

***Plasmodium* (mammalian 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 malaria in humans, and 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 (monozygic 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>Progarinia</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.

Humans are hosts for four main *Plasmodium* species, although they can occasionally be infected by other species from nonhuman primates. Most species are confined to tropical and subtropical areas depending on the distribution of their insect vectors. On a global basis, ~40% of human infections are due to *P. falciparum*, ~10% are due to *P. malariae*, ~50% to *P. vivax* and <1% to *P. ovale*. It is estimated by global healthcare agencies that some 300 million people become infected each year, with around 1.5 million deaths.

<i>Plasmodium</i> species	Mammalian intermediate hosts (IH)	Periodicity* (erythrocytic cycle)	Pathogenicity	Definitive hosts (DH) (vectors)	Geographic distribution
Subgenus: <i>Lavernia</i> (large erythrocytic schizonts, crescentic gametocytes, in primates)					
<i>P. (L.) falciparum</i> [type species]	Primates: hominid (human, gorilla, chimpanzee, bonobo); aotid (night monkey)	tertian (48 hrs)	high	Diptera: culicid (<i>Anopheles</i> spp.)	worldwide in tropics, subtropics & temperate regions
Subgenus: <i>Plasmodium</i> (large erythrocytic schizonts, round gametocytes, in primates)					
<i>P. (P.) malariae</i> [type species]	Primates: hominid (human, chimpanzee), atelid (howler monkey)	quartan (72 hrs)	low	Diptera: culicid (<i>Anopheles</i> spp.)	scattered in tropics and subtropics
<i>P. (P.) ovale</i> [incl. subspp. <i>curtisi</i> , <i>wallikeri</i>]	Primates: hominid (human, chimpanzee)	tertian (49-50 hrs)	moderate	Diptera: culicid (<i>Anopheles</i> spp.)	mainly tropical Africa
<i>P. (P.) vivax</i> [incl. subspp. <i>vivax</i> , <i>hibernans</i> , <i>chesson</i> , <i>multinucleatum</i>]	Primates: hominid (human, orangutan, chimpanzee), atelid (howler monkey), callitrichid (tamarin)	tertian (48 hrs)	variable	Diptera: culicid (<i>Anopheles</i> spp.)	worldwide in tropics and subtropics

*cycles first classified by ancient Romans who did not recognize zero, thus 'tertian' enigmatically refers to a 2-day cycle and 'quartan' to a 3-day cycle.

Another 60 *Plasmodium* spp. have previously been described in mammals, mostly primates and rodents, predominantly on the basis of host occurrence and parasite morphology. Contemporary molecular phylogenetic studies are helping to unlock their taxonomic affinities and resolve their evolutionary origins.

<i>Plasmodium</i> species	Mammalian intermediate hosts (IH)	Periodicity (erythrocytic cycle)	Pathogenicity	Definitive hosts (DH) (vectors)	Geographic distribution
Subgenus: <i>Lavernia</i> (large erythrocytic schizonts, crescentic gametocytes, in primates)					
<i>P. (L.) "adleri"</i> (= <i>P. GorA</i>)	Primates: hominid (gorilla)				West Africa
<i>P. (L.) billbrayi</i>	Primates: hominid (chimpanzee)				Central Africa
<i>P. (L.) billcollinsi</i>	Primates: hominid (chimpanzee)				Central Africa
<i>P. (L.) "blacklocki"</i> (= <i>P. GorB</i>)	Primates: hominid (gorilla)				West Africa
<i>P. (L.) "gaboni"</i>	Primates: hominid (chimpanzee)				West Africa
<i>P. (L.) lomamiensis</i>	Primates: hominid (bonobo)				West Africa
<i>P. (L.) praefalciparum</i>	Primates: hominid (gorilla)				West Africa
<i>P. (L.) reichenowi</i>	Primates: hominid (chimpanzee, gorilla)	tertian (48 hrs)	low	Diptera: culicid (<i>Anopheles</i> spp.)	West Africa
Subgenus: <i>Plasmodium</i> (large erythrocytic schizonts, round gametocytes, in primates)					
<i>P. (P.) brasilianum</i>	Primates: cercopithecoid (spider monkey), aotid (night monkey), pitheciid (uakari), cebid (capuchin, squirrel monkey), atelid (woolly monkey, howler monkey)	quartan (72 hrs)	moderate	Diptera: culicid (<i>Anopheles cruzi, freeborni, maculatus, stephensi, gambiae</i>)	South America
<i>P. (P.) coatneyi</i>	Primates: cercopithecoid (macaque, leaf monkey)	tertian (48 hrs)	low	Diptera: culicid (<i>Anopheles hackeri, dirus</i>)	South-East Asia
<i>P. (P.) cynomolgi</i> [incl. subspp. <i>bastianellii, ceylonensis, cyclopis, cynomolgi</i>]	Primates: cercopithecoid (macaque, leaf monkey, langur), rarely hominid (human)	tertian (48 hrs)	low	Diptera: culicid (<i>Anopheles balabacensis, atroparvus, freeborni, maculatus, quadrimaculatus, stephensi, dirus, hackeri, elegans, introlatus, dirus</i>)	South-East Asia
<i>P. (P.) eylesi</i>	Primates: hylobatid (gibbon)	tertian (48 hrs)	nil		South-East Asia
<i>P. (P.) fieldi</i>	Primates: cercopithecoid (macaque)	tertian (48 hrs)	nil	Diptera: culicid (<i>Anopheles balabacensis, maculatus, stephensi, hackeri, introlatus, dirus</i>)	South-East Asia
<i>P. (P.) fragile</i>	Primates: cercopithecoid (macaque)	tertian (48 hrs)	high	Diptera: culicid (<i>Anopheles balabacensis, elegans, dirus</i>)	India, Sri Lanka
<i>P. (P.) georgesi</i>	Primates: cercopithecoid (mangabey)				Central Africa

