Theileria
(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. In mammals, piroplasm parasites multiply in blood cells by a form of merogony forming small characteristic pear-shaped merozoites. Theileriid species develop firstly in lymphocytes (which can undergo clonal expansion) and then in erythrocytes. When ingested by ixodid ticks, the parasites form unique paired bodies (strahlenkorper) which give rise to numerous schizonts leading to the production of numerous sporozoites in the salivary glands. *Theileria* infections persist in ticks during metamorphosis (trans-stadial transmission) but do not undergo vertical (trans-ovarian) transmission. Many *Theileria* spp. have been detected in mammalian hosts and some have been associated with severe disease syndromes (tick fevers).

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:	Piroplasmida (pear-shaped stages in blood cells of vertebrates, tick vectors)
Family:	Theileriidae (merogony in leucocytes then erythrocytes, transstadial transmission in ticks)
Genus:	*Theileria* (parasitic in ruminants, leucocytes/erythrocytes, indirect (ixodid tick vectors))
Species:	various species cause tick fever (theileriosis) in mammals

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 endogeny (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	Trans-mission*
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)	*Plasmodium*	mammals, birds, reptiles	liver, erythrocytes	indirect (v-b)
	Haemoproteidae (schizogony in tissues, haemozoin pigment)	*Haemoproteus*	birds	endothelia, erythrocytes	indirect (v-b)
	Leucocytozoidae (schizogony in tissues, no haemozoin pigment)	*Leucocytozoon* (*Akiba*)	birds	tissues, leucocytes	indirect (v-b)
Order: Piroplasmida (pear-shaped blood stages, tick vectors)	Babesiidae (merogony in erythrocytes, trans-stadial + trans-ovarian transmission)	*Babesia*	mammals	erythrocytes	indirect (v-b)
	Theileriidae (merogony in leucocytes, trans-stadial transmission in ticks)	*Theileria*	ruminants	leucocytes, erythrocytes	indirect (v-b)
Class: Coccidiomorphea [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)	*Haemogregarina*	reptiles, amphibia, fish	tissues, blood	indirect (v-b)
		Hepatozoon	mammals, reptiles	tissues, blood	indirect (v-b)
	Klossiellidae (sporocysts)	*Klossiella*	mammals	kidney	direct (f-o)
Suborder: Eimeriorina (no syzygy, >4 microgametes)	Eimeriidae (monoxenous, endogenous merogony and gamogony, exogenous sporogony)	*Caryospora*	birds, reptiles	gut	direct (f-o)
		Cyclospora	mammals, reptiles	gut	direct (f-o)
		Isospora	birds, reptiles	gut	direct (f-o)
		Eimeria	vertebrates	gut, tissues	direct (f-o)
		Epieimeria	fish	gut	direct (f-o)
		Goussia	fish	gut	direct (f-o)
	Sarcocystidae (heteroxenous, 1:2:4 oocyst:sporocyst:sporozoite configuration)				
	subfamily Cystoisosporinae (monozoic cysts)	*Cystoisospora* (no Stieda bodies)	carnivores, omnivores	gut, tissues	direct (f-o), indirect (p-p)
	subfamily: Sarcocystinae (thick-walls, metrocytes)	*Sarcocystis* (*Frenkelia*)	mammals, birds, reptiles	gut, muscles	indirect (p-p)
	subfamily: Toxoplasmatinae (thin-walled cysts without metrocytes)	*Besnoita*	mammals, reptiles	gut, tissues	indirect (p-p)
		Hammondia	mammals	gut, tissues	indirect (p-p)
		Neospora	herbivores, dogs	gut, tissues	indirect (p-p)
		Toxoplasma	vertebrates, cats	gut, tissues	indirect (p-p)
Class: Gregarinomorphea (gregarines, trophonts with specialized attachment epimerite or mucron, syzygy)					
Subclass: Cryptogregaria (epicellular parasites of vertebrates with feeder organelle but lacking apicoplast)					
	Cryptosporidiidae (naked sporozoites)	*Cryptosporidium*	vertebrates	gut, lungs	direct (f-o)

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

Piroplasms undergo unique ‘sexual’ reproduction involving pairing of ray-bodies (Strahlenkorper) in tick ‘vectors’ (making them definitive hosts) and then asexual developmental (merogony) in erythrocytes, and sometimes other circulating and fixed cells, in vertebrates (making them intermediate hosts). They differ from other blood-borne Apicomplexa (haemosporidia and haemococcidia) in that they do not form conoids, oocysts, spores or pseudocysts. Infections by piroplasms have been detected in over 130 species in mammals and in some birds and reptiles. Three families are recognized essentially on the basis of their site of development in their vertebrate hosts: Babesiidae (in erythrocytes of mammals and some birds); Theileridae (in lymphocytes then erythrocytes of mammals); and Haemohormidiidae (in nucleated erythrocytes of reptiles). The parasites undergo trans-stadial transmission in their tick vectors (parasites persist when ticks metamorphose from larvae to nymphs to adults) while some babesiids also undergo trans-ovarian (vertical) transmission (eggs become infected in gravid female ticks).

