Human toxoplasmosis: current advances in the field

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Purpose of review
Human toxoplasmosis remains a significant, yet often underrecognized, global health concern. This review highlights emerging advances in prevention and management, offering timely updates for clinicians and researchers.

Recent findings
Recent venison-associated outbreaks in the United States have emphasized the risk of ocular toxoplasmosis and severe disease in immune competent individuals and the need for heightened clinical suspicion. Updated guidelines for hematopoietic stem cell transplant (HSCT) recipients now recommend systematic screening, qPCR monitoring, and prophylaxis to reduce mortality from *Toxoplasma gondii* reactivation. Emerging evidence suggests that chronic *T. gondii* infection may contribute to adverse pregnancy outcomes, challenging the long-held assumption that chronic infection is protective against these complications. Although the potential association between chronic *T. gondii* infection and neuropsychiatric disorders remains debated, its public health relevance warrants further investigation.

Summary
Improved clinical awareness, applied preventive strategies, and expanded research are essential to mitigate the broader health impact of chronic *T. gondii* infection. Future well designed studies and rigorous analyses are critical to defining maternal-fetal risks and potential neuropsychiatric effects, providing the evidence needed to update clinical guidelines and inform public health policies.

Keywords
chronic infection, qPCR, *Toxoplasma gondii*, transplantation, venison

INTRODUCTION

Human toxoplasmosis is a zoonotic disease caused by *Toxoplasma gondii*, an obligate intracellular parasite. The definitive hosts of *T. gondii* are members of the *Felidae* family, including both domestic and wild cats. Following a primary infection, young cats can shed millions of oocysts into the environment over a period of 1–3 weeks [1]. These oocysts sporulate and become infectious within 1–5 days, although the timeline may vary depending on environmental conditions. Once sporulated, oocysts are highly resistant and can remain viable in the environment for weeks to months [1]. In humans, *T. gondii* can be transmitted through the ingestion of sporulated oocysts that contaminate water, soil, and, subsequently, vegetables, fruits, various types of seafood, and unpasteurized milk [2]. Infection occurs also via the consumption of tissue cysts containing bradyzoites present in undercooked meat from animals previously infected through similar routes [1,2]. Additionally, transmission may happen through the transplacental passage of tachyzoites [3], solid organ transplantation [4], and occasionally though blood transfusion [5].

In immune competent individuals, acute *T. gondii* infection generates a sustained immune response, detectable through persistent antibody titers, and is followed by a lifelong chronic infection due to cysts containing dormant bradyzoites in the brain, muscles, and eye [6]. A systematic review of studies conducted between 1988 and 2019 in pregnant women estimated the global seroprevalence of human toxoplasmosis at 33.8% [95% confidence interval (95% CI): 31.8–35.9] [7]. Marked intercontinental variation have been reported, with the highest seroprevalence in South America (56.2%, 95% CI: 50.5–62.8),

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KEY POINTS

- *Toxoplasma gondii* infection can result from consuming rare and undercooked venison.
- Toxoplasmosis-related mortality can be reduced in hematopoietic stem cell transplant recipients.
- Chronic *T. gondii* infection is linked to adverse pregnancy outcomes, highlighting the need for guidelines.
- Evidence for a link between chronic *T. gondii* and neuropsychiatric disorders remains inconclusive.

followed by Africa (48.7%, 95% CI: 41.5–55.9), the Eastern Mediterranean (35.1%, 95% CI: 31.5–35.6), Europe (31.2%, 95% CI: 28.4–34), North America (28.2%, 95% CI: 16.6–41.5), South-Est Asia (23.4%, 95% CI: 18.7–28.4), and the Western Pacific (11.8%, 95% CI: 8.1–16.0) [7].

