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Review Article

Toxoplasmosis: Mysterious Disease with Paradigm for One Health

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Abstract

Protozoan parasites are probably one of the important emerging pathogens influencing different ecosystems, including humans, domestic animals, wildlife, and aquatic ecosystems. Toxoplasmosis is one such disease, which is highly neglected in developing countries but has significant outcomes affecting the quality of life and mortality of both human beings and animals. As the concept of one health is garnering attention in recent public health emergencies, it will overcome bureaucratic boundaries and will represent an opportunity for new partnerships focused on solutions for humans, animals, plants, and the environment. The complicated relationship across different taxa makes toxoplasmosis a potential candidate for application of One Health approach. With this, we present here a review on toxoplasmosis, global and Indian scenario, foodborne transmission, clinical picture in different animals and humans, and involvement of diverse ecosystems and need for transdisciplinary expertise.

Keywords: Cat, Ecosystems, Oocysts, One Health, Toxoplasmosis, *Toxoplasma gondii*

Introduction

Toxoplasma gondii, a parasite of the apicomplexan group, is the causative agent of toxoplasmosis. It is an obligate intracellular old protozoan parasite of a new concern, which was discovered more than 100 years back. Still, understandings its medical importance and biology of the life cycle have expanded in the last 40 years (Dubey, 2008) (Figure 1).

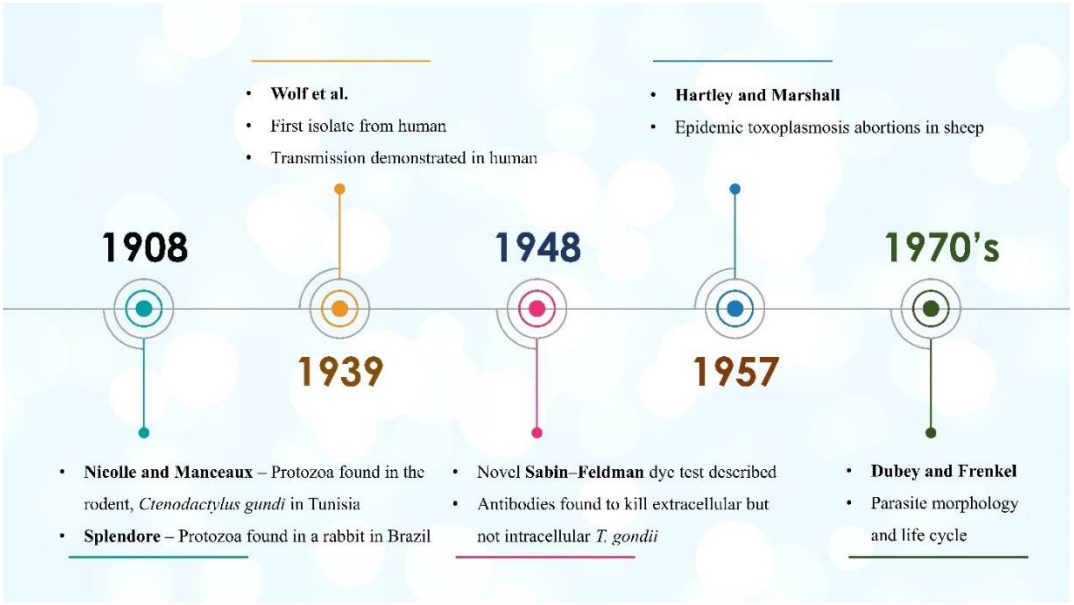

Figure 1: Important landmarks in *Toxoplasma gondii* since its discovery

Toxoplasmosis meets the requirements as a one health disease because it has a significant impact on the health of domestic animals, wildlife, human, and ecosystems and demands consolidated approaches across interdisciplinary boundaries (Aguirre *et al*., 2019). Although it infects a diversified group of warm-blooded animals, wild felids and domestic cats (*Felis catus*) are the known definitive as well as essential hosts having the capacity of shedding hard oocysts in their faeces into the environment. A single infected cat can transfer more than 100 million non-sporulated oocysts, and each oocyst may persist infectious for months to years in the environment (Djurkovic-Djakovic *et al*., 2019).

