palearctic
<i>P. (G.) formosanum</i>	Galliformes: phasianid (partridges); Gruiformes: rallid (rails)	48 hrs		Oriental
<i>P. (G.) gabaldoni</i>	Columbiformes: columbid (pigeons); Anseriformes: anatid (ducks)	24 hrs (pathogenic in young birds)	Diptera: culicid (<i>Aedes aegypti, Culex pipiens</i>)	Neotropical
<i>P. (G.) garnhami</i>	Bucerotiformes: bucerotid (hoopoes); Coraciiformes: coraciid (rollers); Passeriformes: laniid (shrikes)	48 hrs (severe in young birds)	Diptera: culicid (<i>Culex pipiens</i>)	Ethiopian, Southern Palearctic
<i>P. (G.) ghadiriani (species inquirenda)</i>	Passeriformes: alaudid (skylarks), corvid (magpies)			Palearctic
<i>P. (G.) gundersi</i>	Strigiformes: strigid (owl); Galliformes: phasianid (partridges); Passeriformes: fringillid (canaries)	24 hrs (severe in canaries)		Oriental
<i>P. (G.) hegneri</i>	Anseriformes: anatid (teals)	asynchronous		Oriental
<i>P. (G.) leanucleus</i>	Passeriformes: passerid (sparrows), pycnonotid (bulbuls)	24 hrs ()	Diptera: culicid (<i>Culex pipiens, Anopheles dirus</i>)	Oriental
<i>P. (G.) lophurae</i>	Galliformes: phasianid (chickens, pheasant, turkeys); Columbiformes: columbid (doves); Anseriformes: anatid (ducks)	24-36 hrs (organ congestion and anemia, esp. in ducks)	Diptera: culicid (<i>Aedes albopictus, aegypti, atropalpus, Anopheles quadrimaculatus, Culex restuans</i>)	Oriental
<i>P. (G.) octamerium</i>	Passeriformes: estrildid (waxbills), fringillid (canaries, finches), passerid (sparrows), ploceid (weavers), sturnid (starlings), viduid (whydahs); Anseriformes: anatid (ducks); Columbiformes: columbid (doves, pigeons); Galliformes: phasianid (chickens, partridges, quail)	24 hrs (cerebral signs in exptl. infections in partridges)		Ethiopian
<i>P. (G.) pedioecetae</i>	Galliformes: phasianid (grouse, partridges, quail); Tinamiformes: tinamid (nothuras); Passeriformes: fringillid (canaries)			Nearctic, Neotropical
<i>P. (G.) pinottii</i>	Piciformes: ramphastid (toucans); Passeriformes: thraupid (bananaquits, grassquits, thrushes); fringillid (canaries), passerid (sparrows), parulid (warblers); Anseriformes: anatid (ducks); Columbiformes: columbid (doves, pigeons); Galliformes: phasianid (chickens); Gruiformes: rallid (rails)	24 hrs		Neotropical
<i>P. (G.) polare</i>	Passeriformes: cardinalid (cardinals), emberizid (buntings), hirundinid (swallows), muscicapid (chats), parid (tits), passerid (sparrows), pycnonotid (bulbuls), thamnophilid (antshrikes), turdid	24 hrs	Diptera: culicid (<i>Culiseta longiareolata, morsitans</i>)	Holarctic, Neotropical, Ethiopian, Oriental

