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Toxoplasmosis: An Emerging and Re-emerging Zoonosis of Global Public Health Concern

Mahendra Pal[1,*], Gemechu Berhanu[2], Carl H.D. Steinmetz[3], Nino Durglishvili[4]

[1]Narayan Consultancy on Veterinary Public Health and Microbiology, Anand, Gujarat, India
[2]College of Agriculture and Veterinary Medicine, Dambi Dollo University, Ethiopia
[3]Expats and Immigrants B.V., Amsterdam, Netherlands
[4]Ivane Javakhishvili Tbilisi State University, Department of Sociology and Social Work, Vazha Pshavela Ave 25a, Tbilisi, 0177 Georgia
*Corresponding author: palmahendra2@gmail.com

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Abstract Toxoplasmosis is an important emerging and re-emerging zoonotic disease that results from the infection with *Toxoplasma gondii*, which is one of the most common parasites in the world. The disease usually happens through consuming undercooked contaminated meat, exposure from diseased cat feces, or mother-to-child transmission all through pregnancy. Toxoplasmosis is commonly transmitted via the mouth when *Toxoplasma gondii* oocysts or tissue cysts are eaten by chance. Congenital transmission from mother to fetus can also arise. Transmission can arise from the stable organ transplant manner or hematogenous stem cellular transplants. The majority of individuals infected with toxoplasmosis, has no signs and symptoms and is not aware of being infected. However, some people show symptoms and signs similar to those of the flu, inclusive of body aches, swollen lymph nodes, headache, fever, fatigue, confusion, poor coordination, and seizures. Diagnosis of toxoplasmosis in human beings is made through organic, serological, histological, or molecular techniques, or with the aid of combining these techniques. The treatment is commonly encouraged for humans with serious health issues, inclusive of human beings with HIV.The infection may be prevented by eating of cooked meat, drinking wholesome potable water, pasteurization of milk, cleaning of vegetables, wearing gloves when gardening, periodic examination of pregnant women, and health education to the public about the reservoir of infection, mode of transmission and hazards of consuming raw meat.

Keywords: *cat, meat, protozoa, public health, Toxoplasma gondii, women, zoonosis*

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1. Introduction

Zoonosis is an infectious disease that is caused primarily by an animal pathogen, and is transmitted through several routes, such as ingestion, inhalation, direct contact and vector bite [1]. There are over 300 zoonoses of varied etiologies that cause considerable morbidity as well as mortality in humans and in many species of animals [2,3]. Recent decades have witnessed several emerging zoonoses (Nipha virus disease, Hendra virus disease, Monkey pox, bird flu, swine flu, severe acute respiratory syndrome etc.) that attracted the attention of national and international public health organizations [2,3,4,5,6]. There are many protozoan zoonotic diseases, such as amoebiasis, babesiosis, balantidiasis, cryptosporidiosis, giardiasis, leishmaniasis, sarcocystosis, simian malaria, toxoplasmosis, and trypanosomiasis, which may occur in sporadic as well as in epidemic form; and are reported from developing and developed countries of the world [2,7,8]. Among these, toxoplasmosis is an emerging and re-emerging, life-threatening zoonosis of global public health importance [9], and is caused by *Toxoplasma gondii*, a facultatively heteroxenous, polyxenous protozoon that has developed several potential routes of transmission within and between different host species [10]. The infection is commonly encountered in humans, and it is known that one-third of the world's population has been exposed to the disease [11].

The infection due to *T. gondii* may be subclinical and clinical. The seroprevalence of *T. gondii* antibodies in the human population varies geographically with prevalence rates approaching 90% in many European countries, whilst seropositivity rates in the USA range between 10% and 15% [12,13]. HIV infection does not affect *T. gondii* seropositivity, and no difference in the rate of toxoplasmosis infection among AIDS patients with and without cats [13,14]. However, most infections are subclinical, and the disease typically only becomes apparent in congenitally acquired infections and patients with significant immunodeficiencies, such as in acquired immunodeficiency syndrome (AIDS) [15].

The transmission of infection occurs by eating raw or inadequately cooked meat containing cysts of *T. gondii*. The ingestion of contaminated water, milk, and other foods with oocysts from cat's faeces can also cause infection. The congenital infection in children can occur only when a woman has a primary infection due to pregnancy. There are rare case reports of peoples infected by blood transfusions or organ transplantation [2,16]. This manuscript aims at reviewing toxoplasmosis as an important emerging and re-emerging protozoan zoonosis of global public health importance.