Piroplasms	No. spp.	Site of development in vertebrates		Vertebrate hosts	Invertebrate vectors
		meronts	'gamonts'		
Family: Babesiidae (erythrocytes of mammals and birds)					
Babesia	100	erythrocytes	erythrocytes	mammals, birds	ticks
Family: Theileridae (lymphocytes then erythrocytes of mammals)					
Theileria	15	lymphocytes	erythrocytes	ruminants	ticks
Cytauxzoon	4	vascular endothelia	erythrocytes	carnivores	ticks
Family: Haemohormidiidae (nucleated erythrocytes of reptiles and fish)					
Sauroplasma (*Serpentoplasma*)	3	erythrocytes	erythrocytes	lizards, snakes	ticks?
Haemohormidium (*Haematractidium*)	12	erythrocytes	erythrocytes	tortoises, frogs, fish	leeches

Molecular phylogenetic studies clearly distinguished between theileriid and babesiid piroplasms, babesiids split into two major lineages (*Babesia sensu stricto* and *Babesia sensu lato*) separated by an intermediary *Theileria/Cytauxzoon* lineage. The *Babesia sensu stricto* clade comprised those species which formed two merozoites in the erythrocytes of ruminants, carnivores and rodents, while the *Babesia sensu lato* clade consisted of those species which formed four merozoites in the erythrocytes of rodents, carnivores and deer. Species belonging to the intermediary *Theileria/Cytauxzoon* clade (family Theileridae) formed four merozoites in the erythrocytes of ungulates and felids, but they also exhibited pre-erythrocytic merogony (schizogony) which does not occur for any *Babesia* species. Traditionally, *Theileria* spp. were regarded to form meronts first in lymphocytes then erythrocytes; while *Cytauxzoon* spp. formed meronts in histiocytes (macrophages) then erythrocytes. However, recent studies using molecular characterization techniques have revealed wide variations in the host cell phenotypes infected by developing parasites, with schizonts found in leucocytes (B and T lymphocytes and lymphoblasts), monocyte-macrophage lineages, and fixed histiocytes (macrophages, and reticulo-endothelial cells). Further studies are required to resolve the host cell specificity exhibited by the different species. In general, the most pathogenic *Theileria* spp. are considered to be 'transforming' species as their schizonts initiate a pseudo-neoplastic transformation of the infected lymphocytes leading to hyperproliferation (clonal expansion) with parasites infecting all progeny (parasite replication linked to host cell replication). This allows tremendous amplification of the parasites, often leading to inflammatory intravascular and perivascular lesions with fibrin thrombi, necrosis, haemorrhage and oedema. Benign or mildly pathogenic *Theileria* spp. are usually 'non-transforming' species as their schizonts do not induce leucocyte clonal expansion. All species then form small intra-erythrocytic stages which may be round, oval, rod-like, bacilliform, comma-shaped or pyriform, with highly reduced apical complexes (with rhoptries and micropores but lacking conoids, polar rings, micronemes and usually subpellicular microtubules). *Theileria* spp. are transmitted by ixodid tick vectors in which the parasites complete gamogony in the gut before multiplying in tick tissues to form infective sporozoites in the salivary glands. Over 40 *Theileria* spp. have been reported from a wide range of mammals, particularly in domestic and wild ungulates in Africa, Asia and southern Europe as well as in wild and domestic felids in North America. The distribution of infections often mirrors that of their tick vectors. In particular, 2 species (*T. parva* and *T. annulata*) are responsible for substantial economic losses to the cattle industry in Africa and Eurasia by causing East Coast fever and Mediterranean Coast fever, respectively.

***Theileria* species**	**Vertebrate hosts**	**Disease**	**Vectors**	**Distribution**
T. annae (syn. *B. microti*-like) [now *B. vulpes*]	Carnivora: canid (dog, fox)	anaemia, thrombo-cytopenia	three-host ticks (*Dermacentor reticulatus, Rhipicephalus sanguineus, Ixodes canisuga, I. hexagonus*, *I. ricinus*)	North America, Europe
T. annulata (syn. *T. dispar, turkestanica*)	Artiodactyla: bovid (cattle, Asiatic buffalo)	Mediterranean coast fever, tropical theileriosis	two-host ticks (*Hyalomma marginatum, Hy. truncatum, Hy. turanicum, Hy. anatolicum*), three-host ticks (*Hy. detritum, Hy. dromedarii, Hy. excavatum, Hy. asiaticum, Rhipicephalus turanicus*)	North Africa, Southern Europe, India, China
T. aristotelis	Artiodactyla: cervid (sambar)			Indo-Asia
T. barnetti	Artiodactyla: bovid (Cape buffalo)			Africa
T. brasiliensis	Didelphimorphia: didelphid (quica, black-eared opossum)			Americas
T. brimonti	Pilosa: bradypodid (pale-throated sloth)			South America
T. camelensis	Artiodactyla: camelid (camels)		three-host ticks (*Hyalomma dromedarii*)	?