	(blackbirds, thrushes); Anseriformes: anatid (ducks); Caprimulgiformes: caprimulgid (nighthawks); Columbiformes: columbid (doves); Falconiformes: falconid (eagles, falcons); Galliformes: phasianid (francolins, grouse); Gruiformes: gruoid (cranes), Tinamiformes: tinamid (nothuras)			
<i>P. (G.) tranieri</i> (<i>species inquirenda</i>)	Passeriformes: corvid (magpies)			Palaearctic
Subgenus: <i>Novyella</i> (small erythrocytic schizonts and elongate-oval gametocytes, in birds)				
<i>P. (N.) accipiteris</i>	Accipitriformes: accipitrid (sparrowhawks)			Palaearctic
<i>P. (N.) ashfordi</i>	Passeriformes: fringillid (crossbills, siskins), parulid (warblers)			Palaearctic
<i>P. (N.) beaucournui</i> (<i>species inquirenda</i>)	Passeriformes: corvid (magpies)			Palaearctic
<i>P. (N.) bertii</i>	Gruiformes: rallid (rails)	asynchronous		Neotropical
<i>P. (N.) columbae</i>	Columbiformes: columbid (pigeons); Anseriformes: anatid (ducks)	little periodicity (pathogenic in ducklings)		Neotropical
<i>P. (N.) delichoni</i>	Passeriformes: hirudinid (house martin)	asynchronous		Palaearctic
<i>P. (N.) dherteeae</i> (<i>species inquirenda</i>)	Passeriformes: alaudid (skylarks), corvid (magpies)			Palaearctic
<i>P. (N.) dissanaikiei</i>	Psittaciformes: psittaculid (parakeets); Anseriformes: anatid (ducks); Passeriformes: fringillid (canaries)	(anaemia in ducklings)		Oriental
<i>P. (N.) forresteri</i>	Strigiformes: strigid (owls); Falconiformes: falconid (hawks, eagles); Galliformes: phasianid (quail); Anseriformes: anatid (ducks)		Diptera: culicid (<i>Culex restuans</i>)	Nearctic
<i>P. (N.) globularis</i>	Passeriformes: pycnonotid (greenbuls)			African
<i>P. (N.) hexamerium</i> (syn. <i>oti</i>)	Passeriformes: alaudid (skylarks), cardinalid (cardinals), corvid (crows, magpies, jays), emberizid (buntings), fringillid (canaries, finches, grosbeaks), icterid (cowbirds, grackles, troupials, meadowlarks), mimid (catbirds, thrashers), motacillid (pipits, wagtails), parulid (warblers), passerellid (juncos, towhees), passerid (sparrows), sturnid (starlings), turdid (blackbirds, bluebirds, thrushes), tyrannid (kingbirds); Anseriformes: anatid (ducks); Galliformes: phasianid (turkeys); Ciconiiformes: ciconiid (storks); Columbiformes: columbid (doves, pigeons); Accipitriformes: accipitrid (plumbeous kites); Coraciiformes: meropid (bee-eaters); Strigiformes: strigid (scops owls, wood owls)	little periodicity		Nearctic, Neotropical

<i>P. (N.) hoionucleophilum</i>	Passeriformes: parulid (warblers)			Palearctic
<i>P. (N.) homopolare</i>	Passeriformes: fringillid (finches), icterid (cowbirds), parulid (warblers), passerellid (towhees), passerid (sparrows), sittid (nuthatches), thraupid (tanagers), troglodytid (wrens)		Diptera: culicid (<i>Culex tarsalis, restuans, Culiseta particeps</i>)	Nearctic, Neotropical
<i>P. (N.) jeanriouxi (species inquirenda)</i>	Passeriformes: alaudid (skylarks)			Palearctic
<i>P. (N.) kempi</i>	Galliformes: phasianid (turkeys, partridges, peafowl, quail), numidid (guineafowl); Anseriformes: anatid (ducks, geese); Passeriformes: fringillid (canaries)		Diptera: culicid (<i>Culex pipiens, restuans, tarsalis</i>)	Nearctic
<i>P. (N.) lenoblei (species inquirenda)</i>	Passeriformes: corvid (crows, magpies)			Palearctic
<i>P. (N.) lucens</i>	Passeriformes: nectariniid (olive sunbirds)			African
<i>P. (N.) megaglobularis</i>	Passeriformes: nectariniid (sunbirds)			African
<i>P. (N.) multivacuolaris</i>	Passeriformes: icterid (greenbuls)			African
<i>P. (N.) nucleophilum</i> subsp. <i>nucleophilum</i>	Passeriformes: cardinalid (ant tanager), corvid (magpies), emberizid (buntings), fringillid (canaries, finches), furnariid (woodcreepers), grallariid (antpittas), hirudinid (martins, swallows), mimid (catbirds, mockingbirds), monarchid (flycatchers), oriolid (orioles), parid (tits), parulid (warblers), passerid (sparrows), piprid (manakin), ploceid (weavers), sturnid (starlings, mynas), thraupid (grassquits, tanagers), tityrid (becards), turdid (blackbirds, thrushes), tyrannid (kingbirds, tyrannulets), vireonid (vireos, greenlets); Anseriformes: anatid (ducks, geese); Piciformes: ramphastid (toucans); Pelecaniformes: threskiornithid (ibises); Caprimulgiformes: caprimulgid (nightjars); Psittaciformes: psittaculid (parrots); Columbiformes: columbid (doves)	24 hrs		Holarctic, Neotropical, Ethiopian, Oriental
<i>P. (N.) nucleophilum</i> subsp. <i>toucani</i> (syn. <i>P. toucani</i>)	Piciformes: ramphastid (toucans)	24 hrs		Neotropical
<i>P. (N.) pachysomum (species inquirenda)</i>	Passeriformes: motacillid (pipits)			Palearctic
<i>P. (N.) parahexamerium</i>	Passeriformes: muscicapid (white-tailed alethes)			African
<i>P. (N.) paranucleophilum</i>	Passeriformes: thraupid (tanagers), fringillid (canaries)			Neotropical
<i>P. (N.) pfefferi (species)</i>	Passeriformes: corvid (magpies)			Palearctic