Taxonomy

Toxo means "arc," indicating the shape of the parasite, plasma means “creature”, and gondii named after the rodent from where it was first identified.

Table 1: Scientific classification of *Toxoplasma gondii*

Kingdom	Protista	**Family**	Sarcocystidae
Phylum	Apicomplexa	**Subfamily**	Toxoplasmatinae
Class	Conoidasida	**Genus**	Toxoplasma
Subclass	Coccidiasina	**Species**	*T.gondii*
Order	Eucoccidiorida		

Impact of Toxoplasmosis

Toxoplasmosis, a versatile disease, is having some exciting attributes that it can infect almost all mammalian species, including humans. It is estimated that latent toxoplasmosis infecting up to one-third of the global human population. Most importantly, it is the third most common cause of lethal foodborne disease in developed countries. In animals, especially in the intermediate hosts (rat & mice), it is capable of altering their behaviour to favour transmission (Gatkowska *et al*., 2012). In humans, the disease is linked with Intermittent Explosive Disorder (IED), decreased novelty-seeking behaviour, slower reactions, lower rule-consciousness & greater jealousy (in men),

moralistic practice (in women), more exceptional warmth, and conscientiousness, associated with Schizophrenia, Obsessive-compulsive disorder, bipolar illness, suicidal attempts, self-directed violence and memory loss in the elderly population (Flegr, 2013; Webster *et al*., 2013).

Hosts

Infection due to toxoplasma has been reported in more than 350 host species (Dubey, 2010). Its presence has been reported in the members of different ecosystems (Figure 2). Cat is considered as the complete host for this parasite. Definitive hosts are members of Felidae like Cat & wild felines, mountain lions, ocelots, margays, bobcats, Bengal tigers, etc. whereas intermediate hosts are all or most mammals and marsupials. Birds can be a possible intermediate host. Transport hosts are captive snakes, fishes, cockroaches, marine molluscs earthworms, also by runoff of rain and melting snow. Globally, 31 of the 39 felid species have shown evidence of infection. The disease is considered as both saprozoonoses and cyclozoonoses (Tenter *et al*., 2000; Schlüter *et al*., 2014).

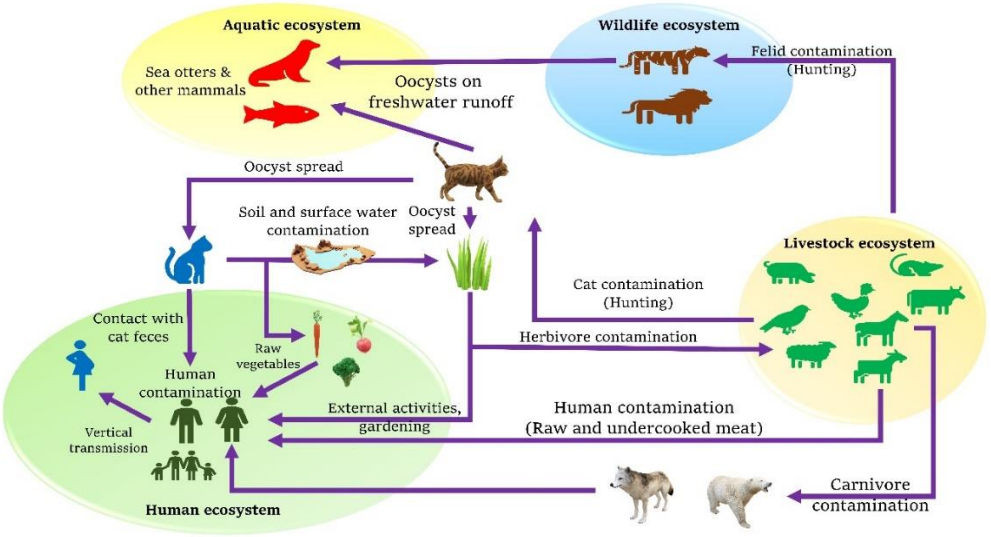

Figure 2: Involvement of different ecosystems in the transmission of toxoplasmosis

