Cryptosporidium
(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. *Cryptosporidium* is a unique genus closely related to the gregarines (parasites of invertebrates) although it was previously grouped with the coccidia as they form non-motile resistant oocysts containing infective sporozoites. Cryptosporidia are monoxenous (one-host) parasites in the digestive and/or respiratory tracts of vertebrate hosts. The parasites develop within the brush border (microvillous layer) of host epithelial cells (not in the host cell proper). Endogenous stages have a prominent attachment organelle and they are located within parasitophorous vacuoles formed by a complete covering of microvilli (intracellular yet extracytoplasmic location). They undergo cyclic asexual merogony (schizogony) followed by gamogony (male microgametes fertilize female macrogametes) resulting in the formation of small oocysts which undergo exogenous sporulation (forming 4 naked sporozoites not contained within sporocysts). Over 60 genotypes have been identified, some in association with mild to severe clinical disease in humans and domestic animals.

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:	Gregarinomorphea (gregarines, gamogony and sporogony in aquatic hosts, trophonts with specialized attachment apparatus, epimerite or mucron, syzygy)
Subclass:	Cryptogregaria (epicellular parasites of vertebrates with feeder organelle but lacking apicoplast)
Family:	Cryptosporidiidae (oocysts with 4 naked sporozoites)
Genus:	*Cryptosporidium* (mucosal parasites in vertebrates)
Species:	various species cause cryptosporidiosis in mammals, birds, reptiles and fish

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: 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)
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: 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: Piroplasmorida (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)

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

Cryptosporidium was previously grouped with the coccidia as they form oocysts (albeit unusual in that they contained 4 naked sporozoites and no sporocysts), but recent biological and molecular phylogenetic studies have indicated that they are more closely related to gregarines than to coccidia. Given that some *Cryptosporidium* spp. have been found to form novel extracellular stages and others appear to be able to complete cyclic development in the absence of a host, the genus *Cryptosporidium* has formally been transferred to a new subclass Cryptogregaria in the class Gregarinomorphea. Cryptosporidia are monoxenous (one-host) parasites in the digestive and/or respiratory tracts of vertebrate hosts. The parasites develop within the brush border (microvillous layer) of host epithelial cells (not in the host cell proper). Endogenous stages have a prominent attachment organelle and they are located within parasitophorous vacuoles formed by a complete covering of microvilli (intracellular yet extracytoplasmic location).

Infections have been detected throughout the world in numerous species of mammals, birds, reptiles and fish. Parasite species were originally described primarily on the basis of host occurrence, site of infection, type of disease and, occasionally, differences in oocyst morphometrics. Epidemiological and experimental cross-transmission studies, however, suggested that different parasite species were specific for individual vertebrate classes rather than individual host species. More recently, molecular

characterization studies conducted on clinical isolates have identified a range of genotypes (and subgenotypes) that vary markedly in their host specificity; some being highly specific for individual mammalian species (e.g. *C. viatorum*) while others were found in multiple host species (e.g. *C. parvum*). Genetic markers used for parasite characterization have included the small subunit (18S) of nuclear ribosomal DNA (SSU rDNA), second internal transcribed spacer of rDNA (ITS-2), 70 kDa heat shock protein (hsp-70), *Cryptosporidium* oocyst wall protein (cowp), thrombospondin-related adhesive protein (TRAP), actin, β-tubulin, 60 kDa glycoprotein (gp60), 47 kDa protein (cp47), 56 kDa transmembrane protein (cp56), mucin-like protein (mucin1), serine repeat antigen (msc6-7), microsatellite loci (ML1 and ML2) and a T-rich gene fragment (chrom3T). In many instances, it has proven difficult to reconcile genotypes with individual species. Many genotypes have been found (> 125 in hosts, and more in environmental water samples) but most have not been formally named as species. In addition, several named species, notably from early descriptions, have yet to be genotyped, and probably never will be. Despite these confounding elements, molecular epidemiological studies have shown strong correlations between specific parasite genotypes (and subgenotypes) and their anthroponotic, zoonotic and epizootic disease potential and have facilitated tracing of many disease outbreaks.