<i>P. (P.) gonderi</i>	Primates: cercopithecoid (mangabey, drill)	tertian (48 hrs)	low	Diptera: culicid (<i>Anopheles balabacensis, freeborni, maculatus, stephensi, dirus</i>)	West Africa
<i>P. (P.) hylobati</i>	Primates: hylobatid (gibbon)	tertian (48 hrs)			South-East Asia
<i>P. (P.) inui</i> [incl. subspp. <i>inui, shortii</i>]	Primates: cercopithecoid (macaque, leaf monkey, bonnet monkey, toque monkey)	quartan (72 hrs)	low	Diptera: culicid (<i>Anopheles balabacensis, maculatus, stephensi, elegans, leucosphyrus, introlatus, dirus</i>)	South-East Asia
<i>P. (P.) jeffreyi</i>	Primates: hylobatid (gibbon)	tertian (48 hrs)	nil		South-East Asia
<i>P. (P.) knowlesi</i> [incl. subspp. <i>edelsoni, knowlesi</i>]	Primates: cercopithecoid (long-tailed macaque, pig-tailed macaque, Old World macaques, banded leaf monkey, olive baboon), callitrichid (New World marmoset), occasionally hominid (human)	quotidian (24 hrs)	moderate	Diptera: culicid (<i>Anopheles balabacensis, hackeri, dirus</i>)	Asia
<i>P. (P.) petersi</i>	Primates: cercopithecoid (mangabey)				Central Africa
<i>P. (P.) pitheci</i>	Primates: hominid (orangutan)	tertian (48 hrs)	nil		Indonesia
<i>P. (P.) rhodaini</i>	Primates: hominid (chimpanzee, gorilla)	quartan (72 hrs)	?		Africa
<i>P. (P.) schwetzi</i>	Primates: hominid (chimpanzee, gorilla)	tertian (48 hrs)	nil	Diptera: culicid (<i>Anopheles</i> spp.)	Africa
<i>P. (P.) simium</i>	Primates: atelid (howler monkey, spider monkey), cebid (squirrel monkey)	tertian (48 hrs)	low	Diptera: culicid (<i>Anopheles cruzi, stephensi</i>)	Brazil
<i>P. (P.) simiovale</i>	Primates: cercopithecoid (macaque)	tertian (48 hrs)	moderate	Diptera: culicid (<i>Anopheles balabacensis, maculatus, dirus</i>)	Sri Lanka
<i>P. (P.) silvaticum</i>	Primates: hominid (orangutan)	tertian (48 hrs)			Indonesia
<i>P. (P.) youngi</i>	Primates: hylobatid (gibbon, siamang)	tertian (48 hrs)	low	Diptera: culicid (<i>Anopheles</i> spp.)	South-East Asia
Subgenus: <i>Vinckeia</i> (small erythrocytic schizonts, round gametocytes, in antelopes, rodents and other mammals (except primates other than lemurs))					
<i>P. (V.) aegyptensis</i>	Rodentia: murid (grass rats)				North Africa
<i>P. (V.) anomaluri</i>	Rodentia: anomalurid (scaly-tailed squirrel)		nil	Diptera: culicid (<i>Anopheles machardyi</i>)?	East Africa
<i>P. (V.) atheruri</i>	Rodentia: hystrioid (porcupine)	quotidian (24 hrs)	nil	Diptera: culicid (<i>Anopheles smithii</i>)	West Africa
<i>P. (V.) berghei</i>	Rodentia: murid (rat, mouse, jerboa, hamster), myoxid (dormouse), heteromyid (kangaroo rat), sciurid (squirrel); Chiroptera: pteropid (fruit bat)	quotidian (22-25 hrs)	moderate	Diptera: culicid (<i>Anopheles</i> spp.)	originally from West Africa
<i>P. (V.) booliati</i>	Rodentia: sciurid (flying squirrel)		nil		Malaysia