<i>inquirenda</i>)				
<i>P. (N.) reniai</i> (<i>species inquirenda</i>)	Passeriformes: alaudid (skylarks)			Palearctic
<i>P. (N.) rouxi</i> (syn. <i>mohammedi</i>)	Passeriformes: alaudid (skylarks), chloropseid (leafbirds), cisticolid (prinias), estrildid (mannikins), fringillid (canaries, finches, grosbeaks), malaconotid (bushshrikes), monarchid (flycatchers), motacillid (pipits, wagtails), muscicapid (robins, wheatears), nectariniid (sunbirds), parulid (warblers), passerid (sparrows), pittid (pittas), platysteirid (batis), ploceid (weavers), pycnonotid (bulbuls, finchbills), thraupid (grassquits, saltators), timaliid (babblers), turdid (blackbirds, thrushes), zosteropid (yuhinas); Apodiformes: apodid (swifts); Gruiformes: rallid (wood rails); Galliformes: phasianid (francolins, partridges, pheasant), numidid (guineafowl); Piciformes: ramphastid (toucans)	24 hrs (anaemia, splenomegaly)	Diptera: culicid (<i>Culex pipiens, tarsalis, territans</i>)	Holarctic, Ethiopian, Oriental, African
<i>P. (N.) sergentorum</i> (<i>species inquirenda</i>)	Passeriformes: alaudid (skylarks), corvid (magpies)			Palearctic
<i>P. (N.) snounoui</i> (<i>species inquirenda</i>)	Passeriformes: corvid (magpies)			Palearctic
<i>P. (N.) stellatum</i> (<i>species inquirenda</i>)	Passeriformes: monarchid (flycatchers)			Palearctic
<i>P. (N.) unalis</i>	Passeriformes: turdid (thrushes)			Neotropical
<i>P. (N.) valkiunasi</i>	Passeriformes: corvid (magpies)			Palearctic
<i>P. (N.) vaughani</i> (type species) [incl. subsp. <i>vaughani, tenuis, merulae, tumbayaensis</i>]	Passeriformes: alaudid (larks), cardinalid (cardinals), cisticolid (camaroptera), conophagid (gnateaters), corvid (crows, jays, magpies), dicaeid (flowerpeckers), dicurid (drongos), estrildid (waxbills), fringillid (canaries, finches, grosbeaks), furnariid (woodcreepers), icterid (bobolink, cowbirds, grackles, marshbirds, meadowlarks), laniid (shrikes), leiiothrichid (leiiothrix), malaconotid (boubous, bushshrikes), mimid (catbirds, mockingbirds), monarchid (flycatchers), motacillid (pipits, wagtails), muscicapid (chats, robins, shamas), nectariniid (sunbirds), parid (tits), parulid (ovenbirds, warblers), passerellid (juncos), passerid (sparrows), pittid (pittas), ploceid (weavers, widowbirds), oriolid (orioles), piprid (manakins), pycnonotid (bulbuls), sturnid (mynas, starlings), sylviid (blackcaps), thamnophilid (antbirds,	24-26 hrs, but often asynchronous (nonpathogenic)	Diptera: culicid (<i>Culiseta morsitans, Culex pipiens</i>)	cosmopolitan (except Antarctic)