***Cryptosporidium* species**	**Oocyst size (µm)**	**Hosts**	**Location (clinical signs)**	**Distribution**
C. abrahamseni (= piscine genotype 7)	3.8 x 3.2	Characiformes: characid (redeye tetra, neon tetra)	intestines	Australia
C. alticolis	5.4 x 4.9	Rodentia: cricetid (common vole, meadow vole)	intestines	Europe
C. andersoni (= *C. muris* genotype A)	7.4 x 5.8	Artiodactyla: bovid (cattle, yak, European bison, sheep, mountain goat), camelid (camel); Rodentia: cricetid (golden hamster, Campbell's dwarf hamster, Djungarian hamster), sciurid (steppe marmot, eastern chipmunk), murid (multimammate mice, mouse, lesser gerbil, Mongolian gerbil, bushy-tailed jird, Tristam's jird); Primates: hominid (human); Galliformes: phasianid (crested partridge)	gastric (chronic)	worldwide
C. apodemi	4.2 x 4.0	Rodentia: murid (striped field mouse, yellow-necked mouse)	enteric	Europe
C. avium (= avian genotype V)	6.3 x 4.9	Psittaciformes: psittaculid (red-crowned parakeet, rosy-faced lovebird, budgerigar), psittacid (blue-fronted amazon), cacatuid (cockateil, Major Mitchell's cockatoo); Galliformes: phasianid (chicken)	intestines	Eurasia, Americas
C. baileyi	6.2 x 4.6	Galliformes: phasianid (chicken, brown quail, Japanese quail, turkey, pheasant, chukar partridge); Anseriformes: anatid (ducks, goose); Gruiformes: gruid (whooping crane, white-naped crane); Passeriformes: ploceid (golden-backed weaver), pycnonotid (gray-bellied bulbul), alaudid (crested lark), estrilid (Gouldian finch, zebra finch, Java sparrow), icterid (crested oropendola, red-rumped cocique), leiothrichid (red-billed leiothrix), sturnid (common myna), corvid (black-billed magpie), thraupid (saffron finch); Suliformes: phalacrocoracid (cormorant): Struthioniformes: struthionid (ostrich); Falconiformes: falconid (falcons); Accipitriformes: cathartid (black vulture); Charadriiformes: larid (black-headed gull); Psittaciformes: cacatuid (cockateil), psittacid (red-crowned amazon); Strigiformes: strigid (scops owl); Piciformes: ramphastid (channel-billed toucan); Rodentia: sciurid (eastern chipmunk, eastern grey squirrel)	enteric, respiratory (acute)	worldwide
C. bollandi (= piscine genotype II)	3.1 x 2.8	Cichliformes: cichlid (oscar, angelfish); Characiformes: characid (neon tetra); Mugiliformes: mugilid (flathead grey mullet)	stomach	North America
C. bovis (= bovine genotype B)	4.9 x 4.6	Artiodactyla: bovid (cattle, African buffalo, sheep), Carnivora: canid (fox); Primates: hominid (mountain gorilla)	enteric (chronic)	worldwide
C. canis (= dog genotype)	5.0 x 4.7	Carnivora: canid (dog, coyote, fox, red fox), ursid (black bear); Primates: hominid (human)	enteric (acute)	worldwide

C. (*Piscicryptosporidium*) *cichlidis*	4.3 x 3.3	Cichliformes: cichlid (blue tilapia, Nile tilapia, redbelly tilapia); Cyprinodontiformes: poeciliid (guppy); Characiformes: characid (neon tetra)	gastric	Middle-East
C. cuniculus (= rabbit genotype)	5.2 x 4.6	Lagomorpha: leporid (rabbit); Rodentia: murid (gerbil, mice), Diprotodontia: macropodid (eastern grey kangaroo); Primates: hominid (human)	enteric (acute)	Australia, China, Europe
C. ditrichi	4.7 x 4.2	Rodentia: murid (yellow-necked mouse, mouse, wood mouse, striped field mouse); Primates: hominid (human)	enteric	Europe
C. ducismarci (= tortoise genotype II)	5.0 x 4.8	Testudines: testudinid (radiated tortoise, pancake tortoise, leopard tortoise, Greek tortoise, Hermann's tortoise, Russian tortoise, Egyptian tortoise, marginated tortoise); Serpentes: pythonid (ball python); Sauria: chamaeleonid (veiled chameleon)	nd	Europe
C. erinacei (= hedgehog genotype)	4.9 x 4.4	Eulipotyphla: erinaceid (European hedgehog, four-toed hedgehog); Perissodactyla: equid (horse); Primates: hominid (human)	enteric (chronic)	Europe
C. fayeri (= marsupial genotype I)	5.0 x 4.3	Diprotodontia: macropodid (yellow-footed rock wallaby, red kangaroo, grey kangaroos), phascolarctid (koala); Peramelemorphia: peramelid (western-barred bandicoot); Dasyuromorphia: dasyurid (Tasmanian devil); Didelphimorphia: didelphid (Virginia opossum); Artiodactyla: bovid (sheep); Primates: hominid (human)	enteric (acute)	Australia
C. felis (= cat genotype)	5.0 x 4.5	Carnivora: felid (cat); Artiodactyla: suid (pig); Primates: hominid (human), cercopithecid (rhesus macaque)	enteric (acute)	Americas, Africa, Europe
C. fragile	6.2 x 5.5	Anura: bufonid (black-spined toad)	gastric (chronic)	Asia
C. galli (incl. *C. 'blagburni'*) (= finch genotype I)	8.2 x 6.3	Passeriformes: fringillid (canary, gold finch, pine grosbeak, fife canary, gloster), estrildid (zebra finch, chocolate parson finch, painted firetail finch, munia, chestnut finch, Gouldian finch), thraupid (red-cowled cardinal, lesser seed-finch, saffron finch, slate-coloured seedeater), leiothrichid (silver-eared mesia), bombycillid (Bohemian waxwing), cardinalid (green-winged saltator), turdid (rufous-bellied thrush); Psittaciformes: psittaculid (turquoise parrot), cacatuid (cockateil); Galliformes: phasianid (chicken, hazel hen, grouse, capercaillie); Bucerotiformes: bucerotid (rhinoceros hornbill); Phoenicopteriformes: phoenicopterid (Cuban flamingo); Dasyuromorphia: dasyurid (Tasmanian devil);	gastric (chronic)	Europe, Australia
C. homai		Rodentia: caviid (guinea pig)	respiratory? (acute)	Australia
C. hominis (= human genotype I)	5.2 x 4.9	Primates: hominid (human), cercopithecid (rhesus macaque, olive baboon); Sirenia: dugongid (dugong); Artiodactyla: bovid (cattle, sheep, goat), suid (pig); Diprotodontia: macropodid (rock-wallaby, eastern grey kangaroo); Anseriformes: anatid (Canada goose); Columbiformes: columbid (rock pigeon); Cypriniformes: cyprinid (goldfish)	enteric (acute-chronic)	worldwide
C. huwi (= piscine genotype I)	4.6 x 4.2	Cyprinodontiformes: poecilid (guppy); Cypriniformes: cyprinid (tiger barb); Characiformes: characid (neon tetra)	stomach (chronic)	Australia
C. macropodum (= marsupial genotype II)	5.4 x 4.9	Diprotodontia: macropodid (grey kangaroos, red kangaroo, rock-wallaby, swamp wallaby), phascolarctid (koala)	enteric (acute)	Australia
C. meleagridis	5.2 x 4.6	Galliformes: phasianid (turkey, chicken, red-legged partridge); Psittaciformes: psittaculid (Indian ring-necked parrot, rose-ringed parakeet), cacatuid	enteric (acute)	worldwide