	squirrel)				
<i>P. (V.) brodeni</i>	Macroscelidea: macroscelidid (elephant shrew)	tertian (50 hrs)	nil		East Africa
<i>P. (V.) brucei</i>	Artiodactyla: bovid (duiker)		low	Diptera: culicid (<i>Anopheles</i> spp.)	East Africa
<i>P. (V.) bubalis</i> [<i>type species</i>]	Artiodactyla: bovid (water buffalo)	quartan (72 hrs)	low	Diptera: culicid (<i>Anopheles</i> spp.)	India
<i>P. (V.) bucki</i>	Primates: lemurid (lemur)				Madagascar
<i>P. (V.) cephalophi</i>	Artiodactyla: bovid (duiker)	quartan (72 hrs)	low		Africa
<i>P. (V.) chabaudi</i> [incl. subspp. <i>chabaudi</i> , <i>adami</i>]	Rodentia: murids (rat, mouse)	quotidian (24 hrs)	low	Diptera: culicid (<i>Anopheles</i> spp.)	originally from West Africa
<i>P. (V.) coulangesi</i>	Primates: lemurid (lemur)				Madagascar
<i>P. (V.) cyclopsi</i>	Chiroptera: hipposiderid (leaf-nosed bat)				West Africa
<i>P. (V.) foleyi</i>	Primates: lemurid (lemur)				Madagascar
<i>P. (V.) girardi</i>	Primates: lemurid (lemur)		low		Madagascar
<i>P. (V.) inopinatum</i>	Rodentia: murid (rat)				Europe
<i>P. (V.?) joyeuxi</i> [maybe <i>Hepatocystis</i> <i>kochi</i>]	Primates: cercopithecoid (guenon)				West Africa
<i>P. (V.) landauae</i>	Rodentia: anomalurid (scaly-tailed squirrel)				West Africa
<i>P. (V.) lemuris</i>	Primates: lemurid (lemur)		low		Madagascar
<i>P. (V.) malagasi</i>	Primates: lemurid (lemur)				Madagascar
<i>P. (V.) odocoilei</i>	Artiodactyla: cervid (white tailed deer)			Diptera: culicid (<i>Anopheles</i> <i>punctipennis</i>)	North America
<i>P. (V.) percygarnhami</i>	Primates: lemurid (lemur)				Madagascar
<i>P. (V.) pulmophilum</i>	Rodentia: anomalurid (scaly-tailed squirrel)				West Africa
<i>P. (V.) roussetti</i>	Chiroptera: pteropodid (fruit bat)		nil		West Africa
<i>P. (V.) sandoshami</i>	Dermoptera: cyanocephalid (colugo)	quartan (72 hrs)	low	Diptera: culicid (<i>Anopheles</i> spp.)	Malaya
<i>P. (V.) traguli</i>	Artiodactyla: tragulid (mouse deer)		low	Diptera: culicid (<i>Anopheles</i> spp.)	Malayasia, Indonesia
<i>P. (V.) uilenbergi</i>	Primates: lemurid (lemur)				Madagascar
<i>P. (V.) vinckei</i> [incl. subspp. <i>vinckei</i> , <i>petteri</i> , <i>lentum</i> , <i>brucechwatti</i>]	Rodentia: murids (rat, mouse)	quotidian (24 hrs)	low	Diptera: culicid (<i>Anopheles</i> spp.)	originally from West Africa
<i>P. (V.) voltaicum</i>	Chiroptera: pteropodid (fruit bat)		nil	Diptera: culicid (<i>Anopheles</i> spp.)	West Africa
<i>P. (V.) watteni</i>	Rodentia: sciurid (flying squirrel)				Taiwan
<i>P. (V.) yoelii</i> [incl. subspp. <i>killicki</i> , <i>nigeriensis</i> , <i>yoelii</i>]	Rodentia: murids (rat, mouse)	quotidian (22-25 hrs)	high	Diptera: culicid (<i>Anopheles</i> spp.)	originally from West Africa
Unplaced or uncertain reports (<i>species inquirenda, nomen dubium</i>)					
<i>P. tyrio</i>	Pholidota: manid (pangolin)	?	-		Asia
<i>P. roubaudi</i>	Carnivora: mustelid (zorilla)		-		Africa
<i>P. narayani</i>	Carnivora: mustelid (otter)		-		India
<i>P. equi</i>	Perissodactyla: equid (horse)	now thought to be a piroplasm			
<i>P. canis</i>	Carnivora: canid (dog)	now thought to be <i>Babesia canis</i>			

All mammalian *Plasmodium* species complete their developmental cycles in anopheline mosquitoes where gamogony and sporogony is completed, however, not all *Anopheles* species are able to support and transmit infections. Observations and experiments on vector specificity and competence are by no means comprehensive for individual parasite species, and a range of species have been implicated in their transmission. It is worth noting that individual mosquito species may transmit multiple parasite species, thus facilitating concurrent/concomitant infections. It is also worth remembering that once a mosquito is infected, it is infected for the remainder of its life and may transmit infections with every subsequent meal.

Invertebrate vectors for human malaria	<i>Plasmodium</i> species				
	<i>P. falciparum</i>	<i>P. malariae</i>	<i>P. ovale</i>	<i>P. vivax</i>	<i>P. knowlesi</i>
<i>Anopheles aconitus</i>	+	+	-	-	-
<i>A. albimanus</i>	+	-	+	+	-
<i>A. albitarsis</i>	+	-	-	+	-
<i>A. algeriensis</i>	+	-	-	+	-
<i>A. annularis</i>	+	-	-	+	+
<i>A. annulipes</i>	-	+	-	-	-
<i>A. aquasalis</i>	+	-	-	+	-
<i>A. argyritarsis</i>	+	-	-	-	-
<i>A. atropos</i>	-	-	-	+	-
<i>A. aztecus</i>	-	+	-	-	+
<i>A. bachmani</i>	-	-	-	+	-
<i>A. balabacensis</i>	+	-	-	-	-
<i>A. bancrofti</i>	+	-	-	-	-
<i>A. barbirostris</i>	+	-	-	+	-
<i>A. bellator</i>	-	-	-	+	-
<i>A. claviger</i>	+	+	-	+	-
<i>A. crucians</i>	+	-	-	+	-
<i>A. cruzi</i>	+	-	-	-	-
<i>A. culicifacies</i>	+	+	-	+	-
<i>A. darlingi</i>	+	+	-	+	-
<i>A. dirus</i>	-	-	-	+	-
<i>A. dthali</i>	+	-	-	-	-
<i>A. farauti</i>	+	-	-	+	-
<i>A. fluviatilis</i>	+	+	-	+	-
<i>A. freeborni</i>	+	+	-	+	-
<i>A. fuliginosus</i>	-	+	-	-	-
<i>A. funestus</i>	+	+	+	-	-
<i>A. gambiae</i>	+	+	+	-	-
<i>A. hackeri</i>	-	-	-	-	+
<i>A. hancocki</i>	+	-	-	-	-
<i>A. hargreavesi</i>	+	-	-	-	-
<i>A. hyrcanus</i>	-	+	-	+	-
<i>A. jeyporiensis</i>	+	+	-	+	-
<i>A. karwari</i>	+	-	-	-	-
<i>A. kochi</i>	+	-	-	+	+
<i>A. koliensis</i>	+	-	-	-	-
<i>A. kweiyangensis</i>	+	-	-	-	-
<i>A. labranchiae</i>	+	+	+	+	+
<i>A. lesteri</i>	+	-	-	-	-
<i>A. letifer</i>	+	-	-	-	+
<i>A. leucosphyrus</i>	+	-	-	-	-
<i>A. lindsayi</i>	-	+	-	-	-
<i>A. ludlowi</i>	+	+	-	+	-
<i>A. maculatus</i>	+	+	-	+	+
<i>A. maculipennis</i>	+	-	-	+	-
<i>A. mangyanus</i>	+	-	-	-	-
<i>A. melas</i>	+	+	-	-	-
<i>A. messeae</i>	-	+	-	-	-
<i>A. minimus</i>	+	+	-	+	-
<i>A. moucheti</i>	+	+	-	-	-
<i>A. multicolor</i>	+	-	-	-	-