	antshrikes), thraupid (bananaquits, grassquits, seedeaters, tanagers), timaliid (babblers), troglodytid (wrens), turdid (blackbirds, solitaires, thrushes), vireonid (vireos), zosteropid (white-eyes, yuhinas); Anseriformes: anatid (dabbling ducks, geese, wood duck); Charadriiformes: turnicid (buttonquail, glareolid (waders); Columbiformes: columbid (doves, pigeons); Coraciiformes: meropid (bee-eaters), alcedinid (kingfishers); Cuculiformes: cuculid (koels, malkohas); Gruiformes: rallid (bush-hens, rails); Piciformes: capitonid (barbets), ramphastid (toucans); Psittaciformes: psittaculid (racket-tails); Musophagiformes: musophagid (turacos)			
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Parasite morphology: The developmental cycles of avian *Plasmodium* spp. are similar to those of mammalian species, but subtle differences are involved. In birds, the parasites may undergo 3 forms of exo-erythrocytic merogony (forming cryptozoic, metacryptozoic and phanerozoic meronts, sometimes enigmatically referred to as cryptozoites, metacryptozoites and phanerozoites even though all of them produce merozoites) and then cyclic erythrocytic merogony that leads to gametocyte formation. In mosquito vectors, the parasites complete sexual development (gamogony) culminating in oocyst formation and sporozoite production (sporogony). There are initially 2 exo-erythrocytic generations of merogony (known as ‘primary’ pre-erythrocytic merogony): the first involving rounded (10-45 µm diameter) basophilic cryptozoic meronts that become multinucleate as they undergo internal division (endogeny) usually forming < 100 ovoid to spindle-shaped merozoites (1-3 µm); and the second generation involving larger ellipsoidal (20-80 µm long) metacryptozoic meronts that become multinucleate as they divide internally usually forming > 100 ovoid-rhomboid merozoites (1-2 µm). A third exo-erythrocytic generation of merogony (known as ‘secondary’ post-erythrocytic merogony) may occur later, involving ellipsoidal-vermiform (up to 120 µm long) basophilic phanerozoic meronts that form up to 180 small ovoid-rhomboid merozoites (1-2 µm). Erythrocytic merogony involves a cyclic process where small rounded (1-3 µm) irregular trophozoites form pleomorphic (plasmodial) stages (rather than ring stages formed by mammalian species), followed by round-irregular (5-10 µm) meronts that divide internally to form 4-36 (frequently 10-24) small round merozoites (1-2 µm). The meronts may occupy up to half the volume of the host erythrocyte and they contain plentiful eosinophilic cytoplasm with brown-black refringent pigment (haemozoin) granules (0.2-1.0 µm). Eventually, merozoites invade erythrocytes and form round-oval (5-10 µm) gametocytes which exhibit sexual dimorphism (accentuated by Giemsa staining giving rise to the paradoxical adage ‘blue for girls, pink for boys’): where macrogametocytes (female) have a basophilic cytoplasm (due to the presence of numerous ribosomes and plentiful endoplasmic reticulum) with a Golgi apparatus, an unusual ‘spherical body’, a compact nucleus with a nucleolus, and usually less than 30 pigment granules; while microgametocytes (male) have a pale eosinophilic cytoplasm (fewer ribosomes and endoplasmic reticulum) with a large pale nucleus (without a nucleolus) and up to 30 pigment granules but no Golgi apparatus or ‘spherical body’. In mosquitoes, male gametocytes undergo exflagellation releasing motile microgametes (8-16 x 0.5-1.0 µm) that fertilize robust macrogametes (5-8 µm) producing a motile zygote (known as an ookinete). The ookinete is an elongate worm-like stage (12-20 x 2-5 µm) containing scattered vacuoles, pigment granules, and eventually a residual body. It matures to form a membrane-bound oocyst containing pigment granules in loose aggregated clumps. The oocysts of most species are rounded (30-50 µm) although those in the subgenus *Bennettinia* may be pedunculated with stalk-like projections used for attachment. The oocysts undergo sporogony and divide internally to form large numbers (hundreds) of elongate to spindle-shaped sporozoites (10-16 x 1-2 µm) with prominent central nuclei.

Site of infection: In birds, the parasites do not undergo exo-erythrocytic multiplication in hepatocytes (like mammalian species) but rather in cells of the reticulo-endothelial system (and the haemopoietic system for the subgenus *Huffia*). Primary meronts (cryptozoic and metacryptozoic) often develop in macrophages and fibroblasts in the skin, but they may occur in numerous organs. Secondary meronts (phanerozoic) develop in endothelial cells of capillaries in various tissues, especially in the brain for some species. Erythrocytic merogony occurs in cells in the circulatory system, with dividing meronts lysing host cells while gametocytes are longer-lasting persistent stages. In mosquito vectors, fertilization of exflagellated microgametes and robust macrogametes occurs in the gut lumen. The resultant ookinete is motile and penetrates the gut to form an oocyst on the outer wall. Mature oocysts release sporozoites into the haemocoel where they invade the salivary glands. Infections have been recorded in numerous bird species belonging to many different families and orders. In general, host specificity has not usually been observed for individual host species, but is often considered to be operational at the level of host family and even order. Parasite species in birds demonstrate broad host specificities, with some species considered to be regionally specific infecting many sympatric bird species. Parasite