		(cockateil), bombycillid (Bohemian waxwing); Columbiformes: columbid (fan-tailed pigeon, rufous turtle dove); Anseriformes: anatid (ducks); Primates: hominid (human, mountain gorilla); Carnivora: canid (dog), Lagomorpha: leporid (rabbit); Diprotodontia: macropodid (brush-tailed rock-wallaby); Rodentia: murid (mice, deer mouse, rats); Artiodactyla: suid (pig), bovid (cattle)		
C. microti	4.3 x 4.1	Rodentia: cricetid (common vole, meadow vole)	intestines	Europe
C. molnari	4.7 x 4.5	Cypriniformes: cyprinid (bream, goldfish, fringe barb, Eurasian carp), gyrinocheilid (golden algae-eater); Cyprinodontiformes: apaniid (Arabian toothcarp), poecilid (guppy); Cichliformes: cichlid (oscar, altum angelfish); Moroniformes: moronid (European sea bass); Perciformes: monodactylid (butter bream); opistognathid (yellowhead jawfish), percichthyid (Murray cod), pomacanthid (red stripe angelfish), pomacentrid (orange clownfish, azure damselfish, green chromis), serranid (peach fairy basslet, Madder seaperch), sparid (gilt-head sea bream); Acanthuriformes: acanthurid (bristletooth tang, wedgetail blue tang, Tomini surgeonfish, blue surgeonfish); Esociformes: esocid (northern pike); Siluriformes: mochokid (blotched upsidedown catfish)	stomach (chronic)	Europe, Australia
C. muris (= *C. muris* genotype B)	8.4 x 6.3	Rodentia: murid (mouse, Algerian mouse, spiny mouse, wood mouse, multimammate mice, brown rat), sciurid (eastern grey squirrel, Siberian chipmunk), cricetid (golden hamster, desert hamster, Campbell's dwarf hamster, Djungarian hamster, Roborovski hamster, bank vole, Brandt's vole), spalacid (East African mole-rat), caviid (guinea pig, Patagonian mara); Lagomorpha: leporid (rabbit); Hyracoidea: procaviid (rock hyrax); Carnivora: felid (cat), canid (dog, coyote), phocid (ringed seal); Peramelemorphia: thylacomyid (greater bilby), Dasyuromorphia: dasyurid (Tasmanian devil); Primates: hominid (human, mountain gorilla), cercopithecid (crab-eating macaque), lorisid (Sunda slow loris); Artiodactyla: bovid (cattle, goat, sheep, Cuvier's gazelle), camelid (camel), giraffid (reticulated giraffe), suid (pig); Perissodactyla: equid (horse); Caprimulgiformes: podargid (tawny frogmouth); Struthioniformes: struthionid (ostrich); plus pseudo-parasitism (passive food-borne transmission?) Serpentes: boid (boa constrictor), colubrid (black rat snake, yellow rat snake, corn snake), pythonid (ball python), elapid (taipan); Sauria: varanid (crocodile monitor); Anura: ceratophryid (Argentine horned frog)	gastric (chronic)	worldwide
C. myocastoris (= coypu genotype)	5.0 x 4.8	Rodentia: echimyid (nutria)	intestines	Europe
C. nasoris (syn. *C. nasorum*) (not genotyped) (considered *nomen nudum*)	4.3 x 3.2	Perciformes: acanthurid (lipstick tang)	enteric (chronic)	North America
C. occultus *(= C. suis*-like genotype and *C. parvum* VF383)	5.2 x 4.9	Rodentia: murid (brown rat, Tanezumi rat, house mouse, Mongolian gerbil); Artiodactyla: bovid (cattle, yak, water buffalo); Primates: hominid (human)	intestines	Eurasia, Americas, Australia
C. ornithophilus	6.1 x 5.1	Struthioniformes: struthionid (ostrich);	intestines	Eurasia,

