

## ***Toxoplasma gondii***

*Toxoplasma gondii* is a protozoan parasite that causes the disease toxoplasmosis. It is a very common parasitic infection in humans and other warm-blooded animals, with approximately a third of the world's human population estimated to have been exposed to the parasite. Toxoplasmosis can be asymptomatic (no clinical symptoms) or can have more severe consequences such as congenital birth defects, eye disease, or potentially fatal toxoplasmic encephalitis in immunocompromised individuals.

### **Description of the organism**

*T. gondii* is a protozoan parasite which belongs to the phylum *Apicomplexa*, subclass *Coccidiasina* and family *Sarcocystidae* (Hill et al. 2007; Pereira et al. 2010). The infective stages of the parasite can take three different forms – sporozoites, tachyzoites and bradyzoites. Following sporulation in the environment, oocysts containing sporozoites are infective, and give rise to tachyzoites when ingested by an intermediate host. Most species of mammals and birds are susceptible to infection and may serve as an intermediate host (Thompson et al. 2009). Tachyzoites are the rapidly replicating stage of the parasite and are disseminated around the body via the bloodstream and infect a variety of tissues. The rapid replication and release of tachyzoites from host cells causes tissue damage and provokes a strong inflammatory response and therefore is responsible for the clinical manifestations of disease. Bradyzoites are structurally similar to tachyzoites but replicate slowly in tissue cysts that form intracellularly in brain, cardiac and skeletal muscle tissue of the host. Bradyzoites are not responsible for acute clinical disease; and can persist for the life of the host without causing a host inflammatory response (Dubey et al. 1998; Montoya and Liesenfeld 2004).

### **Growth and survival characteristics**

Depending on environmental conditions, the time taken for oocysts to sporulate and become infectious ranges from one day to several weeks. Conditions such as aeration and temperature affect the length of time required for sporulation to occur, with lower temperatures slowing the sporulation rate (Lindsay et al. 2002; Jones et al. 2003; Hill et al. 2007). A study conducted by Lindsay (2002) demonstrated that unsporulated oocysts can survive in the environment at 4°C and retain their ability to sporulate for at least 3 months. Sporulated oocysts are more resilient than unsporulated oocysts. Once sporulated, oocysts maintain infectivity in moist soils for up to 18 months (Frenkel et al. 1975) and in water and seawater for several years at 4°C (Dubey 1998a; Lindsay and Dubey 2009). The duration of infectivity, however, decreases with increasing temperatures. Infectivity is maintained for at least 200 days in the temperature range of 10–25°C, for 1 month at 35°C, for 1 day at 45°C and sporulated oocysts become non-infective after 1 minute at 60°C (Dubey 1998a). Unsporulated oocysts die within 24 hours when stored at 37°C, whereas sporulated oocysts can survive for over a month at 35°C and 9 days at 40°C (Lindsay et al. 2002). Constant freezing at -21°C kills unsporulated and sporulated oocysts within 1 and 28 days, respectively (ESR 2010).

*T. gondii* tissue cysts remain viable in infected meat stored at refrigeration temperatures of 4°C for up to 19 days. Cooking infected meat to internal temperatures of 67°C or higher inactivates the tissue cysts (Dubey et al. 1990; Dubey 2004). Freezing meat at -10°C for 3 days or -20°C for 2 days or treatment with gamma irradiation at a dose of 75 krad is also sufficient to kill tissue cysts (El-Nawawi et al. 2008). Tachyzoites that may be found in the milk of intermediate hosts are inactivated by pasteurisation (Tenter et al. 2000).

Bradyzoites found in tissue cysts are resistant to gastric digestion, whereas tachyzoites are usually destroyed by the acid and proteolytic enzymes of the stomach (Tenter 2009). Experimental evidence indicates that tachyzoites may survive in acid-pepsin solution for up to 2 hours (Dubey 1998b) and the type of meal eaten may also increase the pH of the stomach and allow tachyzoites to traverse the stomach into the small intestine in an infective state (Tenter 2009).

## Symptoms of disease

Most human infections with *T. gondii* are asymptomatic, but infection may result in severe clinical disease and on occasion be fatal. Infection in humans may be acquired postnatally or *in utero* and may result in fetal death, congenital toxoplasmosis, toxoplasmic encephalitis, ocular toxoplasmosis or less severe acute self-limiting disease (Montoya and Liesenfeld 2004).