<i>A. nigerrimus</i>	+	-	-	-	-
<i>A. nili</i>	+	-	-	-	-
<i>A. nuneztovari</i>	+	-	-	-	-
<i>A. oswaldi</i>	+	-	-	-	-
<i>A. pattoni</i>	+	-	-	-	-
<i>A. pharoensis</i>	+	-	-	+	-
<i>A. philippinensis</i>	+	-	-	+	+
<i>A. plumbeus</i>	+	+	-	+	-
<i>A. pseudopunctipennis</i>	+	-	-	+	-
<i>A. pulcherrimus</i>	+	-	-	-	-
<i>A. punctimacula</i>	+	-	-	+	-
<i>A. punctipennis</i>	+	+	-	+	-
<i>A. punctulatus</i>	+	+	-	+	-
<i>A. pujutensis</i>	-	-	-	-	+
<i>A. quadrimaculatus</i>	+	+	+	+	-
<i>A. sacharovi</i>	+	+	-	-	-
<i>A. sergenti</i>	+	-	-	-	-
<i>A. sinensis</i>	+	-	-	-	-
<i>A. splendidus</i>	-	+	-	-	-
<i>A. stephensi</i>	+	+	-	+	+
<i>A. strodei</i>	-	-	-	+	-
<i>A. subpictus</i>	+	-	-	+	-
<i>A. sundaicus</i>	+	+	-	+	+
<i>A. superpictus</i>	+	-	+	-	-
<i>A. tessellatus</i>	+	+	-	-	-
<i>A. umbrosus</i>	+	-	-	+	-
<i>A. vagus</i>	+	-	-	+	+
<i>A. varuna</i>	+	+	-	+	-
<i>A. walkeri</i>	+	-	-	-	-
<i>A. wilmorei</i>	-	-	-	+	-

Parasite morphology: Malarial parasites form four developmental stages in humans (hepatic meronts (schizonts) and then intraerythrocytic trophozoites, meronts (schizonts) and gamonts) and three developmental stages in mosquitoes (ookinetes, oocysts and sporozoites). Liver meronts appear as clusters of small basophilic bodies (merozoite nuclei) located within host hepatocytes, measuring 40-80 µm in diameter when mature. Intraerythrocytic stages consist of small rounded trophozoites (ring forms) measuring 1-2 µm in diameter, amorphous multinucleate meronts measuring up to 7-8 µm in length, and microgametocytes (male) and macrogametocytes (female) ranging in length from 7-14 µm. The morphological characteristics (size, shape and appearance) of the blood stages are characteristic for each *Plasmodium* spp. Infected erythrocytes may also exhibit unique inclusions: Maurer's clefts associated with protein trafficking in cells infected with *P. falciparum*; and Schuffner's dots associated with caveola-vesicle complexes in cells infected with *P. ovale* or *P. malariae*. In the mosquito, long slender microgametes (15-25 µm in length) produced by exflagellation fertilize the rounded macrogametes to form motile ookinetes (15-20 x 2-5 µm) which migrate through the gut wall to form ovoid oocysts (up to 50 µm in diameter) on the exterior surface. The oocysts produce thousands of thin elongate sporozoites (12-15 x 1 µm) which ultimately infect the salivary glands.

Site of infection: Sporozoites injected by mosquitos into the hosts bloodstream move rapidly to the liver where they first undergo massive amplification by asexual exoerythrocytic merogony (schizogony) in liver cells. Some sporozoites of *P. vivax* and *P. ovale* may also exhibit arrested development in the liver forming hypnozoites (dormozoites) which are quiescent stages responsible for malaria relapses. Merozoites released from the liver then invade erythrocytes and transform into trophozoites which undergo merogonous (schizogonous) division. This cycle of asexual multiplication in the red blood cells occurs with regular periodicity. Ultimately, intraerythrocytic gametocytes are formed which do not divide further in the human host. When ingested by mosquitoes during feeding, mature gametocytes undergo fertilization in the mosquito gut forming motile ookinetes which migrate through the gut wall to form oocysts. The oocyst then produces hundreds of sporozoites which migrate into the salivary glands where they remain a source of infection for the remainder of the mosquito's life.

Pathogenesis: There are five *Plasmodium* spp. which infect humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Infection with these parasites results in an acute febrile illness known as malaria. Disease occurs through several pathways, some of which are species specific. One common feature is the pathology caused by parasites multiplying within host erythrocytes resulting in their rupture and the release of parasite material causing periodic fever/chill cycles. The disease malaria is characterized by its