Biology of the Parasite

There are three important infective or transmission stages of *T. gondii*, namely a rapidly dividing invasive tachyzoite, a slowly dividing bradyzoite in tissue cysts, and an environmentally robust stage, the sporozoite, protected inside an oocyst. Oocysts play a vital role in the epidemiology of this zoonotic parasite (WHO, 2015) (Figure 3).

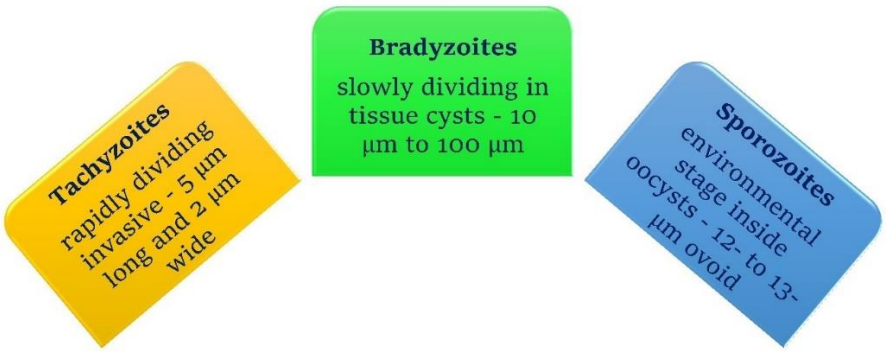

Figure 3: Biology of *Toxoplasma gondii*

Decoding the Complex Life Cycle

Life cycle functions in a prey-predator system for the parasite that alternates between intermediate (asexual replication) and definitive (sexual reproduction) hosts. The system is distinctive because the transmission can occur not only between definitive (sexual cycle) and intermediate hosts but also between definitive hosts or even between intermediate hosts via carnivorism (asexual cycle) (Robert-Gangneux and Darde, 2012). The prepatent period varies for the different forms of the parasite like 3 – 10 days for tissue cyst in domesticated cats, more than 18 days for tachyzoites or Oocysts and in a transition stage; it can range from 11 – 17 days. Sporozoites become infectious 24 hours after the cat sheds the oocyst via faeces. In ideal conditions, sporulation time occurs within 1-5 days (Dubey *et al*., 1998). Once infected, the oocysts are excreted for 1-2 weeks by the definitive hosts. In some hosts, tissue cysts develop as promptly as 7 to 10 days post-infection and may remain throughout life. Oocysts can remain infectious for more than one year in warm, humid environments because of its durable nature.

Toxoplasmosis in Humans

Humans may get the infection through different routes. Oocyst ingestion is the primary route of infection in humans (Jones and Dubey, 2012). Symptoms and other manifestations are highly unpredictable. The disease can result in either chronic or acute with no predetermined certainty. Contaminated water serves as an important source of infection due to the long-term viability and sturdiness of the oocysts. The oocysts are not readily destroyed by moderate or even freezing temperatures, physical and chemical treatments including ozone treatment and chlorination (Dubey, 2004). Toxoplasmosis is of greater concern to the physicians owing to its multifaceted clinical manifestations such as of acute, congenital, ocular, and chronic/reactivation toxoplasmosis (McAuley, 2014).

Toxoplasmosis in Wildlife

Infection in wildlife occurs by means of direct oocysts ingestion from the contaminated environment, congenital transmission of tachyzoites transplacental from the infected parent, predation or scavenging of infected intermediate hosts, and consumption of infected felids. Contamination of the environment is the most important source of infection in wildlife (Yan *et al*., 2016). Seroprevalence in wild felids is usually very high and may reach up to 100%. Disease in wildlife is highly complex and involves various determinants such as physical (size and weight of the animal species), biological (susceptibility, diet and feeding behaviour of the host species), and ecological characteristics (climate). Marine mammals are considered as sentinels for toxoplasmosis. Infection in marine animals, especially mammals like sea lions, dolphins, and otters, is taxonomically and geographically widespread and driven mainly by land-to-sea travel of oocyst by coastal pollution linked to stormwater runoff of oocysts (Cole *et al*., 2000; Deepak *et al*., 2019).