T. capreoli	Artiodactyla: cervid (European roe deer)			Europe
T. caviae	Rodentia: caviid (guinea pig)			South America
T. cellii	Primates: cercopithecid (toque macaque)			Sri Lanka
T. cervi	Artiodactyla: cervid (fallow deer, wapiti, white-tailed deer, mule deer, sika deer, barking deer, red deer, reindeer)	-	three-host ticks (*Amblyomma americanum*)	Europe, North America, Japan
T. equi	Perissodactyla: equid (horses, donkeys, zebra)	biliary fever, piroplasmosis	one-host ticks (*Dermacentor albipictus, D. nitens, Hyalomma scupense, Rhipicephalus microplus*), two-host ticks (*Hy. anatolicum, Hy. marginatum, Rhipicephalus bursa, R. evertsi*), three-host ticks (*Amblyomma cajennense, D.nuttalli, D. reticulatus, D. variabilis, Hy. detritum, Hy. dromedarii, Hy. lusitanicum, R. sanguineus*)	Southern Europe, Africa, Asia, Americas, Australia
T. felis	Carnivora: felid (cat, bobcat), and experimentally Artiodactyla: bovid (sheep), Lagomorpha: leporid (rabbit)	'cytauxzoonosis'	three-host ticks (*Dermacentor variabilis*)	United States
T. gorgonis	Artiodactyla: bovid (blue wildebeest)			Africa
T. grunnei	Artiodactyla: bovid (yak)			Central Asia
T. haneyi	Perissodactyla: equid (horse)			North America
T. herpestis	Carnivora: herpestid (Egyptian mongoose)			Africa
T. hippotragi	Artiodactyla: bovid (roan antelope)			Africa
T. hirci (syn. *T. lestoquardi*)	Artiodactyla: bovid (sheep, goats)	malignant ovine/caprine theileriosis	two-host ticks (*Hyalomma anatolicum, Rhipicephalus bursa*), three-host ticks (*R. turanicus*)	Mediterranean, Asia Minor
T. jakimovi	Rodentia: sciurid (Siberian chipmunk)			Asia
T. leporis	Lagomorpha: leporid (European hare, Tolai hare)			Eurasia
T. lotozkyi	Artiodactyla: cervid (red deer)			Europe
T. luwenshuni	Artiodactyla: bovid (sheep, goats), cervid (red deer)		three-host ticks (*Haemaphysalis qinghaiensis, longicornis*)	China, Europe
T. marti	Carnivora: mustelid (beech marten)			Eurasia
T. melis	Carnivora: mustelid (European badger)			Europe
T. microti [formerly *Babesia microti*]	Rodentia: murid (mice, field mice, thicket rats), cricetid (deer mice, pack rats, voles, red-backed voles); sciurid (ground squirrels); Eulipotyphla: soricid (shrews, water shrews); Lagomorpha: leporid (cottontail	small (1.5-2.0 μm)	three-host ticks (*Ixodes muris, I. ricinus, I. scapularis* syn. *dammini*)	Northern Hemisphere (+ lab model worldwide)

	rabbits), occasionally Primates: hominid (human), plus experimentally Rodentia: murid (gerbils, mice, multimammate mice), cricetid (cotton rats, hamsters, lemmings), Primates: cebid (capuchins, squirrel monkeys), cercopithecid (baboons, guenons, macaques), hominid (chimpanzees)			
T. mutans	Artiodactyla: bovid (cattle, buffalo, sheep)	benign African theileriosis I	three-host ticks (*Amblyomma hebraeum, A. cohaerens, A. gemma, A. lepidum, A. variegatum*)	Africa, Caribbean
T. ninakohlyakimovae	Carnivora: canid (fox)			Eurasia
T. orientalis (syn. *T. sergenti, T. buffeli*)	Artiodactyla: bovid (cattle, buffalo)	bovine anaemia, oriental theileriosis	three-host ticks (*Amblyomma cohaerens, A. hebraeum, A. moreliae, A. variegatum, Haemaphysalis bispinosa, Ha. douglasi, Ha. longicornis, Ha. megaspinosa, Ixodes ovatus, I. persulcatus*)	Africa, Asia, Japan, India, Australia, North America
T. ornithorhynchi	Monotremata: ornithorhynchid (platypus)		three-host ticks (*Haemaphysalis bancrofti, Ha. longicornis*)	Australia
T. ovis (syn. *T. recondita, T. separata*)	Artiodactyla: bovid (sheep, goats), cervid (deer)	benign ovine theileriosis	one-host ticks (*Ornithodorus lahorensis, O. moubati*), two-host ticks (*Hyalomma marginatum* syn. *plumbeum, Rhipicephalus evertsi, R. bursa*), three-host ticks (*Dermacentor marginatus, Haemaphysalis punctata, Ha. sulcata, Ixodes persulcatus, R. sanguineus, R. turanicus*)	Africa, Europe, India
T. parva [type species] (incl. subspp. *parva*, *bovis*, *lawrencei*) (syn. *T. bovis, lawrencei*)	Artiodactyla: bovid (cattle, Cape buffalo, Asiatic buffalo, waterbuck)	East Coast fever, Corridor disease, January disease	two-host ticks (*Hyalomma anatolicum*), three-host ticks (*Hy. dromedarii, Hy. impressum, Rhipicephalus appendiculatus, R. duttoni, R. zambeziensis, R. simus, R. evertsi*)	East, Central and Southern Africa
T. peramelis	Peramelemorphia: peramelid (bandicoots), Diprotodontia: potoroid (potoroo)		three-host ticks (*Haemaphysalis bancrofti, Ha. longicornis*)	Australia
T. rossica	Rodentia: murid (striped field mouse)			Eurasia
T. stordyi	Artiodactyla: bovid (Grant's gazelle)			Africa
T. strepsicerosi	Artiodactyla: bovid (Cape kudu)			Africa
T. sylvicaprae	Artiodactyla: bovid (common duiker)			Africa
T. tachyglossi	Monotremata: tachyglossid (short-beaked echidna)		three-host ticks (*Haemaphysalis bancrofti, Ha. longicornis*)	Australia
T. talpae	Eulipotyphla: talpid (European mole), soricid (Eurasian shrew),			Eurasia