(= avian genotype II)		Galliformes: phasianid (chicken), Anseriformes: anatid (goose); Psittaciformes: cacatuid (cockateil, galah, Major Mitchell cockatoo), psittacid (sun conure, white-eyed parakeet), psittaculid (eclectus parrot, Alexandrine parrot, princess parrot)		South America, Australia
C. parvum (= *C. parvum* mouse genotype I)	5.2 x 4.6	Artiodactyla: bovid (cattle, sheep, blue wildebeest, slender-horned gazelle, bongo antelope, eland, yak, sable antelope), suid (pig), camelid (alpaca), cervid (swamp deer, roe deer, red deer, sika deer); Perissodactyla: equid (horse); Carnivora: canid (dog, raccoon dog, red fox, gray wolf), mephitid (skunk); Lagomorpha: leporid (rabbit); Rodentia: sciurid (eastern grey squirrel, Siberian chipmunk, marmot), murid (mouse, Algerian mouse, wood mouse, yellow-necked mouse, deer mouse, black rat), caviid (capybara), cricetid (vole, golden hamster, Djungarian hamster, Campbell's dwarf hamster, southern red-backed vole); Chiroptera: vespertilionid (mouse-eared bat, big brown bat); Eulipotyphla: erinaceid (European hedgehog); Cetacea: delphinid (striped dolphin, bottlenose dolphin); Diprotodontia: macropodid (red kangaroo, rock-wallaby), phascolarctid (koala); Primates: hominid (human, mountain gorilla), cercopithecid (gray langur, purple-faced langur, rhesus macaque); Anseriformes: anatid (Canada goose); Ciconiiformes: ciconiid (white stork); Falconiformes: falconid (gyrfalcon); Gruiformes: rallid (Eurasian coot); Psittaciformes: cacatuid (cockateil); Passeriformes: estrildid (Bengalese finch); Charadriiformes: chionid (stone curlew); Testudines: testudinid (marginated tortoise); Sauria: gekkonid (gecko, leopard gecko), iguanid (green iguana), varanid (monitor); Carangiformes: carangid (mackerel scad); Cichliformes: cichlid (Nile tilapia); Clupeiformes: clupeid (Atlantic herring, pilchard), engraulid (European anchovy); Cypriniformes: cyprinid (common roach, goldfish, Java barb); Esociformes: esocid (northern pike); Gadiformes: gadid (Atlantic cod), lotid (blue ling); Perciformes: latid (barramundi), percid (European perch), sillaginid (golden whiting); Salmoniformes: salmonid (Arctic char, common whitefish, rainbow trout, brown trout); Scombriformes: scombrid (chub mackerel, Atlantic mackerel)	enteric, gastric in some fish (acute-chronic)	worldwide
C. pestis (= genotype C or *C. parvum* bovine genotype II)	4-5	Primates: hominid (human); Rodentia: murid (mouse); Artiodactyla: bovid (cattle)	enteric (acute- chronic)	worldwide
C. proliferans (= *C. muris* strain TS03)	7.7 x 5.3	Rodentia: murid (mouse, spiny mouse, multimammate mice, Tristam's jird, bushy-tailed jird, lesser gerbil, Mongolian gerbil), cricetid (Brandt's vole), sciurid (gray squirrel), spalacid (mole-rat); Perissodactyla: equid (donkey, horse), bovid (African buffalo)	gastric (chronic)	Eurasia, Africa, Americas
C. proventriculi (= avian genotype III)	7.4 x 5.8	Psittaciformes: cacatuid (cockateil)	proventriculus, ventriculus	Australia
C. ratti (= rat genotype 1)	4.9 x 4.7	Rodentia: murid (brown rat)	enteric	Europe
C. (*Piscicryptosporidium*) *reichenbachklinkei*	2.9	Anabantiformes: osphronemid (gourami); Cichliformes: cichlid (freshwater angelfish, oscar); Characiformes: characid (neon tetra)	gastric	Middle-East, Asia
C. rubeyi	4.7 x 4.3	Rodentia: sciurid (California ground squirrel,	enteric	North