In healthy adults and children the majority of postnatally acquired infections are asymptomatic with only 10–20% of individuals developing a self-limiting and non-specific illness (Montoya and Liesenfeld 2004; Pereira et al. 2010). Symptoms of disease may include mild, flu-like illness with low grade fever, muscular pain, swollen lymph nodes, lethargy and headache (Abu-Madi et al. 2010; ESR 2010). Enlarged lymph nodes are the most commonly observed clinical manifestation of human toxoplasmosis (Hill and Dubey 2002). The onset of illness is 3–25 days (mean of 11 days) (Hill et al. 2007; Ayi et al. 2009; ESR 2010).

Toxoplasmic retinochoroiditis (inflammation of the retina and choroid) can be associated with congenital or postnatally acquired disease as a result of acute infection or reactivation of a latent infection (Montoya and Liesenfeld 2004). In humans, the parasite multiplies in the retina causing inflammation in the choroid; the parasite does not multiply in the choroid (Dubey et al. 2012). Typical findings of both postnatally acquired and congenital retinochoroiditis include white-appearing lesions with overlying severe inflammation of the viscous fluid at the back of the eye (Montoya and Liesenfeld 2004; Delair et al. 2011). These symptoms occur as a consequence of active retinal lesions, leading to retinal scarring. Toxoplasmic retinochoroiditis is a significant cause of vision loss. The natural course of ocular toxoplasmosis and the long term impact on vision depends on the frequency of recurrences, with retina destruction minimised if active disease is treated early. Recurrence of retinochoroiditis can occur for both postnatally acquired and congenital toxoplasmosis. Severe complications associated with ocular toxoplasmosis may include fibrous bands, retinal detachment, cataracts and inflammation and damage to the optic nerve (Delair et al. 2011). Ocular disease is one of the most important clinical manifestations of acute, postnatally acquired toxoplasmosis, particularly in countries such as Brazil. The majority of cases of ocular toxoplasmosis are postnatally acquired (Dubey et al. 2012).

Congenital toxoplasmosis occurs when a woman becomes infected with *T. gondii* during pregnancy. Tachyzoites circulating in the mother's bloodstream can invade and multiply in the placenta and subsequently infect the foetus. Transmission of the parasite *in utero* can cause congenital defects or spontaneous abortion. These congenital defects can include ocular toxoplasmosis, hydrocephalus (big head), mental retardation and intracranial calcifications (Hill et al. 2007; Zhou et al. 2011). Although the risk of transmission is less common in the first trimester, congenital infections acquired during the first trimester are more severe than those acquired in the second or third trimester of pregnancy (Montoya and Liesenfeld 2004; Hill et al. 2007; Ayi et al. 2009).

In infected immunocompromised individuals, the parasite may be uncontrollably released due to the rupture of tissue cysts in the brain (Feustel et al. 2012). This leads to symptoms that affect the central nervous system, including headache, altered mental status, seizures, hemiparesis (muscle weakness on one side of the body),

ataxia and/or facial weakness. If left untreated; the infection may progress to fatal toxoplasmic encephalitis (Walker and Zunt 2005; Feustel et al. 2012). Immunocompromised individuals are susceptible to toxoplasmic encephalitis from either acquired infection or reactivation of a latent infection, however it is believed the majority of toxoplasmic encephalitis cases are due to the latter (Montoya and Liesenfeld 2004). Reactivation occurs if the bradyzoites are released from the cysts and convert into tachyzoites due to the suppression of the host immune response that previously inhibited parasite activity. This rupture of the cysts in immunocompromised individuals generally occurs in the brain (Feustel et al. 2012). In Australia the rate of hospitalisations due to toxoplasmic encephalitis declined substantially from a peak in 1993 due to prophylactic treatment of human immunodeficiency virus (HIV) patients (Huppertz et al. 2009).

### Virulence and infectivity

*T. gondii* virulence and infectivity are reliant on factors that control parasite-host cell interactions and/or moderate the host immune response (Dubremetz and Lebrun 2012). The population structure of *T. gondii* is comprised of three highly abundant and overrepresented genetic lineages, commonly referred to as genotypes I, II and III, amongst a diverse array of related genotypes (Su et al. 2012). The three clonal lineages are very closely related but the small genetic differences result in distinct phenotypic differences in infectivity and virulence (Sibley and Ajioka 2008).