long persistence in infected individuals in endemic areas, with characteristic recrudescences (*P. falciparum*, *P. malariae*, *P. knowlesi*) or relapses (*P. vivax*, *P. ovale*), sometimes after years of subclinical infection. Infection with *P. falciparum* causes the most severe clinical disease in humans frequently resulting in the death of susceptible individuals such as children, pregnant women and travellers. Clinical expression is characterized by cyclic paroxysms of fever/chills (produced by host inflammatory responses), haemolysis and erythrophagocytosis (resulting in anaemia), and organ hypoperfusion due to ischaemia (in the case of *P. falciparum* this arises through cytoadherence of infected cells to vascular endothelia), disseminated intravascular coagulation, erythrocyte rosetting, and haemozoin pigment accumulation. Vague prodromal signs may first develop prior to parasitaemia, including headache, anorexia and mild fever. Thereafter, characteristic febrile paroxysms and haemolytic anaemia develop and become progressively worse. Depending on the parasite species involved, severe complications may arise, including splenic rupture, cerebral signs, haemolytic anaemia, cardiac, pulmonary and renal failure. Paroxysms coincide with intraerythrocytic parasite developmental cycles (tertian = 2-day cycle, quartan = 3-day cycle) and may be accompanied by dizziness, nausea, vomiting, delirium, hepatosplenomegaly, leucopenia and thrombocytopenia. Infected cells are removed from the circulation by erythrophagocytosis during passage through the spleen. Some uninfected cells may also be removed if damaged or coated with debris or parasite antigens, thus exacerbating anaemic conditions. As the parasites grow within erythrocytes, they ingest and digest haemoglobin leaving behind characteristic dark pigment deposits, termed haemozoin (metabolic byproducts containing the indigestible iron-containing part of the haemoglobin molecule). Haemozoin may accumulate in organs and tissues resulting in impaired function. In the case of *P. falciparum*, infected erythrocytes develop sticky protrusions by which they adhere to vascular endothelial cells (cytoadherence), or clump together (rosetting), resulting in restricted blood flow (ischaemia) and end-organ anoxia. Molecular studies are slowly unravelling the complex host-parasite interactions involved in infection and disease. A range of molecules associated with parasite membranes or secreted from parasites (mostly from apical complex organelles) have been implicated in host cell attachment, invasion via tight junctions, parasitophorous vacuole formation and erythrocyte membrane alteration (including merozoite surface proteins (MSP), apical membrane antigens (AMA), subtilisin-like proteases, erythrocyte-binding antigens, Duffy-binding proteins, thrombospondin-related adhesive proteins (TRAP), knob-associated histidine-rich proteins, erythrocyte membrane-associated proteins (EMP), and various cytoadherence ligands). Several host receptor molecules have also been associated with parasite interactions (including CD36 on monocytes and endothelial cells, intracellular adhesion molecules (ICAM) in the brain, and chondroitin sulfate A (CSA) in the placenta).

Characteristics	<i>P. falciparum</i>	<i>P. malariae</i>	<i>P. ovale</i>	<i>P. vivax</i>
Type of malaria:	malignant tertian	benign quartan	benign tertian	benign tertian
Erythrocytic cycle:	48 hours	72 hours	48 hours	48 hours
Exoerythrocytic cycle:	9 days	14-15 days	9 days	8 days
Gametocytes:	crescent	ovoid	ovoid	ovoid
Disease:	recrudescant malaria		relapsing malaria	
Persistence:	continuance of infection by persistent erythrocytic forms		persistent exoerythrocytic schizogony and occurrence of hypnozoites	

P. falciparum causes malignant tertian malaria (sometimes known as malaria tropica), a severe disease with high parasitaemia because the parasites infect both young and mature erythrocytes. Unlike other human malaria species, however, erythrocytes infected with *P. falciparum* do not remain in the circulation for their entire developmental cycle as those containing mature trophozoites adhere to endothelial cells - this sequestration contributing to the severity of disease caused by *P. falciparum*. Symptoms appear 8-12 days after infection, being vague for 3-4 days (aches, pains, headache, fatigue, anorexia) then becoming acute in onset (fever, severe headache, nausea, vomiting, epigastric pain) with paroxysms exhibiting a periodicity of <48 hours. Schizogony often occurs in vessels in organs so disease severity may not correlate with parasitaemia. Various complications may arise due to ischaemic changes, including cerebral malaria (comatose), bilious remittent fever (hepatomegaly), dysentery (malabsorption diarrhoea), algid malaria (circulatory collapse) and blackwater fever (haemoglobinuria). Cerebral malaria occurs when capillaries are blocked by infected erythrocytes causing small haemorrhages which rapidly increase in size (conspicuous in retina). Symptoms include abnormal behaviour, fits, change in level of consciousness, coma, elevated cerebrospinal fluid (CSF) pressure, and classic decerebrate rigidity associated with hypoglycaemia. There are often neurological sequelae, such as hemiparesis, cerebral ataxia, cortical blindness, hypotonia, mental retardation, generalized spasticity, or aphasia.

P. malariae causes benign quartan malaria, a moderately severe disease with reduced parasitaemia because parasites only infect mature erythrocytes. The incubation period ranges from 27-40 days, with vague symptoms developing for 3-4 days (headache, photophobia, muscle aches, anorexia) followed by severe paroxysms of chills and fevers every 72 hours (long chill stage, more severe symptoms during fever stage). Proteinuria is common in infected individuals and a nephrotic syndrome may develop in children.

P. vivax and *P. ovale* cause benign tertian malaria, a moderately severe disease with high parasitaemia as both species preferentially infect reticulocytes (young erythrocytes). *P. vivax* infections are clinically similar to those of *P. ovale*, but they are more severe and relapses occur more frequently. Symptoms appear 7-10 days after infection and are vague for 3-4 days (headache, photophobia, muscle aches, anorexia), developing to steady or irregular low-grade fever then paroxysms with a regular 2-day cycle. Many patients exhibit slow irregular recovery over 3-8 weeks but relapses may occur after weeks/months/years when dormant zites

(hypnozoites) in the liver are reactivated. Splenomegaly is evident during the first few weeks of infection and leukopenia is usually present. Severe complications are rare but *P. vivax* infections can sometimes include cerebral malaria with neurological signs, haemolytic anaemia, renal failure and pulmonary failure.