Toxoplasmosis in Domesticated Animals

Toxoplasmosis is common in both birds and livestock species such as sheep, goats, pigs, and chickens. They can act as intermediate hosts (Tenter, 2000). Horses and cattle are particularly resistant to the disease. It is of prime concern to veterinarians due to severe economic losses in sheep flocks induced by the abortive potential of the parasite. Due to their habit of feeding close to the ground, free-range chickens are indeed considered as a good indicator of environmental contamination by Toxoplasma oocysts (Saichua *et al*., 2017).

Global Scenario

Annually more than a million cases were reported in the European region due to contaminated food (Jones and Dubey, 2012). Seroprevalence reports in humans in Central & Southern Europe, Latin America, and tropical African countries is around 30 to 50%, in South East Asia, North America and Northern Europe is about 10 to 30%. Globally, seroprevalence for *T. gondii* in domestic cats is reported to be around 30 to 40% (Robert-Gangneux and Darde, 2012).

Indian Scenario

The overall prevalence in adult humans ranges from 5 to 80% in India (Khan *et al*., 2017). Regional prevalence is highest in South India (37.3%), because of favourable conditions for sustenance and proliferation of oocysts, and

lowest in West India (8.8%). Some studies have found that prevalence is higher in married women (25.8%) than single women (4.3%) and shows an increasing trend with age; 18.1% in 18—25 years age group and 40.5% in more than 40 years group were also reported. Importantly, 66% of those women's residing in mud houses (Singh *et al*., 2014). More people belong to the socioeconomically backward community and tribal populations, barefoot workers, and people who are consuming contaminated water or vegetables. Prevalence is 9.7 – 33.7% in domestic animals with the highest seroprevalence in pigs (31.5%). Sheep, Goats, and Pigs have a high threat for toxoplasmosis transmission to humans (Singh, 2016).

Foodborne Aspects

Toxoplasmosis has been eyed as an important food-borne pathogen in developed as well as developing countries (Jones and Dubey, 2012). Toxoplasmosis was observed to be the second leading cause of foodborne illness-related deaths behind non-typhoidal Salmonella and the fourth leading cause of food-borne illnesses behind non-typhoidal *Salmonella* spp., norovirus, and *Campylobacter* spp. in the United States of America (Scallan *et al.*, 2011). A study in Greece has suggested toxoplasmosis as one of the top 4 diseases to impart loss of DALYs and YLLs among people of Greece (Gkogka *et al*., 2011). A case-control study in the USA has suggested the following risk factors for toxoplasmosis infection namely (Jones and Dubey, 2012):

a. Eating raw ground beef
b. Eating rare lamb
c. Eating locally procured cured, dried, or smoked meat
d. Working with meat
e. Drinking unpasteurized goat's milk
f. Eating raw oysters, clams, or mussels

A meta-analysis study conducted by Pinto-Ferreira and co-workers in 2019 on previously reported outbreaks has indicated that oocytes (> 1,400) tend to cause more cases than cysts (around 290 persons).

Vehicles for Foodborne Transmission

Milk

Consumption of unpasteurized goat milk is considered as one of the risk factors for food-borne transmission as per studies conducted in the United Kingdom and the United States. However, there is no consensus reached on an international scale regarding the risk of milk-borne transmission due to lack of adequate studies on the secretion of the parasite in milk (Jones and Dubey, 2012). Pasteurization conditions can kill *T. gondii* in goat milk and can render it safe for consumption (Dubey, 2010). Preparation of milk products from unpasteurized milk still presents a risk and it has been reported that the organisms can survive in milk and unprocessed cheese for up to 10 days (Singh and Munnawar, 2010). Antibodies have been detected in milk samples of different species but there are comparatively lesser reports on the detection of antigen or the parasite DNA in the milk samples. Tachyzoites have been identified in the milk of farm animals such as cattle and small ruminants as well.