(= genotype Sbey03c)		prairie dog)	(chronic)	America
C. ryanae (= deer-like genotype)	3.7 x 3.2	Artiodactyla: bovid (cattle, water buffalo?, zebu?)	enteric (chronic)	worldwide
C. scophthalmi (not genotyped)	4.4 x 3.9	Pleuronectiformes: scophthalmid (turbot)	enteric (chronic)	Europe
C. scrofarum (= pig genotype II)	5.2 x 4.8	Artiodactyla: suid (pig); Rodentia: murid (brown rat, Asian house rat); rarely Primates: hominid (human); Perciformes: sillaginid (western school whiting)	enteric (chronic)	worldwide
C. serpentis	6.2 x 5.3	Serpentes: elapid (death adder, tiger snake, taipan), viperid (Bornmueller's viper, mountain viper, Nikolski viper, diamondback rattlesnake, timber rattlesnake, tropical rattlesnake, jararaca, jararacussu), colubrid (rat snakes, bull snake, king snakes, pine snake, fox snake, milk snake, leaf-nosed snake, corn snake), boid (tree boas, boa constrictor, rainbow boas, green anaconda, viper boa, rosy boa), pythonid (ball python, green python, Burmese python, Boelen's python, rock python); Sauria: agamid (bearded dragon, frilled lizard), chamaeleonid (Madagascar chameleon, mountain chameleon), gekkonid (gargoyle gecko, leopard gecko), scincid (skink), varanid (desert monitor, emerald monitor, Nile monitor, Savannah monitor); Artiodactyla: bovid (cattle); Rodentia: murid (mouse)	gastric (chronic)	worldwide
C. suis (= pig genotype I)	4.6 x 4.2	Artiodactyla: suid (pig), bovid (cattle, sheep); Rodentia: murid (mice, Asian house rat); Primates: hominid (human)	enteric	Europe, Australia
C. testudinis (= tortoise genotype I)	6.4 x 5.9	Testudines: testudinid (radiated tortoise, Chaco tortoise, serrated tortoise, leopard tortoise, Greek tortoise, Hermann's tortoise, Russian tortoise, marginated tortoise, Indian star tortoise); Serpentes: pythonid (ball python)	nd	Europe
C. tyzzeri (= mouse genotype I)	4.6 x 4.2	Rodentia: murid (mouse, yellow-necked mouse, brown rat, Asian house rat), cricetid (voles); Chiroptera: vespertilionid (large-footed bat); Carnivora: felid (cat, black leopard), ailurid (lesser panda); Artiodactyla: suid (pig), bovid (American bison, Barbary sheep, takin); rarely Primates: hominid (human); Serpentes: boid (boa constrictor, emerald tree boa), colubrid (black rat snake, king snake, corn snake, fox snake, milk snake), elapid (red-bellied black snake), pythonid (ball python, Woma python); Sauria: varanid (mangrove monitor)	enteric (chronic)	worldwide
C. ubiquitum (= deer genotype)	5.0 x 4.7	Artiodactyla: bovid (sheep, goat, cattle, impala, blesbok, African buffalo, nyala, alpine ibex, mouflon), cervid (swamp deer, roe deer, red deer, sika deer, white-tail deer); Diprotodontia: macropodid (rock-wallaby); Carnivora: procyonid (raccoon); Rodentia: murid (mouse, deer mouse, gerbil), sciurid (American red squirrel, Eurasian red squirrel, eastern grey squirrel, fox squirrel, eastern chipmunk, woodchuck), castorid (beaver), erethizontid (prehensile-tailed porcupine); Primates: hominid (human)	enteric (acute)	worldwide
C. varanii (syn. *C. saurophilum*) (= desert monitor genotype)	4.8 x 4.7	Sauria: varanid (desert monitor, emerald monitor), agamid (bearded dragon), chameleonid (mountain chameleon, veiled chameleon), gekkonid (African fat-tailed gecko, gargoyle gecko, leopard gecko), gerrhosaurid (plated lizard), iguanid (green iguana), lacertid (green lizard), scincid (ocellated skink,	enteric (chronic)	worldwide