2. Review

2.1. Life Cycle of Protozoa

Toxoplasma gondii is an important parasite, which occurs in wide areas of the world [2]. It can infect a wide range of hosts and many different host cells [17,18]. Intermediate hosts may be all warm-blooded animals comprising most livestock, and humans [2]. Definitive hosts are members of the family Felidae, for example, domestic cats [2,19,20].

In intermediate hosts, *T. gondii* undergoes two phases of asexual development [21]. In the first phase, tachyzoites (or endozoites) multiply rapidly by repeated endodyogeny in many different types of host cells. The tachyzoites of the last generation initiate the second phase of development which results in the formation of tissue cysts. Within the tissue cyst, bradyzoites (or cystozoites) multiply slowly by endodyogeny [22]. Tissue cysts have a high affinity for neural and muscular tissues. They are located predominantly in the central nervous system (CNS), the eye as well as skeletal and cardiac muscles. However, to a lesser extent, they may also be found in visceral organs, such as the lungs, liver, and kidneys [23]. Tissue cysts are the terminal life-cycle stage in the intermediate host and are immediately infectious. In some intermediate host species, they may persist for the life of the host [24]. The mechanism of this persistence is unknown. However, many investigators believe that tissue cysts break down periodically, with bradyzoites transforming to tachyzoites that reinvade host cells and again transform to bradyzoites within new tissue cysts [19,25]. If ingested by a definitive host, the bradyzoites initiate another asexual phase of proliferation which consists of initial multiplication by endodyogeny followed by repeated endopolygeny in epithelial cells of the small intestine [26]. The terminal stages of this asexual multiplication initiate the sexual phase of the life cycle. The gamogony and oocyst formation also take place in the epithelium of the small intestine. Unsporulated oocysts are released into the intestinal lumen and passed into the environment with the feces. The sporogony occurs outside the host and leads to the development of infectious oocysts, which contain two sporocysts, each containing four sporozoites [24,27].

There are three infectious stages in the life cycle of *T. gondii* comprising tachyzoites, bradyzoites contained in tissue cysts, and sporozoites contained in sporulatedoocysts [24]. All three stages are infectious for both intermediate and definitive hosts, which may acquire *T. gondii* infection mainly via one of the following routes (A) horizontally by oral ingestion of infectious oocysts from the environment, (B) horizontally by oral ingestion of tissue cysts contained in raw or undercooked meat or primary offal (viscera) of intermediate hosts, or (C) vertically by transplacental transmission of tachyzoites [28]. Besides, in several hosts, tachyzoites may also be transmitted in the milk from the mother to the offspring [29,30]. Accidental laboratory infection is also reported. There is evidence to believe that housefly or cockroach may transmit the infective oocysts from cat feces to humans and animal food [2].

2.2. Epidemiology

The epidemiology of toxoplasmosis is complex as it involves many animal species [2]. The overall seroprevalence of *T. gondii* in the United States is approximately 15%, and rates of *T. gondii* exposure in HIV patients are similar to those of the general public [12,31]. In patients with AIDS who have positive *T. gondii* antibodies, the risk of developing toxoplasmosis is roughly 30% unless prophylactic or antiretroviral medications are commenced [32,33]. Among immunocompetent patients, clinically evident toxoplasmosis is more likely to occur after the fifth decade of life [34]. Congenital toxoplasmosis is thought to depend on the trimester during which the maternal infection is acquired, with 10-25% of infections occurring in the first trimester, 30% in the second trimester, and 50% in the third trimester [35,36]. The development of toxoplasmosis among immunocompetent patients does not seem to vary from region to region; however, the prevalence of immunocompromised patients is higher in some nations as a function of both HIV/AIDS infection and also organ transplantation and immunomodulatory medication prescribing [37,38].

2.2.1. Importance of Cats in the Epidemiology of *Toxoplasma gondii* Infection

Infections with *T. gondii* in cats are usually asymptomatic, and vertical transmissions occur only infrequently. However, latent infections with *T. gondii* are common in domestic cats and wild felines throughout the world [39,40]. At least 17 species of wild felines have been reported to shed oocysts of *T. gondii*, i.e. European and African wild cats, Pallas cat, bobcat, leopard cat, Amur leopard cat, iriomote cat, ocelot, Geoffroy's cat, Pampas cat, jaguarundi, cougar, leopard, jaguar, tiger, lion, and cheetah, and there is serological evidence of *T. gondii* infection in several species of animals [2,41,42]. In domestic cats, antibodies to *T. gondii* may be detected in up to 74% of adult cat populations, depending on the type of feeding and whether cats are kept indoors or outdoors [43,44].