Many other *Plasmodium* spp. infect a wide range of animal hosts (mammals, birds and reptiles) but comparatively few cause severe clinical disease (sometimes even when parasitaemias are very high). Many theories have been postulated as to why non-primate hosts are more refractory to disease, if not infection. Conventional dogma considered animals to be more tolerant of haemosporidian parasites by virtue of their longer co-evolutionary histories (with human hosts being late arrivals). However, there is little evidence to suggest that parasitism evolves from virulence upon initial contact to avirulence in long-established relationships. Studies on the capacity of parasites to cause disease (virulence) and the ability of hosts to ameliorate disease (resistance) have been attributed changes to habituation, adaptation, immuno-regulation, immuno-evasion, proliferation, reproduction, population density, infection kinetics and dynamics, transmission biology and vector competence. A negative correlation has been observed between parasite virulence and transmission (increasing one decreases the other) suggesting a trade-off between these two linked traits. Further studies on host-parasite molecular interactions may help unravel the many complexities involved in parasite virulence and host resistance.

Developmental cycle and mode of transmission: Malaria has long been recognized as one of the great fevers afflicting human populations throughout history. Infections were initially thought to be associated with exposure to bad air (*mal-aria*) or swamp gases (miasmas), but we now know infections are vector-borne, being transmitted by *Anopheles* mosquitoes which breed profusely in standing waters and swamps. Some 460 species of *Anopheles* are found worldwide, but malaria has only been shown to be transmitted by around 100 species, with 30 species considered to be the most important vectors. Infections are only transmitted by female mosquitoes - only females feed on blood as they require high protein diets in order to produce eggs. The mosquito is not simply a vector, it acts as the definitive host in which sexual reproduction of the parasite occurs. Gametocytes ingested during feeding undergo fertilization forming an ookinete which moves through the gut wall to form an oocyst on the outer wall. The oocyst undergoes sporogony to form numerous sporozoites which are liberated into the haemocoel and penetrate the adjacent salivary glands. Once a mosquito is infected, it is infected for life and may continue to transmit infections. Sporozoites are injected with saliva into vertebrate hosts during the process of feeding, as mosquito saliva has anticoagulant properties and prevents vertebrate blood from clotting in the mouthparts. Sporozoites are swept away in the host circulation and invade hepatocytes in the liver where they undergo exo-erythrocytic schizogony, producing hundreds to thousands of merozoites. In several *Plasmodium* spp., some sporozoites in the liver form hypnozoites (dormozoites) which can undergo arrested development for long periods, ultimately resuming development leading to relapses of infection. Merozoites released from the liver invade host red blood cells in the circulation and undergo erythrocytic schizogony, first forming ring-stage trophozoites and then meronts (schizonts) which divide to form several merozoites which are released by erythrolysis. Most species undergo several cycles of erythrocytic schizogony before merozoites invade red blood cells to form gametocytes (macro = female, micro = male). These stages are infectious to mosquitoes when ingested during feeding.

Differential diagnosis: Diagnosis is conventionally made by a combination of clinical symptomatology and the detection of parasites in thick or thin peripheral blood smears stained with one of the Romanowsky's stains, usually Giemsa's, Leishman's or Field's stains. Fluorochrome stains have also been used to detect parasites in blood samples, but the morphological features of the stages detected are often obscure. It is important that infections by individual parasite species be differentiated as it impacts on treatment and prognosis. All infections should be considered to be immediately life-threatening, and a complete clinical history should be taken (symptoms/signs), including history of travel, transfusions, recreational drug use, and previous medications (especially anti-malarials). A variety of immunological tests have been developed to detect host antibodies (fluorescent-antibody tests, haemagglutination tests, enzyme immunoassays) or parasite antigens (immunochromatography) in blood samples. While these tests have proven useful for preliminary screening, they have exhibited several problems in sensitivity and specificity. Molecular biological techniques using polymerase chain reaction (PCR) amplification of gene fragments are now under development and they have shown great potential not only for differential diagnosis but also for the detection of drug resistance. PCR targets have included nuclear genes [18S (small subunit) ribosomal DNA, 28S (large subunit) ribosomal DNA, adenylosuccinate lyase, nuclear elongation factor 2, lactate dehydrogenase, dihydrofolate reductase-thymidylate synthase], mitochondrial genes [cytochrome b, cytochrome oxidase 1] and plastid genes [caseinolytic protease C, protein synthesis elongation factor A].

Treatment and control: A variety of drugs have been developed for therapeutic (treatment) and prophylactic (preventive) use. While most enjoyed years of efficacy, there are now widespread problems with drug resistance amongst the parasites. Early explorers noticed that Peruvian Indians used brews from 'fever bark' (*Cinchona*) trees to stave off fevers. The active drug quinine was isolated from the bark around 1820 and this became the mainstay for malaria treatment throughout the world, essentially based on *Cinchona* tree plantations in tropical colonies. Supply shortages due to the World Wars prompted research on synthetic drugs. Pamaquine, mepacrine and chloroquine were developed in the 1930s, proguanil in the 1940s, and pyrimethamine in the 1950s. Chloroquine, in particular, was found to be highly effective, cheap to produce and had low toxicity. However, resistance to chloroquine emerged in the 1960s and soon spread around the world. Sulphonamides were developed in the 1960s, mefloquine and a series of related drugs in the 1970s, and artemisinin was discovered in a Chinese herbal remedy in the 1980s. A holistic and

strategic approach to the treatment of infected individuals is required based on whether suppressive, radical or preventive treatment is required, and the level of drug resistance present. Antimalarial drugs of choice are primaquine, chloroquine (despite the emergence of chloroquine-resistant strains), sulfadoxine, pyrimethamine, mefloquine, quinine, artemisinin and tetracycline. Preventive measures based on vector control programmes had many early successes (including those using DDT), but the rapid emergence of insecticide resistance (and the recognition of the toxicity of DDT and its prohibition) have led to the resurgence of malaria in many countries. At present, the best protection is the avoidance of mosquito bites, using screens, bed nets, insect repellents, and residual insecticide sprays.