species richness is greatest in Passeriformes, Galliformes, Columbiformes, Coraciiformes and Piciformes, medium in Ciconiiformes, Anseriformes, Falconiformes, Gruiformes, Charadriiformes and Strigiformes, and poorest in relatively old groups such as Sphenisciformes, Struthioniformes, Tinamiformes, Pelecaniformes, Turniciformes, Musophagiformes, Coliiformes and Trogoniformes. Infections have been found in birds from all landscape regions (from mountains to shores), often spanning multiple zoogeographic regions: being most prevalent in Nearctic (North America), Palearctic (Europe and Asia = Eurasia), Ethiopian/African (sub-Saharan Africa) and Oriental (India, South-East Asia, Western Indonesia) regions, and poorest in Australasian (Australia, Eastern Indonesia, New Guinea, New Zealand) and Neotropical (South America) regions. The vast majority of parasite species have been recorded in birds in tropical or subtropical countries or in Holarctic migrants overwintering in warmer regions, but several species have become widespread cosmopolitan parasites in many bird species throughout the world. The parasites exhibit greater host specificity for their invertebrate vectors (which act as definitive hosts), being found only in mosquitoes of the family Culicidae (genera *Aedes*, *Anopheles*, *Coquillettidia*, *Culisetta*, *Culex*, *Mansonia*, *Psorophora*, *Theobaldia* and *Wyeomyia*). Some avian *Plasmodium* spp. may develop in up to 26 culicid species, while others only develop in 1-2 culicid species.

Pathogenesis: Many *Plasmodium* infections in birds are asymptomatic and have not been associated with any clinical signs, but several species may cause mild-severe episodic disease, with outbreaks involving mortalities recorded in domestic poultry and waterfowl, captive and aviary birds and wild bird populations. The parasites may cause disease either by merogony within tissues causing lesions or by merogony within erythrocytes causing haemolytic anaemia, both possibly contributing to ischaemia. Infections proceed through 3 phases of infection corresponding to pre-erythrocytic, erythrocytic and post-erythrocytic merogony. Initial pre-erythrocytic generations usually cause little damage as the parasites are sparse and develop rapidly eliciting few inflammatory reactions. Subsequent erythrocytic generations occur more frequently over protracted periods sometimes resulting in chronic conditions but often only resulting in low chronic parasitaemias. However, merozoites from earlier phases may undergo secondary post-erythrocytic merogony in host tissues which cause greater damage due to their larger size and persistence. All developmental stages may contribute to clinical disease characterized by circulatory perturbations. Blood stages have been associated with haemolytic anaemia, exacerbated by erythrophagocytosis by reticuloendothelial cells with enlargement and whitening of the spleen and liver and the accumulation of haemozoin pigment in organs. Persistent intra-erythrocytic gametocytes vary in their effect on host cells, and only some species cause hypertrophy, vacuolation and/or nuclear displacement. Tissue stages cause the most serious pathology by blocking capillaries in various organs (including the brain for some species) with downstream ischaemia due to the disrupted blood supply resulting in anoxia, cell death, necrosis, oedema, cellular infiltrates, and sometimes cerebral paralysis (e.g. *P. gallinaceum*, *P. cathemerium*, *P. durae*, *P. lophorae*, *P. elongatum*, *P. octamerium*). Post-mortem findings include anaemia, splenomegaly (occasionally with infarcts), hepatomegaly, and pigment deposits in many visceral organs. It has often been speculated that subclinical infections may impact on host fitness by reducing competitiveness, feeding efficiency, nutrition, reproduction, immunology and behaviour (such as migration or irruption). Infections in birds are often marked by their recrudescence due to the resumption of erythrocytic merogony, or by relapses due to the activation of exo-erythrocytic merogony (rather than the reactivation of dormant sporozoites (hypnozoites) as occurs in mammals). Relapses of avian malaria may be seasonal (especially in spring) or nonseasonal (usually in countries with warm climates). Infections occur in birds of all ages, with young birds being more susceptible but adult birds having greater exposure. Chronic infections may last for the lifespan of the bird species, generally 2-10 years depending on size (smallest birds with shortest lifespans). Outbreaks have also been associated with birds kept in stressful situations (captivity, intensive husbandry, poor nutrition) presumably due to their reduced immunocompetence. Immunological studies have shown birds to vary considerably in their natural innate immunity (resistance/susceptibility to infection) and in their acquired immunity (humoral and cellular responses) following infection. It is thought that birds may develop premunitive immunity whereby small numbers of parasites persist but elicit strong protection against disease from challenge or super-infections.