2.2.2. Mortality and Morbidity

The routine use of cotrimoxazole prophylaxis both in the United States and internationally has also likely significantly decreased the incidence of CNS toxoplasmosis [45]. Although toxoplasmosis is well studied in women of childbearing age because of its detrimental effects on the fetus, no difference in prevalence between the sexes is reported [46]. No

difference in seroprevalence based on age has been noted; however, except of *T. gondii* chorioretinitis, older individuals are more likely to manifest clinically evident reactivation of *T. gondii* infection. Congenitally acquired *T. gondii* chorioretinitis is more likely to recur in those older than 40 years [47].

2.2.3. Infection in the Immunocompetent Host

Eighty to ninety percent of *T. gondii* infections in immunocompetent hosts are asymptomatic. Generally, when an acute infection is symptomatic; symptoms include symmetric lymphadenopathy, fever, and a nonspecific rash. The vast majorities of cases are benign and resolve within weeks. However, severe manifestations of infection, including chorioretinitis, can occur in immunocompetent hosts [48].

Chorioretinitis or ocular toxoplasmosis is a relatively common manifestation of *T. gondii* infection. Ocular toxoplasmosis occurs when cysts deposited in or near the retina become active, producing tachyzoites. Focal necrotizing retinitis is the characteristic lesion, but retinal scars from prior reactivation are typically present. The presentation usually involves eye pain and decreased visual acuity. Adults who acquired disease in infancy usually present with bilateral eye involvement. Adults with acute infection generally present with unilateral ocular involvement [49,50]

2.2.4. Congenital Infection

Approximately 10-20% of pregnant women infected with *T. gondii* become symptomatic. The most common signs of infection are lymphadenopathy and fever. If the mother was infected before pregnancy, there is virtually no risk of fetal infection, as long as she remains immunocompetent; however, if the infection is acquired during the pregnancy, there is a risk of infection to the fetus. The rate of transplacental infection has been estimated to be 50% for untreated mothers and 25% for treated mothers [51,52].

The rate of fetal infection varies with trimester with 10-25% of infections occurring in the first trimester, 30% in the second trimester, and 50% in the third trimester [35]. Infection during the first or second trimesters appears to be most severe. The clinical features of congenitally acquired *T. gondii* infection include chorioretinitis, blindness, seizures, microcephaly, anemia, and encephalitis. Infections acquired during the third trimester are usually subclinical; however, clinical disease may still occur later in life. Seventy-five percent of infants congenitally infected with *T.gondii* manifest no symptoms, 14% had evidence of chorioretinitis and 9% demonstrate signs of CNS involvement [51,53,54].

2.2.5. Infection in Immunocomprimised Patients

Most cases of toxoplasmosis in immunocompromised patients are a consequence of latent infection and reactivation [55]. In patients with AIDS, *T. gondii* tissue cysts can reactivate with CD4 counts less than 200 cells/μ L, and, with counts less than 100 cells/μ L, the clinical disease becomes more likely. Patients with CD4 counting less than 100 cell/μ L and who are *T. gondii* IgG antibody positive have a 30% risk of eventually developing reactivation disease without adequate prophylaxis or restoration of immune function [14,33].

Although toxoplasmosis in immunocompromised patients may manifest as chorioretinitis, reactivation disease in these individuals is typically in the central nervous system with brain involvement being common [56]. Toxoplasmic encephalitis and brain abscess presents most commonly as headache, but focal neurologic deficits and seizures are as common. With significant disease, patients may also demonstrate the signs and symptoms of elevated intracranial pressure. Cerebral toxoplasmosis is generally identified on CT scan as multiple ring-enhancing lesions; however, solitary lesions may be seen, and negative CT or MRI scans should not rule out the diagnosis of CNS toxoplasmosis [57,58].

Aside from CNS toxoplasmosis, toxoplasmic pneumonitis, myocarditis, as well as disseminated toxoplasmosis are also commonly identified in immunocompromised patients [56]. Toxoplasmic pneumonitis typically presents with symptoms typical for an infectious pulmonary process, including fever, dyspnea, and cough. Chest radiography is often nonspecific, but findings may have an appearance similar to that of *Pneumocystis jiroveci* pneumonia. Diagnosis is established via bronchoalveolar lavage (BAL). Most patients with extra-CNS manifestations of toxoplasmosis will also be noted to have CNS lesions when appropriate radiographic studies have been performed [8,59].