	Rodentia: cricetid (short-tailed vole)			
T. tarandi	Artiodactyla: cervid (reindeer)			Eurasia, North America
T. taurotragi	Artiodactyla: bovid (common eland, cattle, zebu, sheep, goats)	Turning sickness, benign African theileriosis II	three-host ticks (*Rhipicephalus appendiculatus, R. pulchellus, R. zambeziensis*)	Eastern, Southern and Central Africa
T. tragelaphi	Artiodactyla: bovid (harnessed bushbuck)			Africa
T. uilenbergi	Artiodactyla: bovid (sheep), cervid (red deer, sika deer)		three-host ticks (*Haemaphysalis qinghaiensis*)	China
T. velifera	Artiodactyla: bovid (cattle, buffalo)		three-host ticks (*Amblyomma hebraeum, A. lepidum, A. variegatum*)	South and Central Africa, Caribbean

Parasite morphology: *Theileria* spp. form 2 different types of developmental stages in vertebrates (meronts forming merozoites in lymphocytes, piroplasms in erythrocytes) and 6 types in tick vectors (gamonts, gametes, zygotes, kinetes, sporoblasts and sporozoites). In vertebrates, sporozoites invade host leucocytes and develop into intracytoplasmic trophozoites which form meronts (previously called schizonts, an interchangeable name that persists in much of the literature, but the term meront is used here to denote an asexual divisional process known as merogony). Meronts appear as rounded basophilic syncytial stages that become multinucleate as they divide internally to produce numerous merozoites with irregular eosinophilic nuclei. The meronts may occur singly or in small aggregations in lymphocytes (while those of *Cytauxzoon* are multiple and form large aggregations). Two types of meronts may be formed: macro-meronts (sometimes called Koch's blue bodies) ranging in size from 5-25 μm and producing 5-18 merozoites (0.4-2.0 μm); and micro-meronts ranging in size from 4-10 μm and forming 8-12 merozoites (2 x 1 μm). Merozoites from micro-meronts invade host red blood cells to form pleomorphic intraerythrocytic piroplasms initially within parasitophorous vacuoles but then free in the cytoplasm. Piroplasms are small (1.5-2.0 x 0.5-1.0 μm) and vary in size and shape during infection and between species, being pear-shaped (pyriform), comma-shaped, rod-shaped, oval or round. They have a highly reduced apical complex (but always including rhoptries) and an eccentric nucleus, and they do not contain haemozoin pigment, although some may possess a rectangular veil-like body (crystalline substance) and a bar-like structure connecting them to the host cell membrane. Piroplasms in erythrocytes may or may not divide depending on the species. For example, those of *T. parva* do not divide, while those of *T. orientalis, T. mutans* and *T. equi* do divide into 2 or 4 daughter cells, with those of *T. equi* often forming tetrads (Maltese crosses). In vectors, piroplasms develop into elongate (5-10 μm) stages (gamonts) with small anterior arrowhead-shaped organelles. Gametogenesis is completed to form male and female gametes which pair up (syzygy) and fuse (syngamous fertilization) to produce a transitory nonmotile zygote which invades an epithelial cell. Zygotes are round-elongate stages (4-12 μm) that produce motile pyriform kinetes which penetrate the gut wall and move through the haemolymph to the salivary glands. The kinetes invade specific acinar cells and undergo sporogony to form polymorphic multinucleated sporoblasts (10-40 μm). Kinetes do not invade other tick tissues and do not undergo trans-ovarian transmission. The sporoblasts produce hundreds of small ovoid-pyriform sporozoites (1-1.5 μm) which are released into the saliva of feeding ticks.

Site of infection: In vertebrate (intermediate) hosts, *Theileria* spp. first infect lymphocytes (sometimes macrophages and dendritic cells) in various host organs (esp. spleen, lymph nodes, liver) where they form asexual multiplicative forms (meronts or schizonts producing merozoites). They undergo at least 2 cycles of merogony with macro- and micro-meronts producing numerous merozoites. Merozoites from micro-meronts then invade erythrocytes in the circulation and form piroplasms. Some species exhibit intraerythrocytic merogony yielding uninucleate merozoites which are released by erythrolysis to infect other cells. All species ultimately form gamonts which persist in erythrocytes and are infective to ticks. In tick vectors (definitive hosts), ingested gamonts form gametes in the gut which fuse (fertilization) to produce zygotes that move into the gut wall. These stages transform to kinetes which migrate to the body cavity and haemolymph to invade the salivary glands (specific acinar cells) where they produce numerous sporozoites (infective to vertebrates). Some 44 *Theileria* spp. have been recorded in over 75 mammalian host species, including ungulates (bovids, cervids, camelids, equids), carnivores (canids, felids, mustelids, herpestids), marsupials (didelphids, peramelid, potorid), monotremes (tachyglossid, ornithorhynchid), lagomorphs (leporids), shrews (soricids, talpids), rodents (cricetids, murids, sciurids, caviid), sloths (brachypodid) and primates (cebids, cercopithecids and hominid (including humans)). Infections are particularly common in domestic and wild ungulates in Africa, Asia and southern Europe as well as in wild and domestic felids in North America. All *Theileria* spp. have ixodid tick vectors, mostly three-host ticks (*Amblyomma, Dermacentor, Hyalomma, Rhipicephalus, Haemaphysalis, Ixodes*) but also some two-host ticks (*Hyalomma, Rhipicephalus*) and a few one-host ticks (*Dermacentor, Hyalomma, Rhipicephalus, Ornithodorus*). The distribution of infections by *Theileria* spp. infections often mirrors that of their tick vectors.