Developmental cycle and mode of transmission: Avian *Plasmodium* spp. have indirect heteroxenous (2-host) life-cycles involving serial transmission between birds (acting as intermediate hosts in which parasites undergo asexual proliferation) and mosquito vectors (acting as definitive hosts in which parasites undergo sexual reproduction). Infective sporozoites injected into birds by feeding mosquitoes invade reticulo-endothelial cells and form exo-erythrocytic cryptozoic meronts that produce numerous merozoites. The merozoites are not infective to erythrocytes but infect macrophages forming exo-erythrocytic metacryptozoic meronts that produce numerous merozoites. These merozoites are highly infective for various host cells and may lead to several different outcomes. Some infect other macrophages leading to a new cycle of metacryptozoic merogony. Some infect red blood cells leading either directly to gametocyte formation but more usually leading to erythrocytic merogony. Some infect capillary endothelial cells in host tissues forming secondary exo-erythrocytic phanerozoic meronts that produce numerous merozoites. Erythrocytic merogony is cyclic (periodicity of 24-36 hours) with invading merozoites transforming into pleomorphic trophozoites that mature into meronts (sometimes called schizonts) to produce numerous merozoites. These merozoites may infect additional red blood cells to undergo further merogony or to begin gamogony forming sexually dimorphic gametocytes, or they may infect endothelial cells and form post-erythrocytic phanerozoic meronts whose progeny may initiate new cycles of erythrocytic merogony and gamogony. The prepatent period (from the time of infection to the first formation of gametocytes) is usually < 120 hours. Infections are transmitted to mosquitoes when they feed on bird blood and ingest gametocytes in red blood cells. Only female mosquitoes feed on blood as they require high protein diets in order to produce eggs. Male microgametocytes undergo exflagellation in the gut to release motile microgametes which fertilize female macrogametes. The resultant zygote (ookinete) moves through the gut wall to form an encapsulated oocyst on the outer wall. The oocyst forms several germinative centres that divide asexually

(sporogony) to form many hundreds of sporozoites that are liberated into the haemocoel and penetrate the adjacent salivary glands. Infections are transmitted to birds when sporozoites and saliva (with anticoagulant properties) are injected during feeding (inoculative transmission). Avian *Plasmodium* spp. usually have a faster rate of sexual development in mosquitoes than mammalian *Plasmodium* spp. (7 days cf. 10-12 days) and once a mosquito is infected, it is infected for life and continues to transmit infections over its remaining lifespan. Predisposing factors for infections in birds include species with large body sizes, long nestling periods, open or ground nests, sedentary activities, and gregarious colony-forming behaviours. Many bird species undertake seasonal migrations to feed and/or breed, but infections are usually not associated with breeding seasons, but rather with 'over-wintering' sites (often near lakes where vectors abound) or in tropical/subtropical regions (where vectors are active all year round).

Differential diagnosis: Infections are conventionally diagnosed by the direct microscopic detection of intra-erythrocytic parasites in thick or thin peripheral blood smears stained with Romanowsky's stains (Giemsa, Leishman's or Field's stains). Test sensitivity may be poor due to very low parasitaemias or diurnal changes in parasitaemias. Host tissues may be collected at autopsy and examined as impression smears or histological sections for exo-erythrocytic meronts. Several experimental studies have used fluorochrome labels and *in situ* DNA hybridization techniques to help reveal parasites, but they have not been developed for routine use. Infections in vectors may be detected by trapping mosquitoes and examining squash or gut preparations for developing oocysts or salivary gland extracts for sporozoites. There are also occasional reports of infections being detected by *in vivo* culture following the subinoculation of samples into susceptible bird species. Several immunoserological tests have been developed to detect host antibodies (fluorescent-antibody tests, haemagglutination tests, enzyme immunoassays) or parasite antigens (immunochromatography), but they have varied in their sensitivity and specificity. Molecular biological techniques have been used to detect and characterize parasites and infer phylogenetic relationships following the polymerase chain reaction (PCR) amplification of nuclear genes (notably small subunit (18S) ribosomal DNA) and mitochondrial genes (particularly cytochrome b).