Most virulence studies have involved genotypes I, II and III and virulence has typically been assessed in a mouse pathogenicity model, with comparatively little known about human infection (Dubremetz and Lebrun 2012). In the mouse model, highly virulent strains are typically genotype I whereas the vast majority of non-virulent strains are genotype II and III (Sibley and Boothroyd 1992). Little is known about atypical or recombinant genotypes (Dubremetz and Lebrun 2012). In humans, the evidence for strain specific virulence is less well studied and relies predominantly on epidemiological evidence. The majority of human cases have been attributed to genotype II (Howe and Sibley 1995) which is likely to be an artefact of an overrepresentation of this genotype in animals in Europe and the United States (US) where most human cases have been documented (Boothroyd and Grigg 2002). The virulent nature of genotype I strains in mice may, however, extend to humans as severe ocular disease in otherwise immunocompetent adults have been attributed to genotype I strains (Boothroyd and Grigg 2002). Furthermore, non-genotype II strains have been associated with more severe disease at birth in congenitally infected newborns in the US (McLeod et al. 2012). More recently, highly virulent atypical genotypes in French Guiana and Brazil have caused severe disease in immunocompromised individuals, fetuses and otherwise healthy individuals (Carme et al. 2009; Dubey et al. 2012). In Australia, genotype II strains have been reported from a human isolate (Sibley and Boothroyd 1992) and a dog isolate (Al-Qassab et al. 2009) and atypical and type II-like strains have been isolated from native Australian wildlife (Parameswaran et al. 2010). Of the few Australian isolates examined thus far, all have been avirulent in mouse bioassays.

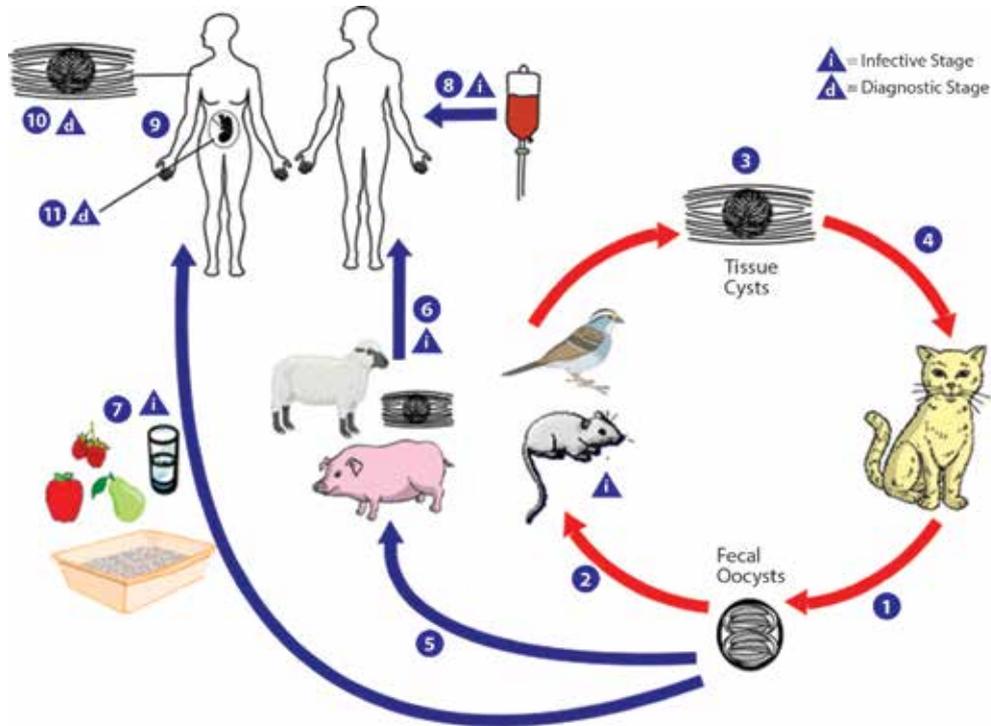
### Mode of transmission

The principal modes of *T. gondii* transmission are ingestion of faecal oocysts or tissue cysts, and the transplacental transmission of tachyzoites from mother to unborn child. Infection with faecal oocysts may occur by accidentally ingesting contaminated soil (e.g. not washing hands after gardening or eating unwashed fresh produce), drinking untreated contaminated water, eating shellfish grown in contaminated water, or contact with cat faeces (e.g. a cat litter box). Infection from tissue cysts may occur by consuming raw or undercooked meat, by accidentally consuming tissue cysts after handling raw meat and not washing hands thoroughly, or by cross-contamination of food prepared using unwashed utensils and chopping boards that have had contact

with raw meat (Abu-Madi et al. 2010; CDC 2010; Pereira et al. 2010). Oocyst-acquired infections in humans are clinically more severe than tissue cyst-acquired infections (Dubey 2004). As tachyzoites are sensitive to environmental conditions they are usually killed rapidly outside the host and so are rarely involved in foodborne transmission of *T. gondii* (Tenter 2009).