Pathogenesis: *Theileria* infections vary significantly in their pathogenicity depending on the parasite species (and strains), the phase of infection (pre-erythrocytic and/or erythrocytic), the duration of infection (acute-chronic), innate host resistance (varies with host

species/breed, age, genetic susceptibility and stress conditions), immune status (acquired immunity), the intensity of infection, and various environmental factors (especially regional and seasonal variations in climate impacting tick burdens). These parasites are unique in that pre-erythrocytic merogony occurs in leucocytes (mostly lymphocytes) and that some species induce host cells to undergo blastogenesis and clonal expansion (pseudo-neoplastic (cancer-like) transformation and immortalization) but in synchrony with parasite proliferation so that all daughter cells are infected. This leads to the rapid multiplication of parasites within the host (up to 10-fold increases approximately every 3 days). The 'transformed' leucocytes become disseminated in peripheral blood and a variety of lymphoid and nonlymphoid organs and may cause overwhelming systemic inflammation and acute fatal theileriosis. *Theileria* spp. are often classified as pathogenic or benign on the basis of whether their meronts induce lymphocyte transformation and proliferation or not (i.e. meront 'transforming' or 'non-transforming'). Pathogenic species typically cause disease by inducing uncontrolled lymphocyte blastogenesis, proliferation and dissemination resulting in widespread lesions, leucocytolysis, acute disease and death (e.g. *T. annulata* causing tropical theileriosis in Africa and Eurasia, *T. parva* causing East Coast fever in Africa). Benign species usually do not induce lymphocyte transformation and have not been associated with disease (e.g. *T. sinensis* and *T. velifera* in cattle, *T. ovis* and *T. separata* in sheep and goats). However, this classification is an oversimplification as some species (and strains) are not consistently pathogenic or benign in mammalian hosts (e.g. non-transforming *T. mutans, T. orientalis* and *T. taurotragi* are occasionally pathogenic in cattle, but disease is due to piroplasm-induced haemolysis and not pre-erythrocytic merogony). *T. taurotragi* may also cause cerebral theileriosis (turning sickness) in some African ungulates due to meronts developing in neural and other tissues. Disease may therefore be caused by the asexual proliferation of meronts in lymphocytes in tissues (e.g. *T. parva*) or the proliferation of piroplasms within erythrocytes in the circulation (e.g. *T. equi, T. orientalis*), or both (e.g. *T. annulata, T. felis, T. lestoquardi*). Acute disease due to meront proliferation is a generalized leucosis-like or lymphoproliferative condition with hyperplasia, oedema and hyperaemia of lymph nodes and lymphoid tissues leading to necrosis, often inducing immunosuppression in the host. The incubation period varies from 7-24 days and the disease may last for 4 days to several weeks. Clinical signs include lymphadenopathy, pyrexia (fevers up to 42°C), petechial and ecchymotic haemorrhages on mucous membranes of the conjunctiva and buccal cavity, haemorrhagic diarrhoea, anorexia, loss of condition, depression, lethargy, weakness, wasting, emaciation and exercise intolerance (some animals may collapse and die if forced to run). Other signs are occasionally observed, including haematuria, anaemia, icterus (jaundice), tachycardia (rapid heartbeat), respiratory difficulties (due to interlobular emphysema and pulmonary oedema), frothy nasal discharges, faint cough, lacrimation (runny eyes), swollen eyelids, corneal opacities and progressive leucopenia. Surviving animals develop acquired protective immunity to disease, but often remain carriers. Persistent chronic infections may lead to decreased growth rates in calves and limit production in adults by reducing weight gain and milk production as well as causing prenatal and postnatal mortalities (abortions and stillbirths are common in pregnant cows). Infections by 'non-transforming' species cause milder disease as piroplasms proliferate in erythrocytes resulting in haemolytic anaemia, jaundice, lethargy, tachycardia and late-term abortion in pregnant animals. The anaemia can be variable depending upon piroplasm multiplication rates, being low in some species (e.g. *T. annulata, T. lestoquardi, T. felis*) but high in others (e.g. *T. mutans, T. orientalis, T. equi*). The incubation period ranges from 10-15 days and the disease may persist for weeks. Common clinical signs include pale mucous membranes, mild fever and progressive loss of condition, but some cases have been reported involving acute septicaemia, laboured breathing with pulmonary oedema and cerebral signs sometimes occasioning death. Many infections may remain subclinical, but stress conditions (due to malnutrition, translocations and concomitant infections) may cause recrudescence of disease. Calves are more susceptible to disease than adult cattle which apparently acquire some protective immunity through prior exposure. However, chronic infections may persist in animals, sometimes for life. Taurine breeds of cattle are more susceptible to infection than zebu or sanga breeds, while wildlife (indigenous ruminants) are often refractory to disease, but may act as reservoirs or long-term carriers of infection.