Drug	TISSUE STAGES		BLOOD STAGES	
	primary	latent	schizonts	gametocytes
Quinine	-	-	+++	++ (early stage I-III)
Chloroquine	-	-	+++	++ (early stage I-III)
Proguanil	++	-	++	++
Pyrimethamine	++	+	++	+++ (reduces transmission)
Primaquine	++	+++	++	+++
Doxycycline	+	?	++	-
Mefloquine	-	-	+++	+ (early stage I-II)
Halofantrine	-	-	+++	-
Artemisinin	-	-	+++	++ (early stage I-III)
	causal prophylaxis	antirelapse radical cure	suppression clinical cure	prevent spread

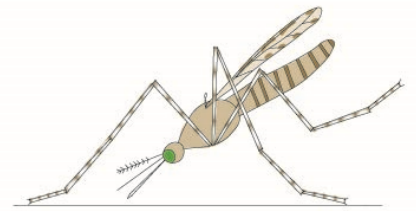
Clinical target		Drug	Main effect	
Non-resistant malaria	Attack	chloroquine	blood schizonts	
	Recrudescence (<i>P.f./P.m.</i>)	chloroquine	blood schizonts	
	Recurrence (<i>P.v./P.o.</i>)	primaquine	tissue zoites	
	Prophylaxis		pyrimethamine	tissue/blood schizonts
			combinations	tissue/blood schizonts
Drug-resistant malaria	Attack	quinine	blood schizonts	
		combinations	blood schizonts	
	Prophylaxis	mefloquine	febrile reaction	

Plasmodium (mammalian species)

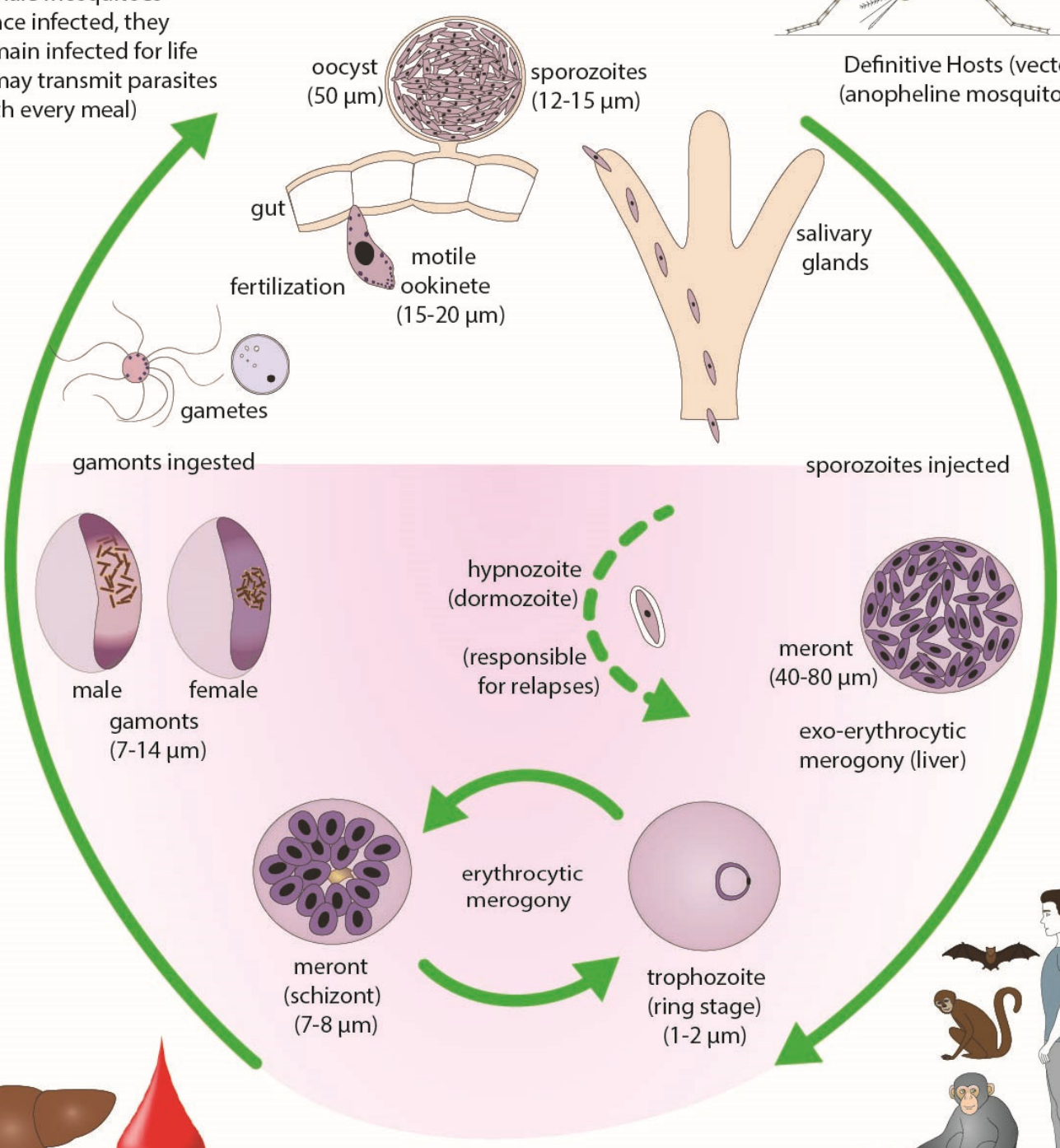
3 subgenera in mammals:
P. (Plasmodium)
P. (Laverania)
P. (Vinckeia)

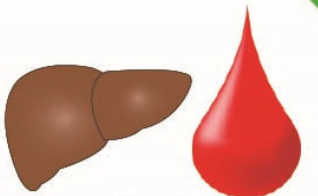
all transmitted by female mosquitoes
 (once infected, they remain infected for life & may transmit parasites with every meal)