Organ transplant recipients can develop toxoplasmosis due to transmission of the parasite with the transplanted organ from a *Toxoplasma*-seropositive donor to a *Toxoplasma*-seronegative recipient. Heart transplantation is the most common type of organ transplantation procedure when this occurs, as cysts form in the cardiac muscles (Martina et al. 2011; Derouin and Pelloux 2012). However, toxoplasmosis is an uncommon outcome from organ transplantation as only 5% of human pathogenic parasites have reportedly caused significant illness in transplant recipients (Barsoum 2006). It is also possible that parasite transmission could occur as the result of blood transfusion or haematopoietic stem cell transplantation. The chance of either of these occurring is very low and could only occur if the donor was recently infected with *T. gondii* and so had tachyzoites present in their blood and bone marrow (Derouin and Pelloux 2012).

Infection of the feline definitive host occurs when a cat consumes an intermediate host (such as a mouse or bird) infected with tissue cysts. Upon ingestion of a tissue cyst by a susceptible cat, the walls of the cyst are digested by proteolytic enzymes and bradyzoites are released. The bradyzoites undergo asexual reproduction followed by sexual reproduction in intestinal epithelial cells to produce microgametocytes and macrogametocytes. The microgametocytes fertilise the macrogametocytes, leading to the production of zygotes. The zygotes differentiate into unsporulated oocysts and are shed in the faeces of the definitive host (Ortega 2007; Jones and Dubey 2010). After a prepatent period of up to 10 days following primary infection with tissue cysts, a cat may shed more than 100 million oocysts into the environment over a 2-3 week period (Tenter et al. 2000).

Figure 1: Life cycle of *T. gondii* (CDC–DPDx 2009)

- (1) Unsporulated oocysts are shed in cat's faeces.
- (2) Intermediate hosts in nature (including birds and rodents) become infected after ingesting sporulated oocysts in contaminated soil, water or plant material.
- (3) Oocysts transform into tachyzoites shortly after ingestion. These tachyzoites localize in neural and muscle tissue and develop into tissue cyst bradyzoites.
- (4) Cats become infected after consuming intermediate hosts harbouring tissue cysts. Cats may also become infected directly by ingestion of sporulated oocysts.
- (5) Food animals and wild game may also become infected with tissue cysts after ingestion of sporulated oocysts in the environment. Humans can become infected by multiple routes:
  - (6) eating undercooked meat of animals harbouring tissue cysts;
  - (7) consuming oocysts in food or water contaminated with cat faeces or by contaminated environmental samples (such as faecally contaminated soil or changing the cat litter box);
  - (8) blood transfusion or organ transplantation; or
  - (9) transplacental transmission of tachyzoites from mother to unborn child.
- (10) Diagnosis is usually achieved by serology, although tissue cysts may be observed in stained biopsy specimens.
- (11) Diagnosis of congenital infections can be achieved by detecting *T. gondii* DNA in amniotic fluid using molecular methods.

(CDC–DPDx 2009)

## Incidence of illness and outbreak data

Toxoplasmosis is one of the most common parasitic zoonoses worldwide. It is estimated that around a third of the world's population have the parasite, with the majority of cases being asymptomatic (Pereira et al. 2010; Innes 2010). Despite a large proportion of the population being seropositive for *T. gondii*, scientific literature indicates that the seroprevalence is decreasing in several countries including France, Belgium, the United Kingdom and the US (Rosso et al. 2008).

The incidence and prevalence of toxoplasmosis in Australia is difficult to estimate since toxoplasmosis is not a notifiable disease (DOHA 2005; AWHN 2009) and most *T. gondii* infections are asymptomatic. Reliable estimates of incidence tend to come from high risk groups such as newborn infants. However, not all new cases can be attributed to foodborne exposure during pregnancy since environmental, water and cat exposure also result in transmission to the mother. Similarly, incidence of toxoplasmosis during pregnancy is not necessarily representative of the wider population. In a small study from south eastern Australia, incidence of congenital toxoplasmosis from 2001–2009 was estimated at 0.17 cases per 10,000 live births (Jayamaha et al. 2012).