Developmental cycle and mode of transmission: *Theileria* spp. have obligate heteroxenous (2-host) life-cycles involving asexual proliferation in vertebrates (acting as intermediate hosts) and sexual development in invertebrate vectors (acting as definitive hosts). Transmission occurs via vector bite when haematophagous ixodid ticks feed on vertebrate blood. In mammals, the parasites proliferate in lymphocytes in at least 2 pre-erythrocytic phases of merogony before invading erythrocytes and forming piroplasms. Sporozoites injected with the saliva of feeding ticks first invade select host leucocytes (lymphocytes) within the localized inflammatory reaction of the tick bite or in local lymph nodes. The form macro-meronts within 5-8 days which divide internally to produce numerous merozoites. The intracellular meronts are closely associated with the mitotic spindle apparatus of the lymphocytes, and some species induce host cells to acquire a pseudo-neoplastic phenotype characterized by reversible blast transformation and clonal expansion. The parasites divide at the same time as the host cells thereby perpetuating infections in all daughter cells which become disseminated throughout host tissues. Mature merozoites are released by host cell lysis (leukocytolysis) at which time leucoproliferation decreases significantly. The merozoites then infect new lymphocytes and form micro-meronts which produce merozoites that are able to infect red blood cells transforming into pleomorphic piroplasms within 10-25 days of infection. The piroplasms of some species do not multiply within erythrocytes (e.g. *T. parva*), those of several species do so sporadically (e.g. *T. annulata, T. lestoquardi*, *T. felis*), while those of other species do so prolifically (e.g. *T. orientalis, T. mutans, T. equi*). Eventually, some merozoites invading erythrocytes form spherical-ovoid stages (gamonts) that are infective to tick vectors. In ticks, the gamonts undergo further development within masses of blood cells in the tick gut and are released into the lumen where they complete gametogenesis. Macrogamonts (female) mature to form uninucleate macrogametes, while quadri-nucleate microgamonts (male) divide to form uninucleate microgametes. Gametes pair up and fuse to produce a nonmotile ovoid zygote which stretches and increases in length using an anterior spike upon contact to invade a gut epithelial cell. The zygote undergoes meiotic division and grows in size producing motile pyriform kinetes (often in synchrony with the process of tick moulting). The kinetes have distinct anterior arrowhead-like structures used to penetrate the gut wall into haemocoel and invade the salivary glands.

Parasites undergo trans-stadial transmission in ticks (from larvae to nymphs to adults), but not transovarian transmission. The kinetes infect specialized acinar epithelial cells in the salivary glands and form giant multinucleated sporonts divided into numerous small sporoblasts. When ticks feed and engorge on new hosts, sporoblasts are triggered to complete sporogony and they bud hundreds of small sporozoites into the saliva to be injected into new vertebrate hosts (inoculative transmission). *Theileria* sporozoites only mature and enter the saliva after ticks attach to a host usually for 48–72 hours, but if environmental temperatures are high, sporozoites may develop before attachment and be infective within hours of attachment. Infected ticks may survive on pastures for up to 2 years depending on climatic conditions. Most transmission cycles involve 3-host ticks, but some 2-host and even a few 1-host ticks may act as vectors. Adult ticks transmit more sporozoites than nymphs, so disease often depends on adult tick abundance and activity (more active in warm wet summer months). The distribution of ticks also varies according to climate (temperature and humidity), land management (suitable vegetation types), farming practices (animal husbandry) and the spatial and temporal availability of suitable vertebrate hosts. Other forms of transmission have occasionally been implicated, with some species (e.g. *T. orientalis*) occasionally being mechanically transmitted between vertebrates by routine husbandry practices involving contaminated equipment, and lice and tabanid flies (March flies) also acting as mechanical vectors under experimental conditions.

Differential diagnosis: The clinical diagnosis of theileriosis on the basis of symptomatology, history and vector distribution is difficult due to other confounding vector-borne diseases, such as heartwater, trypanosomiasis, babesiosis, anaplasmosis, malignant catarrhal fever, and contagious bovine pleuropneumonia. Diagnosis is conventionally made by the microscopic detection of parasites in blood cells in fixed thin blood smears or buffy coat preparations stained with Romanowsky stains, usually Giemsa. Test sensitivity is often poor and may fail to detect low parasitaemias such as occur in chronic infections or asymptomatic carriers. Lymph node biopsies may also be collected and smears or sections examined for developing stages, both meronts (including Koch's blue bodies) and piroplasms. Similarly, various tissues and organs (notably spleen, lungs, kidneys) collected at autopsy may be examined for developing stages. Differential diagnosis to species level is difficult as most piroplasms are morphologically similar and meronts are not always present in superficial lymph nodes. Various haematological and biochemical tests may be conducted but their findings are nonspecific but serve to quantify anaemia and organ damage. Various experimental studies have cultured parasites *in vitro* by passaging bovine lymphoid cells in various media (Leibovitz L-15, McCoy and Leibovitz L-15, Dulbecco DMEM, RPMI 1640 or Eagles's minimum essential medium) usually supplemented foetal calf serum. Early workers cultured parasites *in vivo* for xenodiagnosis by feeding laboratory-reared ticks on test animals. Various immunoserological techniques (especially indirect fluorescent antibody tests and enzyme immunoassays) were then developed to detect specific host antibodies against crude, purified or recombinant antigens, with considerable success despite variable sensitivities and some cross-reactivity. More recently, a range of molecular biological techniques have been used to detect and characterize parasites, such as polymerase chain reaction (PCR) amplification, real-time PCR, loop-mediated isothermal (LAMP) amplification, and restriction fragment length polymorphism (RFLP) analyses of a spectacular range of parasite genes, including mitochondrial cytochrome c oxidase 1, nuclear 18S ribosomal DNA and genes encoding specific proteins (*T. parva* repeat gene family (TpR), *T. parva* macromeront GPI-anchored surface protein (p104), *T. parva* sporozoite surface protein (p67), *T. parva* polymorphic immunodominant molecule (PIM), *T. annulata* merozoite surface 1 antigen (Tams1), *T. annulata* macromeront stage protein (TaSP), *T. orientalis* p33/34 antigens, *T. uilenbergi* immunodominant protein (TuIP), and *T. lestoquardi* 30 kDa mero-zoite surface gene (Tlms)). Genotypic studies have revealed considerable variation both between and within species and strains and now provide a vital tool for molecular epidemiological studies tracing infections and characterizing outbreaks.