Meat

Consumption of undercooked meat has been considered as one of the major routes of food-borne transmission. Consumption of undercooked meat of animals such as goat, sheep, horse, pig, deer, and black bear has been linked with toxoplasmosis in various studies. Even offals have been regarded as an important source of infection (Jimenez-Coello *et al*., 2012). In developed countries, where most of the slaughtered meat is diverted towards commercial value addition and further processing, the addition of salt and water in the meat is said to kill the tissue cysts of *Toxoplasma gondii.* However, it is popularly believed that a shift in preference of consumers towards "organically raised" or "free-range" may increase the susceptibility of the animals. Reports of prevalence of this organism in chicken eggs are very negligible (Jones and Dubey, 2012). Microwave cooking is not efficient in killing *T. gondii* (Jones and Dubey, 2012). However, some of the processing methods which can reduce the contamination in meat include:

a. Irradiation – 0.4-0.7 kGy

b. High-pressure processing – 300-400 MPa
c. Freezing (-12°C)
d. Other methods include salting, curing, and smoking

Seafood

Gastropods and bivalves, being filtering organisms, can serve as a good source of the organism, especially the oocytes washed away by the rivers. *T. gondii* has been detected in fishes as well, suggesting the role of a possible mechanical carrier of the oocyst (Marino *et al*., 2019). The sturdy nature of the oocyst in the environment also adds to the risk of transmission by seafoods.

Vegetables

Toxoplasmosis reports related to the ingestion of vegetables and fruits contaminated during their chain of supply are gradually increasing over the years. So, it is highly imperative to follow adequate cooking of the vegetables before consumption (Pinto-Ferreira *et al*., 2019).

Water

Consumption of water contaminated with oocysts of *T. gondii* has been implicated with several outbreaks in the latter half of the previous century. Since the dawn of the millennium, outbreaks in countries such as Brazil and India were related to the consumption of contaminated municipal water (Marino *et al.,* 2019). Environmental contamination and subsequent exposure can serve as an important source of infection to different animals as well as sea-dwelling mammals (Vieira *et al.,* 2015). Treatment of water such as boiling or filtration can be helpful in eliminating the oocysts (CFSPH, 2017).

Occupational Importance

Toxoplasmosis presents itself as an occupational hazard to meat handlers, game hunters, and persons involved in the skinning of animals (Singh and Munnawar, 2010). However, various studies have necessitated that further research is needed in this regard before arriving at a solid conclusion (Goncalves *et al*., 2006 and Alvarado-Esquivel *et al*., 2011).

Clinical Picture in Animals

Cats may be asymptomatic, but often exhibit respiratory and ocular signs. Intrauterine infections, hepatitis, encephalitis, ascites, perinatal death are the other clinical outcomes. In sheep, early abortion is common (Mike Metzger, 2012). Infection is opportunistic in dogs and may show respiratory and neuromuscular signs. Pigs mostly suffer subclinical infections. In cattle, it is asymptomatic and abortion is uncommon (Weiss and Dubey, 2009).

Clinical Picture in Humans

Different forms of the infection make the clinical signs also differ between each other. Acute toxoplasmosis may be asymptomatic at time and manifest with flu-like symptoms such as myalgia, fever, lymphadenopathy. In immunocompromised people, encephalitis, hydrocephalus, and retinochoroiditis are predominant (Saadatnia and Golkar, 2012). In congenital toxoplasmosis, chorioretinitis, intracerebral calcification, hydrocephalus, or microcephalus are noticed in the neonate (Pappas *et al*., 2009). Chronic form or reactivation is considered problematic in immunocompromised patients. Ocular involvement is manifested as necrotizing retinochoroiditis, strabismus, etc.