2.2.6. Survival of Tissue Cysts of *T. gondii* in Food

Bradyzoites of *T. gondii* are more resistant to digestive enzymes, (i.e. pepsin and trypsin) thantachyzoites [56]. Therefore, the ingestion of viable tissue cysts by a non-immune host will usually result in an infection with *T. gondii*. Although tissue cysts are less resistant to environmental conditions than oocysts, they are relatively resistant to changes in temperature and remain infectious in refrigerated (1–4°C) carcasses or minced meat for up to 3 weeks, i.e. probably as long as the meat remains suitable for human consumption. Tissue cysts also survive freezing at temperatures between −1 and −8°C for longer than a week. Most tissue cysts are killed at temperatures of −12°C or lower, but occasionally some tissue cysts may survive deep-freezing. It has also been suggested that some strains of *T. gondii* may be resistant to freezing [24,60].

By contrast, tissue cysts in meat are killed by heating to 67°C. Survival of tissue cysts at lower temperatures depends on the duration of cooking [61]. For example, under laboratory conditions, tissue cysts remained viable at 60°C for about 4 min and at 50°C for about 10 min. It is important to note that cooking for a prolonged period may be necessary under household conditions to achieve the temperatures that are required to kill all tissue cysts of *T. gondii* in all parts of the meat. Some tissue cysts will remain infectious if cooking procedures are used in which the meat is heated unevenly, for example, microwave cooking [62,63]. It is, therefore, pertinent to mention that meat must be thoroughly cooked before human consumption [2].

Tissue cysts are killed by commercial procedures of curing with salt, sucrose, or low-temperature smoking. Therefore, it has previously been suggested that processed meat is an unlikely source of infection for humans. However, the survival time of tissue cysts varies greatly

with the concentration of the salt solution and the temperature of storage [41,64]. Under the laboratory conditions, tissue cysts were killed in 6% NaCl solution at all temperatures examined (4-20°C) but survived in aqueous solutions with a lower concentration of salt for several weeks. It has also been shown that salting does not necessarily kill tissue cysts in home-made pork sausages. *T. gondii* tissue cysts can be killed by 3% table salt after 3–7 days. This is much later than the usual storage time for pork sausages and, thus, salting alone is probably not sufficient to prevent transmission to humans via tissue cysts [67].Tissue cysts are killed by gamma irradiation at a dose of 1.0 kG. However, irradiation of meat has only been approved in a few countries, it is only feasible in industrialized countries, and is opposed to by consumers in many regions of the world [28,57].

2.2.7. Food-Borne Outbreak of Toxoplasmosis in Humans

Outbreaks of acute toxoplasmosis in humans in various regions of the world demonstrate that the sources of infection vary greatly in different human populations with differences in culture and eating habits [24]. In Canada, an outbreak of congenital toxoplasmosis in a settlement of Inuits in northern Quebec was associated with frequent consumption of caribou meat, in addition to the skinning of fur animals, while seropositivity in pregnant women living in the same settlement was associated with consumption of dried seal meat, seal liver, and raw caribou meat. In Australia, an outbreak of acute and congenital toxoplasmosis was associated with rare kangaroo meat and undercooked lamb stay, which were consumed during a cocktail party in Queensland [40]. Consumption of raw mutton at a party has also been reported as a source of acute toxoplasmosis in humans. It is also important to consider that, in addition to meat, tissue cysts of *T. gondii* may form in visceral organs. Thus, an outbreak of acute toxoplasmosis in humans occurred after consumption of raw spleen and liver of a wild boar, and a second outbreak after consumption of raw liver of a domestic pig, where the raw liver is believed to have special nutritional value. In the latter cases, either tachyzoites or tissue cysts may have been involved [68,69].

The risk of acquiring an infection with *T. gondii* via meat or other edible parts of animals varies with cultural and eating habits in different human populations, data derived from outbreaks of acute toxoplasmosis are usually linked to an occasional point source of infection and, thus, do not necessarily reflect the major, epidemiologically important sources of infection for the whole population [24,41]. It has to be kept in mind that most infections with *T. gondii* in immunocompetent humans are asymptomatic and, thus, will not be recorded unless systematic screening programs for *T. gondii* infections are carried out in the population under study [70].

A European multicentre study including selected cities in Belgium, Denmark, Italy, Norway, Switzerland, and the UK identified the consumption of undercooked lamb, beef, or game, contact with soil, and travel outside Europe and North America as strong risk factors for acquiring an infection with *T. gondii*, with 30-63% of infections in the various regions being attributed to consumption of undercooked or cured meat products [71,72]. Likewise, the consumption of raw pork and tasting of raw meat during meal preparation were the main risk factors for acquiring a *T. gondii* infection. Frequent consumption of meat or consumption of undercooked meat has also been associated with seroconversion or seropositivity for *T. gondii* in case-control studies on healthy adults in France, Yugoslavia, and the USA [73].