International estimates of incidence or prevalence at birth tend to be higher than Australia, but caution should be exercised in drawing conclusions since many European countries have prenatal screening programs. Incidence or prevalence at birth of congenitally acquired toxoplasmosis, both reported as cases per 10,000 live births, have been reported for France (2.9/10,000) (Villena et al. 2010), Poland (11/10,000) (Paul et al. 2001), Sweden (0.7/10,000) (Evangard et al. 2001), Denmark (1.6/10,000) (Roser et al. 2010), Brazil (10-13/10,000) (Vasconcelos-Santos et al. 2009; Bichara et al. 2012), Columbia (9.8/10,000) (Gomez-Marin et al. 2011) and Mexico (20/10,000) (Vela-Amieva et al. 2005). In Poland, when only susceptible women (i.e. non-immune mothers) were taken into account, the incidence of congenital toxoplasmosis increased to 20 cases per 10,000 live births (Paul et al. 2001). A study of birth prevalence in non-immune mothers in Western Australia found 2.3 cases per 10,000 live births (Walpole et al. 1991).

It is widely accepted that outbreaks of toxoplasmosis involving more than a single family or small group are rare and infrequently reported (Demar et al. 2007). Water and undercooked meat have been associated in *T. gondii* outbreaks (refer to Table 1).

**Table 1: Selected major foodborne outbreaks associated with *T. gondii* ( $\geq 5$  cases and/or  $\geq 1$  fatality)**

Year	Total no. cases	No. congenital cases	Food	Country	Comments	Reference
2001-2002	176	0	Water and ice cream	Brazil	Kittens lived on top of the water reservoir tank. Rainfall may have carried oocysts into water reservoir. Ice cream prepared from contaminated water	(de Moura et al. 2006)
1995	5	0	Pork liver	Korea	Consumption of raw pork offal from a domestic pig	(Choi et al. 1997)
1994	13	1	Kangaroo meat	Australia	Consumption of undercooked meat	(Robson et al. 1995)
1993	17	0	Mutton	Brazil	Consumption of raw mutton	(Bonametti et al. 1997)

## Occurrence in food

The type of food most often associated with toxoplasmosis is raw or undercooked meat, including lamb, pork, venison, free-range poultry and game meat (Jones et al. 2009; Jones and Dubey 2012; Chumpolbanchorn et al. 2013). Beef consumption is not considered important since cattle are a poor intermediate host (Jones and Dubey 2012). Ingestion of unfiltered water contaminated with *T. gondii* oocysts has also been associated with toxoplasmosis (Jones et al. 2003; Bahia-Oliveira et al. 2003; Pereira et al. 2010). Tachyzoites of *T. gondii* have been found in unpasteurised milk of sheep, goats and cows; however, only consumption of unpasteurised goat's milk has been associated with human toxoplasmosis (Tenter et al. 2000).

Poor hygiene is also a major contributor towards food contamination. Contamination can occur due to a person failing to wash their hands prior to food preparation after contact with plants or soil in the garden, a cat, cat faeces, or the cat litter box. Infrequent washing of kitchen utensils used to prepare raw meat or other contaminated foods also represent a potential cause of food contamination (Jones et al. 2003).

## Host factors that influence disease

People most at risk of developing clinical symptoms include immunocompromised individuals, pregnant women who acquire (or have a reactivation of) the infection during gestation, foetuses that are congenitally infected and individuals who have previously been infected *in utero* (Tenter et al. 2000; Jones et al. 2003; Montoya and Liesenfeld 2004; ESR 2010). Factors that increase the risk of acquiring a *T. gondii* infection include owning a pet cat, undercooking meat and maintaining poor personal hygiene.

## Dose response

The number of faecal oocysts or tissue cysts required to cause *T. gondii* infection in humans has not been established (ESR 2010). However, using a pig animal model Dubey et al. (1996) demonstrated that as few as one sporulated oocyst was able to cause infection.

## Recommended reading and useful links

CDC (2008) Parasites - Toxoplasmosis (*Toxoplasma* infection).

<http://www.cdc.gov/parasites/toxoplasmosis/index.html>

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[www.food.gov.uk/multimedia/pdfs/committee/acmsfirtaxopasm.pdf](http://www.food.gov.uk/multimedia/pdfs/committee/acmsfirtaxopasm.pdf)

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