Laboratory Animals

Common laboratory animals being used for diagnosis of toxoplasmosis are mice, hamsters, and rabbits. Route of infection is preferably intraperitoneal. Mice are the commonly used laboratory animals for routine maintenance of strains of *T. gondii* by serial intraperitoneal passages (Jamra, 1991). It is also commonly used for the isolation of the parasite from the clinical specimens (Liu *et al*., 2015). Toxoplasma may appear in the blood within 4 hours of

inoculation. It disappears from the circulation shortly but persists for weeks together in the tissues of the internal organs such as the spleen, liver, and other organs.

Diagnosis

Diagnosis is usually attempted by direct methods that identify the parasite or its antigen and indirect methods that detect the immune response of the hosts (Figure 4) (OIE, 2017). Isolation of tachyzoites, bradyzoites can be possible directly from fluids like ocular, amniotic fluids, etc. and indirectly by inoculating mice intraperitoneally and isolating three days after inoculation. Fecal oocysts examination can be performed by different staining techniques, including modified Kato-Katz with Kinyoun stain (Norhamizah *et al*., 2016).

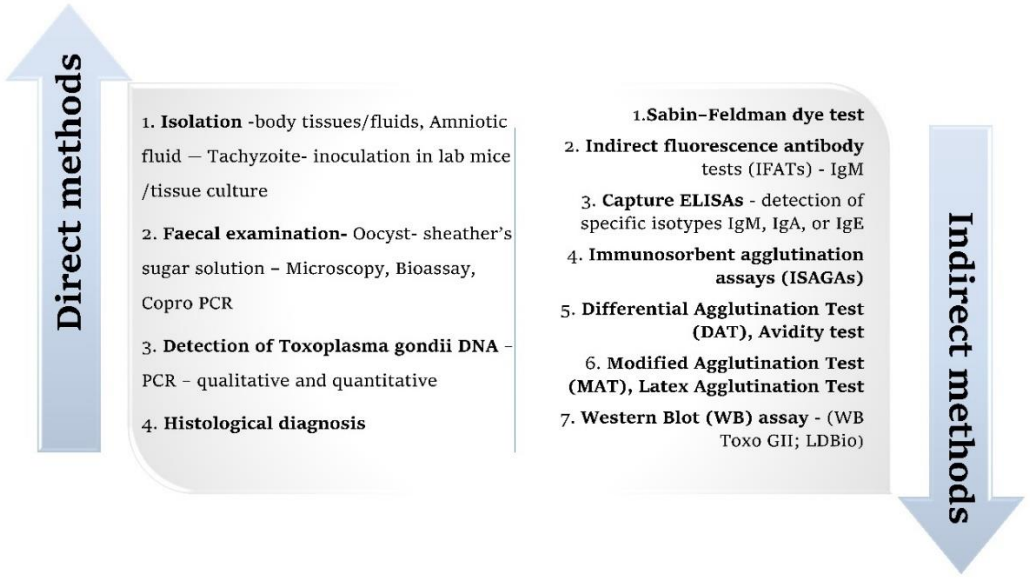

Figure 4: Diagnostic methods for Toxoplasmosis

Sabin-Feldman Dye Test (DT)

Sabin-Feldman Dye test is the first reliable test developed for detecting the toxoplasmosis infection (Ybanez *et al*., 2020). It works on the principle that of the presence of specific antibodies prevent methylene blue dye from entering into the cytoplasm of *T. gondii* organisms. Even till date, the method is used as a reference in the serodiagnosis. In the first step, the patient serum will be treated with toxoplasma tachyzoites and then with complements, which will act as an activator, and after incubation, methylene blue is added. In negative results, tachyzoites with intact membranes are stained, and in a positive result, tachyzoites are not stained. But the drawbacks in this test are difficulty in maintaining the live tachyzoites, inability to differentiate recent or past infection and tendency to produce false-positive results.