In the United States, as in many countries, human toxoplasmosis is not a nationally notifiable disease, and national surveillance or maternal screening programs are lacking [8]. Currently, human toxoplasmosis is reportable in only eight states (Arkansas, Delaware, Hawaii, Kentucky, Minnesota, Nebraska, Pennsylvania, and Wisconsin) [8]. Despite the absence of comprehensive surveillance, data from the National Health and Nutrition Examination Survey (NHANES) and European studies indicate a declining trend in *T. gondii* seroprevalence in recent years [9–11]. This trend is likely attributable to improved public health interventions aimed at reducing transmission. The increasing proportion of seronegative individuals expands the population at risk of severe outcomes from acute *T. gondii* infection, especially among vulnerable groups such as pregnant women and immunocompromised patients. This public health concern is amplified by the parasite's multiple modes of transmission routes, as well as its broad and often nonspecific clinical presentation [6]. In immune-competent individuals, human toxoplasmosis is typically asymptomatic or present with mild, nonspecific symptoms [6]. Nevertheless, severe and life-threatening manifestations have been reported, especially when atypical nontype II strains are involved [12▪▪]. Severe outcomes of human toxoplasmosis are more frequently observed in immunocompromised individuals due to the reactivation of chronic *T. gondii* infection. These include people living with HIV with $CD4^+$ lymphocyte counts below 100 cells/μl as well as recipients of allogenic hematopoietic stem cell transplants (HSCTs) (rare in autologous) [4,13].

To minimize the risk of infection, it is essential to educate susceptible populations, particularly those at higher risk of severe disease, on preventive measures and to ensure timely communication during outbreaks. Clinicians should be equipped to recognize acute human toxoplasmosis and its potential complications, apply appropriate diagnostic tools at different stages of infection, and monitor patients at risk of reactivation. This review summarizes key findings on venison-related foodborne outbreaks, explores new strategies for preventing human toxoplasmosis reactivation in HSCT recipients, and discusses outcomes of chronic *T. gondii* infection.

VENISON OUTBREAKS IN THE UNITED STATES

While it is widely recognized that *T. gondii* infection can result from the consumption of undercooked or raw meat, particularly pork and lamb, which are estimated to account for up to 60% of human toxoplasmosis cases, far fewer people are aware that game meat also represents a significant, yet often overlooked, source of infection [2]. Wild animals such as white-tailed deer and wild boars, which can harbor tissue cysts (bradyzoites), pose a risk of infection when their meat is consumed undercooked or raw. In the United States, 36–49% of white-tailed deer test positive for *T. gondii* antibodies, with regional prevalence ranging from 28.7 to 74.4% [14,15▪]. Also, 76–80% of black bears in North Carolina and Pennsylvania and 62% in Central Appalachian Mountains are seropositive [16,17]. According to Dubey *et al*. [14,17], haplogroup 12 is identified as the most dominant type in white-tailed deer in the USA (66.6% of isolates), whereas there is high genetic diversity in bears. The most effective methods for inactivating tissue cysts in meat from infected animals include freezing at subzero temperatures for more than three weeks or thoroughly cooking meat to an internal temperature of at least 64°C [18]. However, venison (deer meat) is often consumed rare or even raw, increasing the risk of infection among *T. gondii* seronegative individuals.

Since the 1980s, sporadic cases and foodborne outbreaks linked with consumption of undercooked venison have been reported in several states (Table 1) [19,20,21▪▪,22–25,26▪▪,27]. Most cases occurred during fall hunting season, in young males, and presented with nonspecific symptoms within a few weeks (range 5–22 days) of ingesting rare or undercooked venison. The nonspecific nature of clinical manifestations often contributes to delayed diagnosis and likely results in underreporting of cases. Moreover, when treatment initiates late, ocular complication may develop one to three months

Table 1. Case report, case series, and foodborne outbreaks of human toxoplasmosis associated with Venison in the United States, 1983–2024