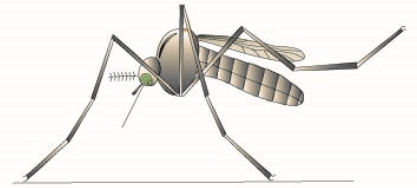
Treatment and control: Various antimalarial drugs have been used to treat infections in birds, including primaquine, chloroquine, proguanil and pyrimethamine, despite some indications that drug-resistance may become problematic. It is recommended that combinations of drugs be used to target both tissue and blood stages, particularly since the former is responsible for much of the pathology associated with bird malaria as well as the persistence of infections. For example, treatment with both primaquine and chloroquine is recommended as primaquine is active against tissue stages while chloroquine is active against blood stages. Medications are usually administered to birds via medicated water supplies or by oral intubation. It is important that birds be isolated and screened for infections, particularly when restocking poultry houses, and translocating exotic species for zoos and aviaries. At present, the best preventive measures involve isolating birds from vectors using physical barriers (screens) and/or chemical barriers (residual insecticides) and undertaking local vector control programmes targeting standing water sources for mosquito larvae, resting sites for adult mosquitoes, and even releasing sterile males to reduce reproduction rates.

Plasmodium (avian species)

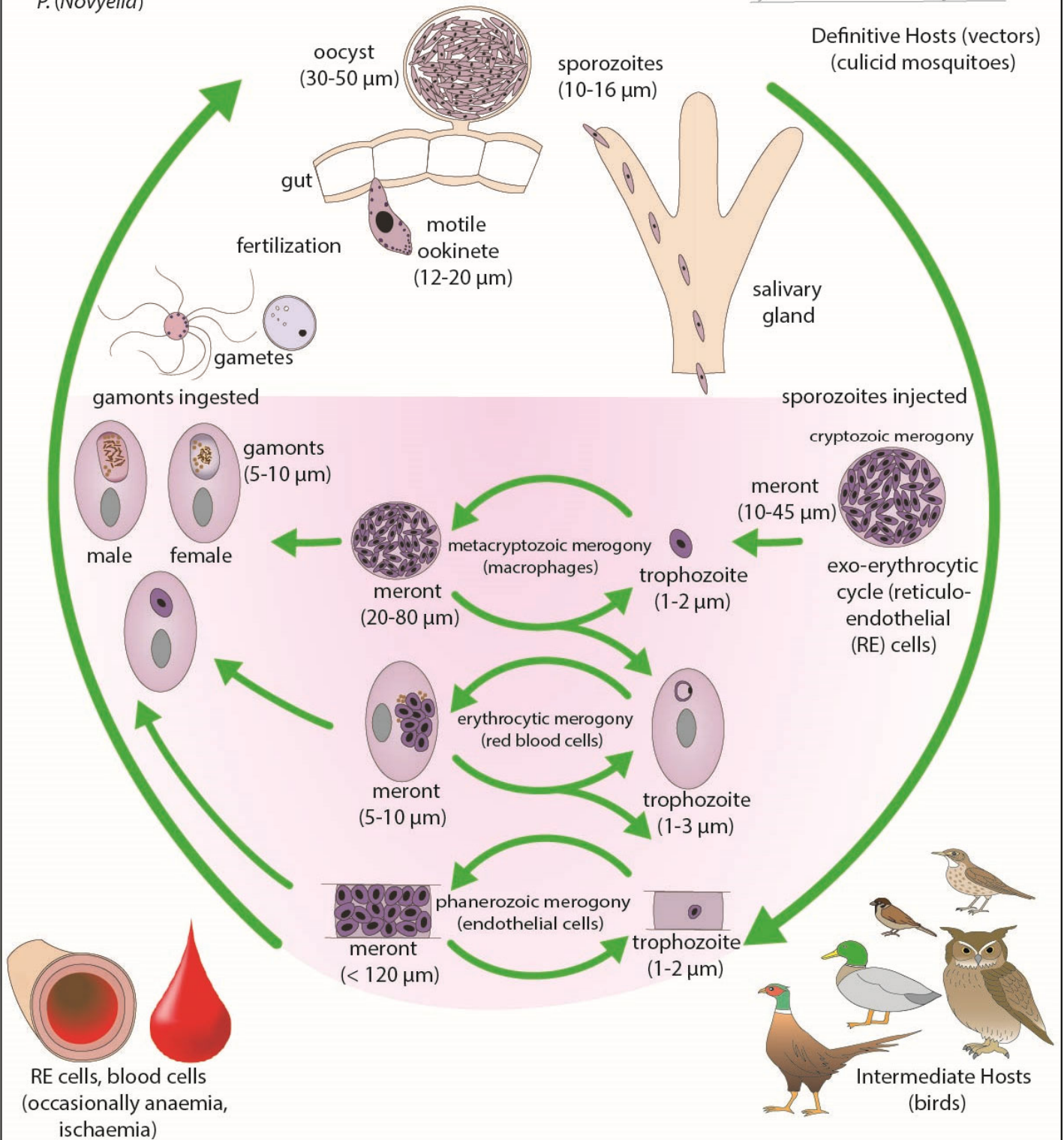
5 subgenera in birds:

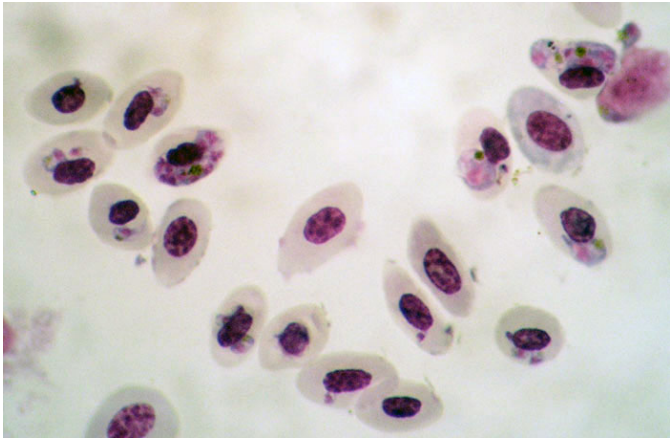
- P. (Haemamoeba)*
- P. (Bennettinia)*
- P. (Hoffia)*
- P. (Giovannolaia)*
- P. (Novyella)*

heteroxenous (2-host) cycle
vector-borne transmission
(sexual development in invertebrate host)
(asexual development in vertebrate host)

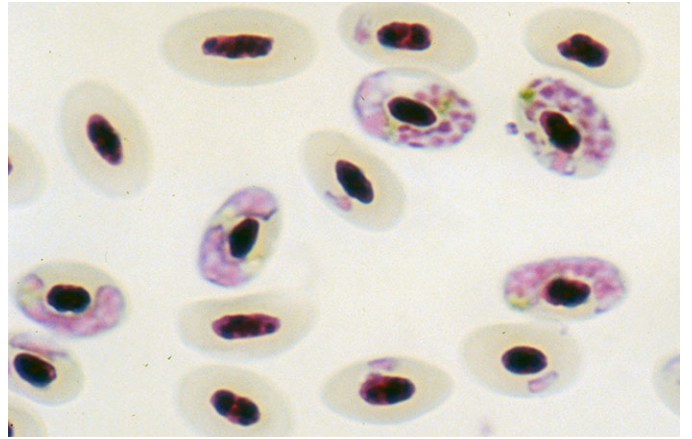


Definitive Hosts (vectors)
(culicid mosquitoes)

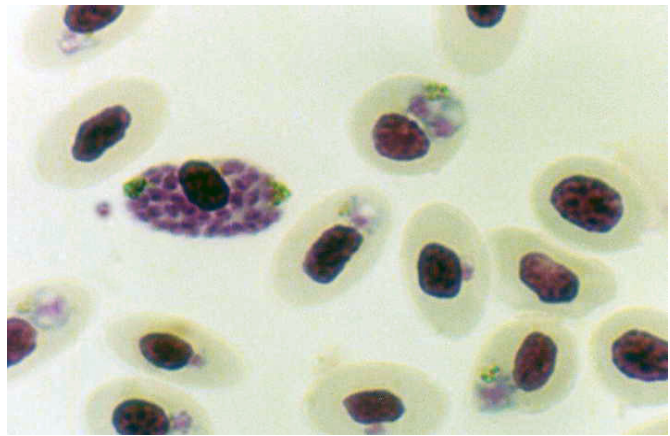




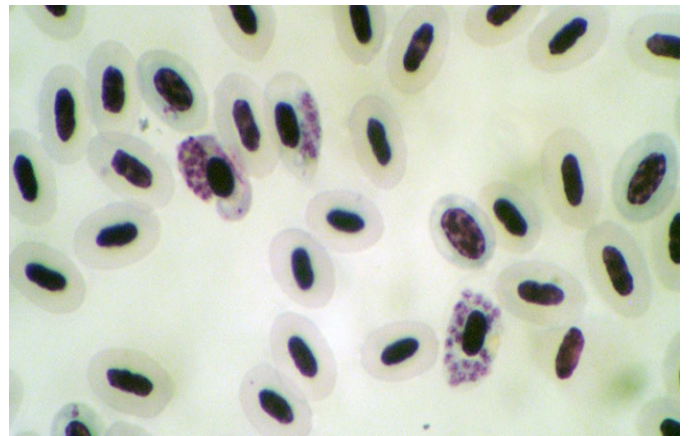
Plasmodium stages in bird blood



Plasmodium stages in bird blood



Plasmodium stages in bird blood



Plasmodium stages in bird blood