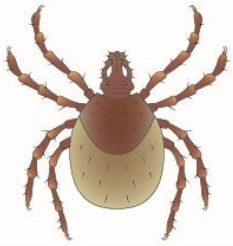
Treatment and control: Few treatments are effective once clinical signs of theileriosis have become apparent, and even then, chemotherapy may not eradicate infections leading to the development of carrier hosts. Treating bovines with naphthoquinones (parvaquone and it derivative buparvaquone) is often successful during the early stages of disease prior to the destruction of lymphoid and haematopoietic tissues. Clinicians have reported some successes using antibiotics (oxytetracycline), urea derivatives (imidocarb), antimalarials (pamaquine, primaquine) or coccidiostats (halofuginone) to treat various infections if applied during the incubation period. Disease control often depends on rigorous health surveillance and vector control. Livestock should be screened for infections before translocations or during quarantine isolation. Tick populations may be managed by various chemical, physical and/or biological control programmes, although the long-term use of acaricides is costly and may lead to the development of drug-resistance in tick populations. Immunological studies have led to the development of several vaccines for *T. parva* and *T. annulata*, using live attenuated parasites (low virulence strains or cultured lines), recombinant subunit antigens (surface proteins) or sporozoite challenge followed by tetracycline treatment (chemo-immunization). Immunized animals developed strong protective immunity against disease, but they sometimes remained carriers of chronic infections. Epidemiological studies have consistently shown indigenous ungulates to be highly resistant to disease while introduced ruminants remain highly susceptible. This suggests native animals have developed a state of enzootic or endemic stability whereby low levels of infection lead to premunitive protective immunity. Care should therefore be taken with treatment and control interventions as they may reduce the force of infection leading to endemic instability and sporadic outbreaks of clinical disease in hitherto resistant host populations.

Theileria

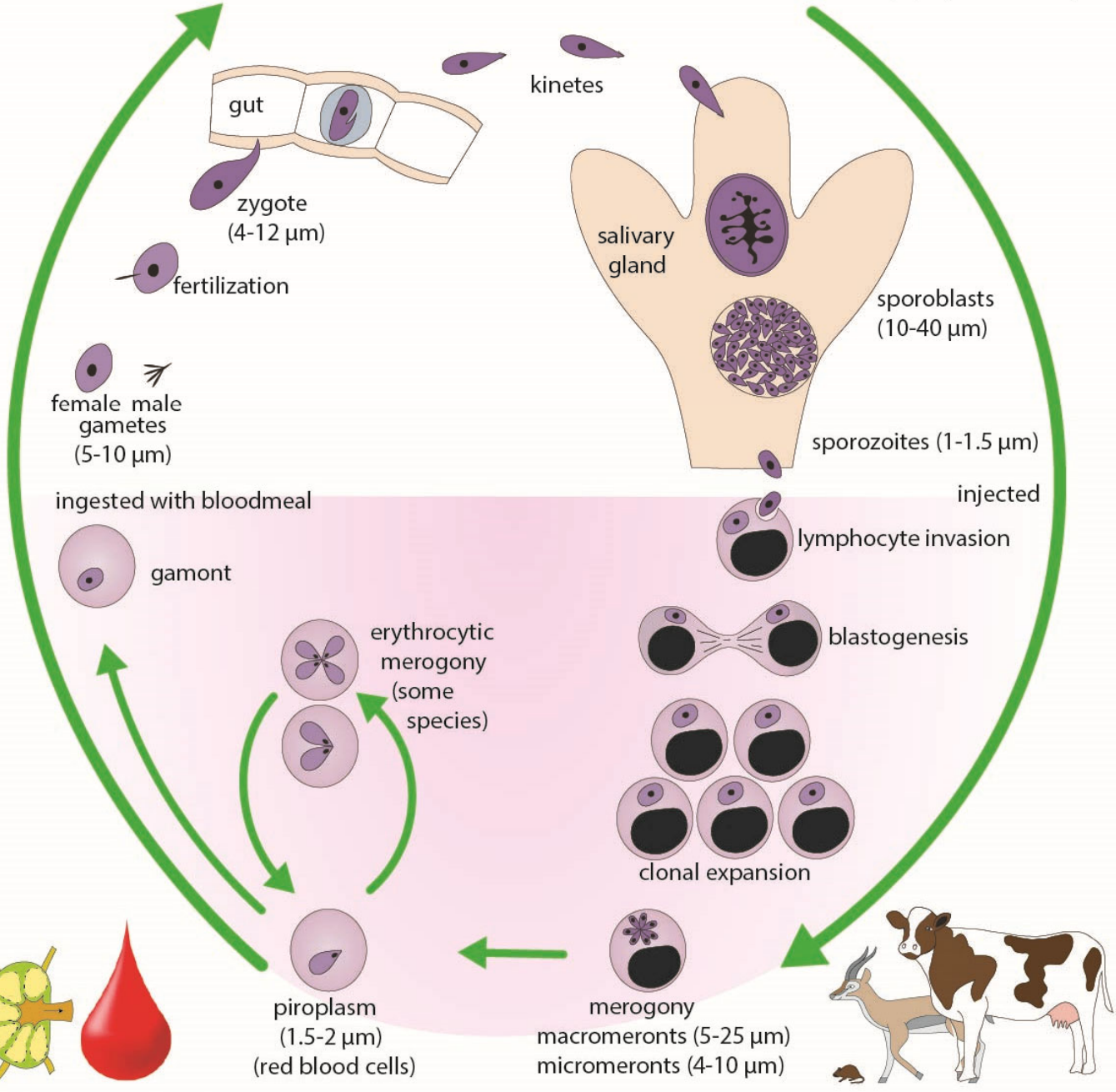
most pathogenic are 'transforming' species as meronts initiate pseudo-neoplastic transformation of infected lymphocytes leading to proliferation (parasites infect all progeny cells)