Ref.	Cases or outbreak	Outbreak Year	State	Age (years)	Sex	Exposure	Incubation (days)	Symptoms	Imaging	Complication	Notes
Sacks *et al.* [24]											
	Case 1	1979	South Carolina	32	M	November	20	fever, chills, headache, malaise, weakness, nonproductive cough, weight loss	X-ray peribronchial infiltrates in the right lung base	None	
	Case 2	1979	South Carolina	33	M	November	20	fever, chills, sweats, cough, scratchy throat, malaise, weakness, low back pain	X-ray infiltrates in the right upper lobe	None	
	Case 3	1980	Alabama	32	M	February	10	fever, chills, myalgia, headache, conjunctivitis, anorexia, rash	None	None	One immunosuppressed patient due to chronic use of methotrexate (psoriasis)
Ross *et al.* [25]											
	Case 1		Michigan	16	M	NA	NA	Fever, headache, myalgia, malaise, lymphadenopathy, decreased vision in one eye and recurrent headache	CT brain was negative	Unilateral chorioretinal scar	
	Case 2		Michigan	34	M	NA	NA	Fever, headache, myalgia, malaise, lymphadenopathy, decreased vision in one eye, night sweats, fatigue, headaches, arthralgias, cervical lymph node swelling	CT abdomen was negative	Unilateral retinitis and focal periphlebitis	
	Case 3		Michigan	45	M	NA	NA	Fever, headache, myalgia, malaise, lymphadenopathy, decreased vision in one eye, headaches, malaise, cervical lymph node swelling	CT abdomen was negative	Unilateral necrotizing retinitis	
	Case 4		Michigan	23	M	NA	NA	Fever, headache, myalgia, malaise, lymphadenopathy, decreased vision in one eye, respiratory symptoms	None	Unilateral necrotizing retinitis	
	Case 5		Michigan	48	M	NA	NA	Fever, headache, myalgia, malaise, lymphadenopathy, decreased vision in one eye, fever, headache, malaise, myalgias	None	Unilateral necrotizing retinitis	

Table 1 (*Continued*)

Ref.	Cases or outbreak	Outbreak Year	State	Age (years)	Sex	Exposure	Incubation (days)	Symptoms	Imaging	Complication	Notes
England *et al.* [23]											
	Case 1	2017	Tennessee	76	M	NA	7	Fever, myalgias, poor appetite, loose stool	Chest x-ray and abdominal ultrasound were negative. CT chest, abdomen, and pelvis showed mild mesenteric lymph- adenopathy and was otherwise unremarkable.	None	Coronary artery disease, hypertension, hyperlipidemia, urticarial vasculitis, and stage II chronic kidney disease.
	Case 2	2017	Tennessee	NA	M	NA	7	Fever, myalgias, poor appetite (not hospitalized)	None	None	
Gaulin *et al.* [22]											
	Outbreak with 10 exposed	2018	Illinois	Range 28–62	100% M	November	7	6 (60%) of 10 exposed persons experienced fever, sweats, headache, and joint pain. One individual was hospitalized	None	None	Canadian deer hunters who went to the United States to hunt deer. Leftover raw meat from only one patient tested negative for *T. gondii* by PCR
Schumacher *et al.* [20]											
	Outbreak with 11 exposed	2017	Wisconsin	Median 51 Range 22–75	100% M	September	median 7 Range 5-22	9 (82%) of 11 exposed persons experienced illness lasting a median of 12 days. All had fever, chills, sweats, headache, muscle aches, fatigue, decreased appetite, arthralgias, dark urine, sore throat. Lymphadenopathy and ocular disturbances were reported in 33% of cases.	None	None	Leftover raw meat tested positive for *T. gondii* by PCR. *T. gondii* strain atypical genotype haplogroup 12.
Conrady *et al.* [27]											
	Outbreak with 8 exposed	NA	Michigan Southeastern	Mean 56 Range 29–71	100% M	NA	2–8 weeks	5/8 had fever, headaches prior to developing unilateral retinochoroiditis (100%)	None	5 (62.5%) patients had recurrence of unilateral retinochoroiditis.	Hunting ($n=5$) and/or consuming wild game ($n=3$), including seven deer and one bear. One immunosuppressed patient due to renal transplantation