		Schneider's skink, skink); Serpentes: boid (boa constrictor, viper boa), colubrid (black rat snake, bull snake, corn snake, pine snake, milk snake), pythonid (green python)		
C. viatorum	5.4 x 4.7	Primates: hominid (human)	enteric (acute)	Europe (ex: India, Africa, Central America)
C. wrairi	5.4 x 4.6	Rodentia: caviid (guinea pig), sciurid (ground squirrel), murid (mouse); Artiodactyla: bovid (cattle, sheep)	enteric (chronic)	North America, Europe
C. xiaoi (= *C. bovis*-like genotype) (syn. *C. agni*)	3.9 x 3.4	Artiodactyla: bovid (sheep, goat, yak), Diprotodontia: macropodid (western grey kangaroo); Perciformes: sillaginid (western school whiting)	enteric (chronic)	Eurasia, Africa, North America, Australia

Parasite morphology: The parasites form three developmental stages: meronts, gamonts and oocysts. Endogenous developmental stages appear as small basophilic bodies (3-6 µm) attached to the luminal surface of host epithelial cells (epicellular location). These stages are located within parasitophorous vacuoles formed by a covering of microvilli (intracellular but extracytoplasmic) and developing parasites form a prominent lamellated feeding organelle at the site of attachment to the host cell at the base of the vacuole. Meronts divide internally to form multiple merozoites while gamonts mature to form uninucleate macrogametocytes (female) and multinucleate microgametocytes (male). Exogenous oocysts appear as ovoid membrane-bound phase-bright bodies (5-7 x 4-6 µm) containing four sporozoites and an eccentric residual body (sporocysts are not formed). Since the development of *in vitro* cultivation techniques for *Cryptosporidium*, several observations have been made reinforcing the belief suggested by molecular phylogenetic analyses that these parasites are gregarines rather than coccidia. In addition to their epicellular location, epimerite-like feeding organelle, myzocytosis-like feeding mechanism and zoite structural heterogeneity, cryptosporidial stages were found to survive and multiply extracellularly (even in biofilms), move using a gregarine-like gliding motion and undergo syzygy (pairing) prior to gamogony.

Site of infection: Most parasite species infect the small intestines of their hosts (mammals) whereas others infect the respiratory tract (birds) or stomach (reptiles). The parasites undergo several cycles of asexual merogonous development before gamonts are formed. After fertilization, the oocysts mature in the gut and are usually infective as soon as they are excreted from the host.

Pathogenesis: Infections vary markedly in their presentation ranging from asymptomatic to mild acute to severe chronic disease. Endogenous intestinal stages may cause microvillus destruction, villus atrophy, impaired glucose and electrolyte transport, impaired carbohydrate and protein digestion manifesting in malabsorptive and maldigestive disease. Most clinical infections in immunocompetent individuals involve transient acute disease characterized by profuse watery foul-smelling diarrhoea or acute respiratory signs, anorexia, depression, ill-thrift and occasionally death. Neonates and malnourished individuals are most susceptible, whereas older animals become resistant (immune) to infection. Infections may persist in immunocompromised individuals (those with congenital or acquired immunodeficiencies or those undergoing immunosuppressive therapy) resulting in protracted chronic disease which may prove fatal (especially in AIDS patients). In contrast, infections in reptiles (and possibly fish) cause chronic gastritis typified by postprandial regurgitation.

Developmental cycle and mode of transmission: Oocysts excreted by infected hosts contaminate the environment and initiate infections when ingested by susceptible hosts (faecal-oral transmission). This direct transmission cycle may involve the contamination of fomites, water and/or food sources. Some (thin-walled) oocysts are thought to be auto-infective and may excyst in the same host. Parasites undergo two cycles of asexual development (type I and type II merogony) followed by sexual development (gamogony), fertilization (oocyst formation) and sporozoite differentiation (sporogony). Most infections are transmitted by fomites between individuals held in close confinement, such as in child day-care centres, hospitals, zoos, and intensive animal rearing facilities. In addition, oocysts are being detected with increased frequency in treated and untreated water supplies. Many water-borne outbreaks of public health significance have been reported involving contamination of potable and recreational waters (lakes, pools, water parks) by sewage and/or agricultural waste. While conventional methods of water treatment (filtration and chlorination) may reduce contamination levels (quantified by log removal and concentration-time parameters), the small tough oocysts are quite resistant and enough persist to pose a significant problem for water providers. Food-borne transmission has also been recorded (involving milk, cider, salads, sausages), probably attributable to contaminated water being used in food production.