Indirect Fluorescence Antibody Tests (IFATs) – IgM

IFAT uses killed organisms as a substrate, with patient serum assayed for activity against them. Fixed tachyzoites are recognized by the patient's antibody (IgG), and a fluorescent-labelled anti-human antibody (IgG) is added next to identify the antibody by fluorescent microscopy. If no antibody against the *T. gondii* tachyzoite is present, no fluorescence is observed (Liu *et al*., 2015).

Differential Agglutination (AC/HS)

Differential agglutination uses preparations of two antigens which expresses antigenic determinants found in both early or acute infection (AC antigen) and the later stages (HS antigen) of infection. Acetone- or methanol-fixed tachyzoites (AC antigen) and formalin-fixed tachyzoites (HS antigen) are employed in this test. In the acute form, high AC and HS titers are noticed whereas in the non-acute pattern, high AC titers and low HS titers will be notified.

The major bottleneck in this test is that acute pattern may persist for a minimum of one or more years following infection (Montoya, 2007).

Avidity Test

The basic principle of avidity test is that the functional affinity of IgG antibodies specific is primarily low after initial antigenic challenge and increases after subsequent weeks and months. Protein-denaturing reagents, including urea, will carry out dissociation of the antibody-antigen complex. The result will be determined based on the ratios of antibody titration curves of untreated and urea-treated serum (Beghetto *et al*., 2003). Ruling out the infection is possible during gestation when the test is performed during the first trimester of pregnancy. The impact of treatment may lead to erroneous the results. Commercially, the first FDA-approved test (Vidas Toxo IgG avidity assay; bioMérieux) was available in 2011.

Modified Agglutination Test (MAT)

MAT primarily detects antibodies to *T. gondii* from animal tissue fluid, serum, or plasma. It is the most cost-effective and the simplest among many available methods for detecting *T. gondii* infection, and there is no requirement for specific equipment. The significant advantage of this method is that it can be used for birds and mammals with easy interpretation of results. In most of the laboratories and research settings, the development of in-house MAT is carried out with the help of tachyzoites harvested by traditional propagation carried out in murine peritoneal cavity in vitro cultivation (Bachand *et al*., 2019).

Latex Agglutination Test

Soluble antigens taken from the cytoplasm and membrane of *T. gondii* (RH strain) are coated by a covalent bond over latex particles. Detection of IgG and/or IgM can be done simultaneously. It is straightforward to read the results because of the use of green counterstain on suspended red latex particles. A two-color image that exhibits green background containing several red aggregates is taken as a positive test. A uniform brown image is obtained for a negative test (https://www.rapidlabs.co.uk/product/toxoplasmosis-latex-test-kit/).

Histologic Diagnosis

A technically simple and rapid method is the detection of *T. gondii* in air-dried slides, stained with Wright-Giemsa-stains for the centrifuged sediment (Montoya, 2002). For establishing the acute infection diagnosis or the latent infection reactivation, multiple tissue cysts near an inflammatory necrotic lesion are probably useful. Often, demonstration of tachyzoites in stained tissue sections conventionally is quite challenging. The immunoperoxidase technique which uses antisera to *T. gondii* has proven to be both sensitive and specific.

Polymerase Chain Reaction (PCR)

The molecular technique, PCR, is used to detect *T. gondii* DNA in body fluids and tissues. Revolution in the diagnosis of *T. gondii* infection in the fetus made possible with the help of PCR (Bin Dajem and Almushait, 2012). It was also useful in the diagnosis of congenital, ocular, cerebral, and disseminated forms of toxoplasmosis. PCR was instrumental for detection of *T. gondii* DNA in cerebrospinal fluid (CSF), brain tissue, aqueous and vitreous fluid, amniotic fluid, urine, peripheral blood, and bronchoalveolar lavage (BAL) fluid. There are specific targets like B1 (Accession no: AF179871), which is the first and most used target for the detection of *T. gondii*. Another target is a 529 base pair fragment (Accession no: AF146527) having 200-300 repeats in the genome, and it is the most sensitive (Edvinsson *et al*., 2006). Some other targets like 18s ribosomal DNA and P30 are also used in PCR detection, but are less sensitive.