However, while consumption of raw or undercooked meat was consistently identified as a risk factor in all of these studies, the relative importance of the risk factor and the type of meat associated with it varied among different countries. For example, in France consumption of undercooked beef was a stronger risk factor than consumption of undercooked lamb, in Norway consumption of undercooked lamb was a stronger risk factor than consumption of undercooked pork, whereas in Poland consumption of undercooked pork was the essential risk factor identified in the study. These findings may reflect differences in eating habits of consumers or different prevalence of infection in meat-producing animals in these regions [71].

2.3. Prevention and Control

Preventive measures can significantly reduce the risk of acquiring an infection with *T. gondii*, but cannot always prevent the infection [39]. Therefore, because of the great impact that *T. gondii* has on the quality of human life several authorities, including the World Health Organization, have advised strategies for surveillance and control of toxoplasmosis in humans [64]. Such strategies are particularly important for risk groups and are directed at the prevention of symptomatic congenital toxoplasmosis and long-term sequelae in children with prenatal *T. gondii* infection, and at prevention of fatal disease in immunocompromised patients [35].

To prevent food-borne horizontal transmission of *T. gondii* to humans, meat and other edible parts of animals should not be consumed raw or undercooked, i.e. they should be cooked thoroughly (70°C) before consumption [2]. Although freezing alone is not a reliable means of rendering all tissue cysts non-infectious, deep-freezing meat (−12°C or lower) before cooking can reduce the risk of infection. Besides, meat should not be tasted during seasoning or cooking, which is of particular importance for non-immune pregnant women [65]. It is also essential that preventive measures reduce the risk of horizontal transmission of *T. gondii* to humans via tissue cysts include a high standard of kitchen hygiene [66]. Thus, in a case-control study in Norway, washing kitchen knives infrequently after preparation of raw meat was independently associated with an increased risk of primary infection during pregnancy. Both tissue cysts and tachyzoites are killed by water and, thus, hands and all kitchen utensils used for the preparation of uncooked meat or other food from animals should be cleaned thoroughly with hot water and soap [67,74].

In some European countries and some states of the USA, screening programmes have been launched that are aimed at either early detection of primary maternal infection with *T. gondii* during pregnancies or detection of prenatal infection in neonates at birth. However, these programmes are not standardised and vary greatly among

different countries [44]. Such variation is largely due to controversy that exists on whether treatment of the mother during pregnancy is effective in reducing the risk of vertical transmission to the foetus, in reducing the risk of symptomatic congenital toxoplasmosis in the neonate, or in preventing long-term sequelae in the child. Consequently, there is debate on the cost-effectiveness of such programmes [75]. While the establishment of these programmes has not clarified the debate about their costs and benefits in public health, they have significantly improved our knowledge on congenital toxoplasmosis as well as on many aspects of the management of, and outcome for, children with prenatal *T. gondii* infection. Also, they have provided invaluable data on the epidemiology of infections with this parasite in humans [64,71].

3. Conclusions

Toxoplasma gondii as a causative agent of zoonosis has great public health importance. Thus, different organizations, including the World Health Organization, have repeatedly advised the collection of accurate epidemiological data on this parasite. Since tachyzoites only survive for a short period outside the host, it has been generally accepted that postnatal infections in humans are acquired by ingesting one of the two persistent stages of *T. gondii*, i.e. tissue cysts contained in meat or viscera of many animals and oocysts shed into the environment by domestic cats of wild felines. However, their relative importance in the epidemiology of *T. gondii* infections remains obscure. On one hand, consumption of undercooked meat has been identified as the essential risk factor in several recent case-control studies on primary infection of *T. gondii* or seropositivity in humans; on the other hand up to 47% of strict vegetarians have been shown to possess antibodies to *T. gondii*. It is likely that the major sources of *T. gondii* infections are different in human populations with differences in culture and eating habits. Water-borne transmission of oocysts to humans may have greater epidemiological importance than has been believed previously. While the risk of acquiring an infection with *T. gondii* via oocysts that are shed by pet cats into the household of their owners may be significantly reduced by preventive measures, it is currently unknown whether measures for quality control of drinking water are sufficient for preventing its contamination with infectious oocysts of *T. gondii* from the environment. As a consequence, the Vancouver outbreak of toxoplasmosis in humans has now initiated research on the oocyst stage of the parasite, and methods are being developed to facilitate their detection in drinking water. It would be preferable if future epidemiological studies on *T. gondii* consider the role of oocysts as potential sources of infection for humans and there is a need for the development of simple, sensitive, and low cost methods to monitor these in the environment.

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Author's Contribution

All the authors contributed equally. They read the final version, and approved it for the publication.

Conflict of Interest

The authors declare that they do not have conflict of interest.

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