Differential diagnosis: Infections are conventionally diagnosed by the detection of oocysts in smears or concentrates of faecal material or respiratory exudates. Unstained oocysts may be confused with yeasts but they are acid-fast and stain well with basic

fuchsin stains. Alternatively, phase-contrast or differential interference contrast microscopy can be used to reveal internal oocyst features, as can vital dyes (DAPI) and fluorescent nucleic acid stains (MPR71059). Although some parasite species can be cultured *in vitro* (in tissue cultures) or *in vivo* (in laboratory or neonatal domestic animals), considerable variation has been observed in parasite infectivity and growth. More success has been reported in detecting oocysts in clinical and environmental samples using specific monoclonal antibodies for immunomagnetic separation or as fluorescent markers for microscopy or flow cytometry. Researchers have also developed several highly sensitive techniques using polymerase chain reaction (PCR) amplification of partial gene sequences followed by electrophoretic fingerprinting (e.g. nested PCR, PCR-RFLP, RT-qPCR. Community epidemiological studies rely on molecular genotyping (and subgenotyping) of clinical and environmental isolates to indicate their anthroponotic and zoonotic potential.

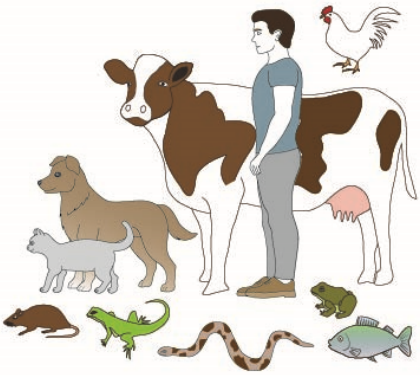
Treatment and control: There is currently no effective chemotherapeutic treatment for cryptosporidiosis, although variable success has been reported using paromomycin, nitazoxanide, tylosin and azithromycin. Supportive treatment by oral or parenteral rehydration may help alleviate symptoms. Some promising results have been obtained using hyperimmune bovine colostrum for passive immunotherapy. Control measures include identification of the source of infection, isolation of infected individuals, maintaining high standards of hygiene, proper effluent disposal, water treatment and disinfection of contaminated surfaces. The oocysts are highly resistant to external environmental conditions and they can survive many commonly used drinking water disinfectants. The oocysts are also very small and may not be removed by inefficient water filtration. Public health authorities recommend boiling water during outbreak situations and also more regularly for high-risk patients groups (such as HIV-positive individuals).

Cryptosporidium

monoxenous (1-host) cycle

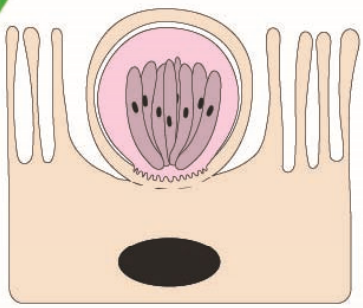
intestines
(malabsorption,
watery diarrhoea)

unique feeder organelle
and parasitophorous vacuole
(epicellular, yet extracytoplasmic)

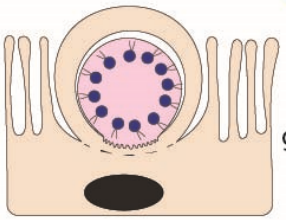


Definitive Hosts
(mammals, birds,
reptiles, fish,
amphibians)

meronts
(3-6 µm)

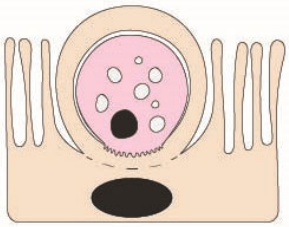


asexual multiplication
(merogony) (several cycles)



micro-
gamont
(male)

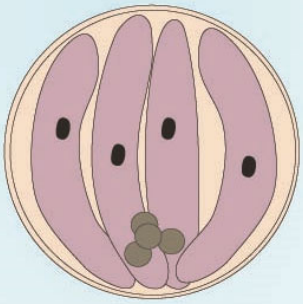
sexual reproduction
(gamogony)



macro-
gamont
(female)