Treatment

Different drugs are available for the treatment in humans as well as animals for various clinical manifestations. Many experimental compounds are in the developmental pipeline. Currently, the recommended drugs for the toxoplasmosis treatment act predominantly against the tachyzoites (acute stage) of *T gondii* and therefore, they do not eliminate the bradyzoite (encysted form). Treatment in animals is seldom warranted. Synergistic action of

Sulfadiazine (15–25 mg/kg) with pyrimethamine (0.44 mg/kg) are widely used for effective treatment. These drugs usually will not eradicate infection. In difficult cases, Atovaquone, diamino-diphenyl-sulfone, and spiramycin are also used in animals. Clindamycin is the treatment of choice for dogs and cats, at 10–40 mg/kg and 25–50 mg/kg, respectively, for 14–21 days (Dubey, 2013)

In pregnant women, Spiramycin is advised (2-3 tablets) daily for three weeks redo after an interval of 2-week till parturition. For congenital and acquired toxoplasmosis, drugs like pyrimethamine, sulfadiazine, and folinic acid are sufficient. In tissue cyst conditions, Atovaquone and Clindamycin are prescribed. In AIDS patients, drugs like clarithromycin, pyrimethamine, sulfadiazine are used for treatment. Treatment in cats is mainly done with clindamycin (Alday and Doggett, 2017).

Prevention and Control

Recommended hygiene measures include use of hand gloves while handling soil, practice of hand hygiene with water and soap after outdoor activities, washing cutting boards, preparing raw meat, knives, sinks, and other appliances that came in touch with the raw meat. Adequate cooking of meat is an effective preventive measure. Regular cleaning of litter box (because the parasite found in cat feces needs one or more days after it is past to become infectious) and thorough hand wash after cleaning the litter box. Avoiding eating raw meat, unpasteurized milk, and uncooked eggs, oysters, clams, and mussels is advisable. Transfusion of blood and its products from seropositive persons to seronegative persons are to be avoided. Ingestion of sporulated *T. gondii* oocysts from feline skin or mucosal contact and fecal specimens with either tachyzoites or bradyzoites in animal or human tissue or culture (https://www.cdc.gov/parasites/toxoplasmosis/prevent.html) is the primary route of infection in the laboratory workers. Presently, Toxovax is the only vaccine effective against toxoplasmosis, which controls congenital infection in sheep and contains a live attenuated S48 strain (Kumar *et al*., 2013). It is to be noted with caution that Toxovax only decreases the rate of abortion but does not eradicate *T. gondii*. Unfortunately, there is no licensed vaccine available against toxoplasmosis for humans (Wang *et al*., 2019). Serologic screening during pregnancy should be carried out routinely. In fetuses, for the rapid prenatal diagnosis, Amniocentesis and cordocentesis should be considered in routine clinical investigation.

How to Tackle

Transdisciplinary collaborations to identify and fill the knowledge gaps are mandatory. Integrative research for risk assessment and vaccine development should be initiated. There is a high need for building local capacities like government agencies, NGOs, policymakers, practicing physicians, veterinarians, and the general public (Aguirre *et al*., 2019).

Research Groups on Toxoplasmosis

a. EUROTOXO PROJECT
b. SYROCOT STUDY GROUP
c. Toxoplasma reference laboratory, Department of Laboratory Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi.

Conclusion

An ecological and integrated approach should be developed for a better understanding of the complex circulation of toxoplasma between its multiple hosts and the environment and, finally, of the risk factors for human infection. One Health approach will be appropriate to understand epidemiology of Toxoplasmosis and find appropriate ways to control the disease, which requires sustainable, effective, and practical solutions, with a deep comprehension of local cultural and socioeconomic factors and also a healthy clutch of multiplex local, national, regional, and international environmental and health policies.

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Conflict of Interests

There is no conflict of interest.

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