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

trans-stadial transmission occurs within ticks
(but not trans-ovarian transmission)

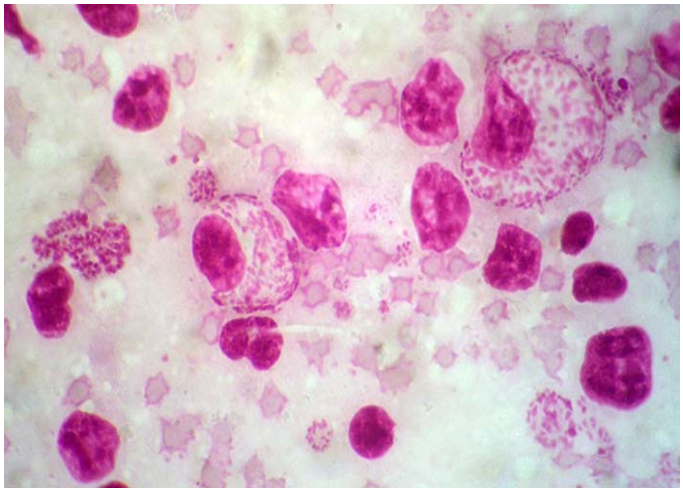


Definitive Hosts (vectors)
(1-, 2-, 3-host ticks)

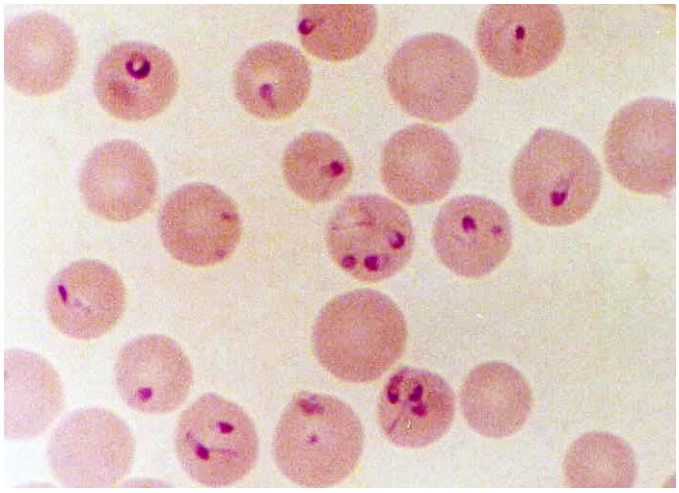


lymphoid tissue, blood
(fever, odema, inflammatory intra- & peri-vascular lesions)

Intermediate Hosts
(mammals, esp. ungulates, rodents)



Theileria schizonts in bovine white blood cells



Theileria piroplasms in bovine red blood cells

OTHER GENERA

Family: Theileridae (lymphocytes then erythrocytes of mammals)

Genus *Cytauxzoon*: This genus was created to accommodate the *Theileria*-like parasites with pre-erythrocytic merogony (schizogony) in macrophages rather than in lymphocytes. However, subsequent studies have shown that the presumed specificity of meronts (schizonts) for various *Theileria* and *Cytauxzoon* spp. is not as strict as previously thought, with meronts reported from a range of cell phenotypes, including leucocytes (B and T lymphocytes) and histiocytes (monocytes, macrophages, vascular endothelial cells). This has led to many species revisions, particularly for those found in African wildlife, but further studies are required to unravel their classification, including not only the molecular characterization of parasite species but also the immuno-phenotypic characterization of the host cells parasitized by meronts. Macrophages engorged by meronts often line the lumina of blood vessels and may obstruct blood flow causing tissue lesions and inflammation. The disease cytauxzoonosis may develop rapidly in felids with haemolysis, regenerative anaemia, jaundice, fever, dehydration, and hepatosplenomegaly occurring in 14-20 days.

***Cytauxzoon* species**	**Vertebrate hosts**	**Disease**	**Pathogenicity**	**Vectors**	**Distribution**
C. felis (syn. *Theileria felis*)	Carnivora: felid (cat, bobcat, Florida panther, Texas cougar, captive white tiger, captive cheetahs), plus experimentally to Artiodactyla: bovid (sheep)]	cytauxzoonosis	high [haemolytic anaemia, thrombo-cytopenia]	three-host ticks (*Amblyomma americanum, Dermacentor variabilis*)	North America
Cytauxzoon spp.	Artiodactyla: bovid (eland, gray duiker, greater kudu, sable antelope, roan antelope, tsessebe)	disease	medium		Africa