oocysts
ingested

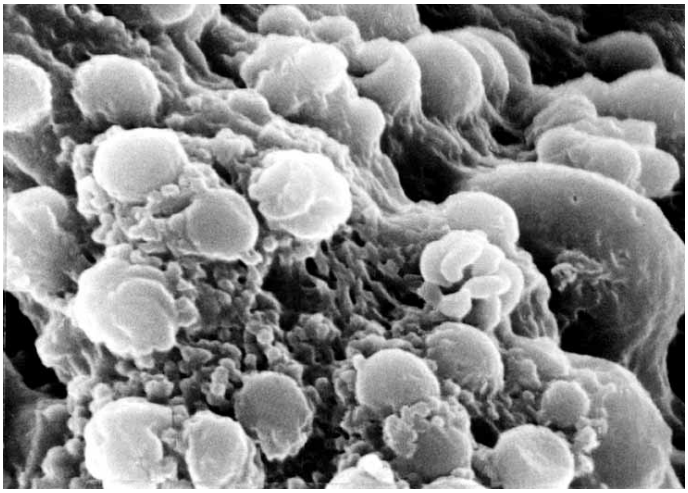
oocysts shed
in faeces



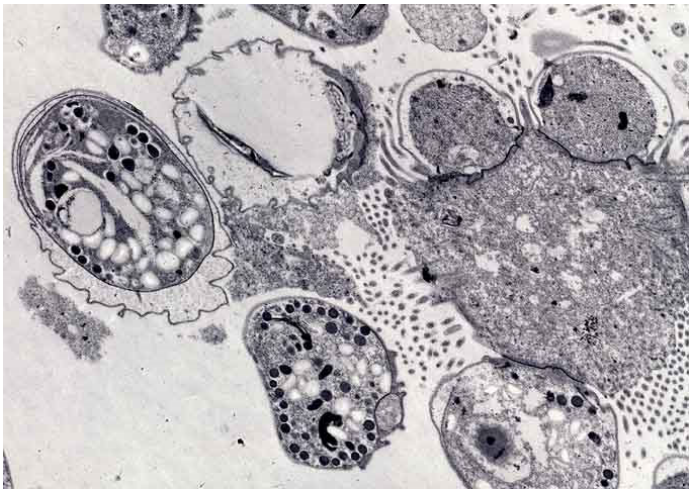
4 naked sporozoites
(no sporocyst)

oocysts
(5-7 µm)

faecal-oral transmission between hosts
via oocysts contaminating environment,
including food/water sources

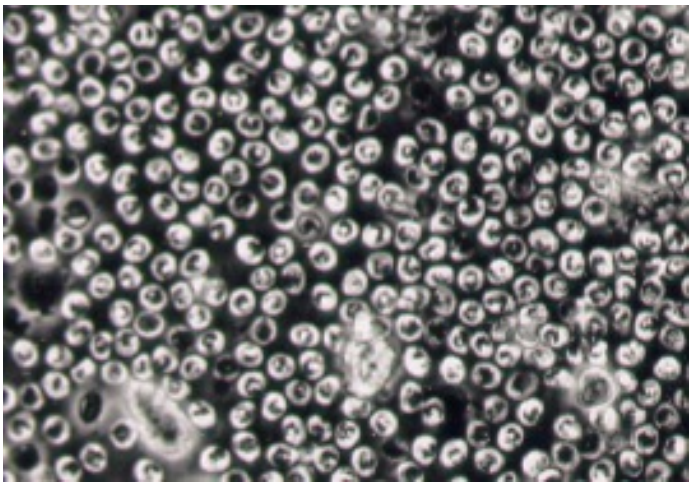


Cryptosporidium endogenous stages (sEM)

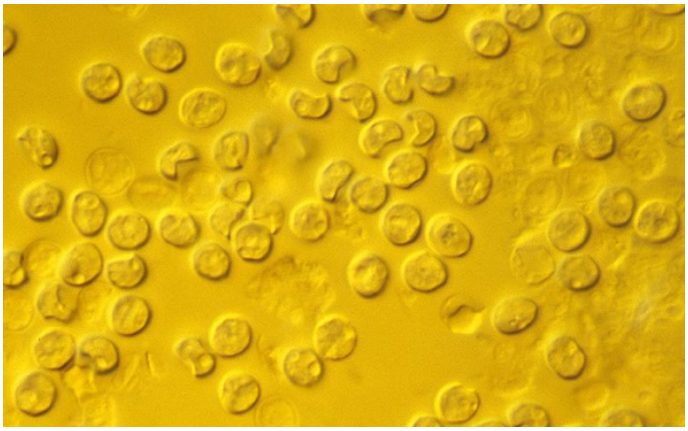


Cryptosporidium endogenous stages (tEM)

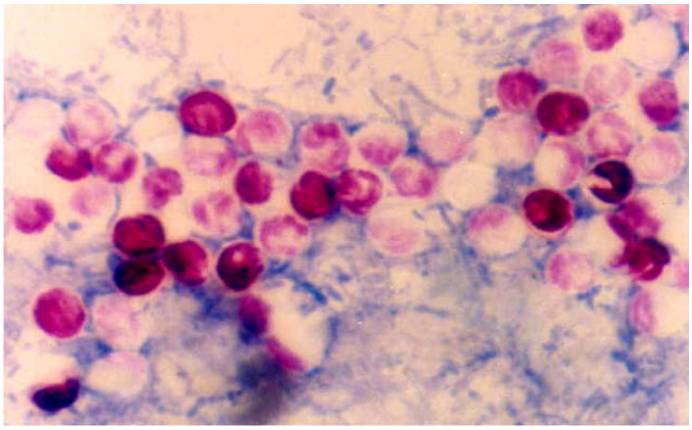
Cryptosporidium endogenous stages on mouse gut



Cryptosporidium oocysts in snake faeces



Cryptosporidium oocysts in faecal float



Cryptosporidium oocysts in faecal smear