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

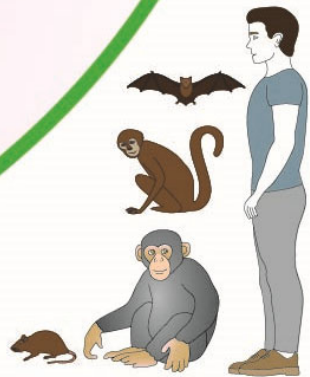


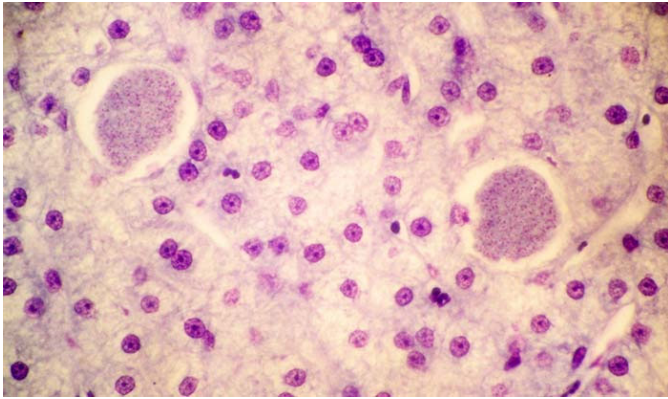
Definitive Hosts (vectors)
(anopheline mosquitoes)



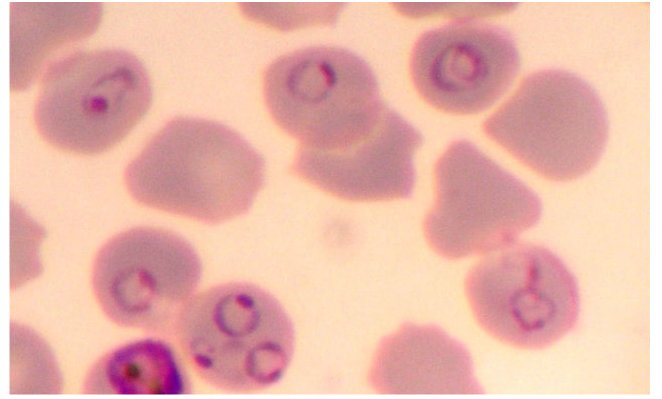

 liver, blood cells
 (cyclic fevers, haemolytic anaemia, ischaemia)

Four species cause severe disease in humans
 (*P. falciparum* causes malignant tertian malaria,
P. malariae causes benign quartan malaria,
P. ovale and *P. vivax* cause benign tertian malaria)

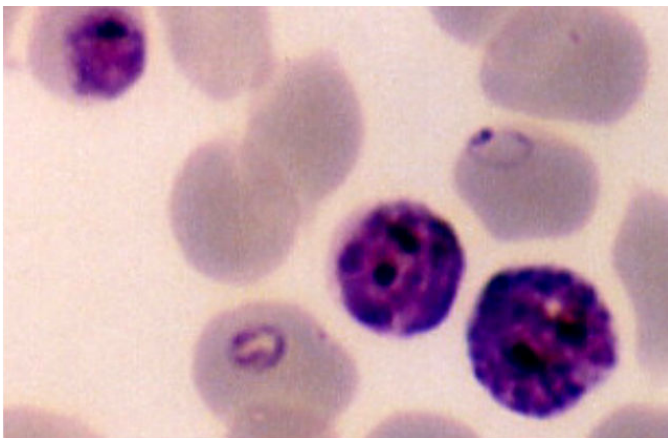

 Intermediate Hosts
 (mammals, esp. primates)



Plasmodium schizonts in human liver



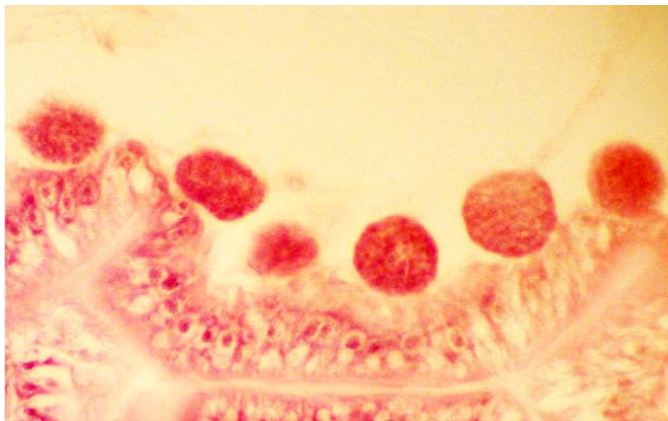
Plasmodium ring-stage trophozoites in human blood



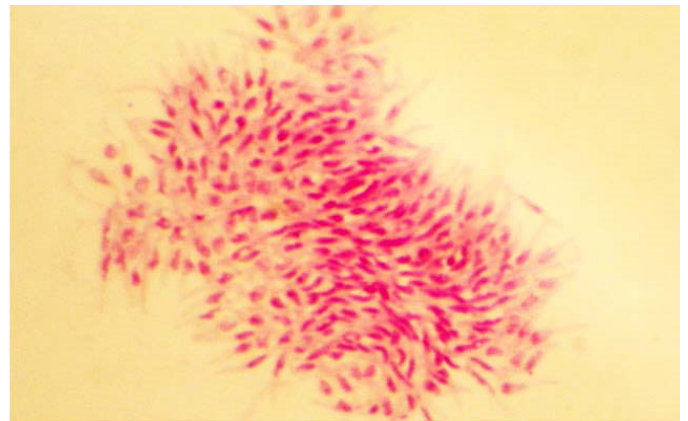
Plasmodium intraerythrocytic schizonts in human blood



Plasmodium gamont in human blood



Plasmodium oocysts on mosquito gut wall



Plasmodium sporozoites from mosquito salivary gland