Table 1 (*Continued*)

Ref.	Cases or outbreak	Outbreak Year	State	Age (years)	Sex	Exposure	Incubation (days)	Symptoms	Imaging	Complication	Notes
Koheler *et al.* [26▪▪]											
	Case 1	2017	Minnesota	56	M	November	14	fever, night sweats, myalgia, weight loss, respiratory symptoms	CT thorax nonspecific nodules and hilar lymphadenopathy	active unilateral retinochoroiditis 2.6 months later. Epiretinal membrane and cystoid macular edema 3 months later.	Case 1 was part of a group of 13 hunters, 6 of whom developed unspecified symptoms
	Case 2	2018	Minnesota	45	M	November	7	headaches, night sweats, myalgias, malaise	None	Unilateral active retinochoroiditis 3 months later	
	Case 3	2018	Minnesota	48	M	November	7	high-grade fever and myalgias	None	Unilateral active retinochoroiditis 1 month later	
	Case 4	2018	Minnesota	75	M	October	months	myalgias, generalized weakness, fatigue, recurrent fever and chills.	None	Unilateral active retinitis and vitritis few weeks later	
Toxoplasmosis Fact Sheet, 2025 [28▪]											
	Outbreak with 43 exposed	2024	Westchester County, New York	44% aged 40–59	98% M	January	NA	At least 43 individuals developed symptoms after attending a seven-course meal that included venison. 35% of the cases reported ocular symptoms	None	NA	Half of the attendees sought medical care, with 15 serologically confirmed cases. Leftover raw meat tested positive for *T. gondii* by PCR
Rutenberg *et al.* [21▪▪]											
	Case 1	2024	Alabama	32	F	NA	10	fever, shortness of breath, cough, sore throat, and myalgias	CT angiography of the chest showed bibasilar consolidations, peribronchiolar nodularity, and septal thickening. CT abdomen and pelvis were negative	progressive respiratory distress that required intubation and mechanical ventilation after 7 day of hospitalization	Leftover raw meat tested positive for *T. gondii* by PCR. *T. gondii* strain atypical genotype haplogroup 12.

CT, computed tomography; F, female; M, male; NA, data not available.

postexposure, significantly increasing the risk of recurrent ocular toxoplasmosis or vision loss. Ocular toxoplasmosis is usually diagnosed during an ophthalmologist's consultation for unilateral necrotizing retinitis with or without vitritis. The largest outbreak of human toxoplasmosis transmitted through venison occurred in Westchester County, New York, in January 2024 (Table 1). At least 43 individuals developed symptoms after attending a seven-course meal that included venison [28▪]. Approximately half of the attendees sought medical care, and 15 cases were serologically confirmed. Among the confirmed cases, 98% were male, 44% were between the ages of 40 and 59 years. PCR analysis of the leftover raw venison detected *T. gondii* DNA, confirming foodborne transmission as the source of the outbreak [28▪]. The high rate of ocular manifestations (35%), along with similar findings from other previous case reports (Table 1), underscores that primary *T. gondii* infections in immune competent individuals are not always limited to mild symptoms and can lead to severe outcomes.

Severe manifestations of human toxoplasmosis in immune competent individuals have been rarely reported, particularly in cases involving atypical genotypes [12▪▪]. According to a systematic review, the lungs were the most commonly affected organ system, followed by the central nervous system, cardiac involvement, and disseminated disease, with a fatal outcome reported in 8% of immune competent patients [12▪▪]. A severe case of human toxoplasmosis has been recently reported following the consumption of venison [21▪▪]. In 2024, a 32-year-old immune competent woman from Florida was hospitalized with severe acute pneumonic human toxoplasmosis after consuming deer meat sourced from Alabama [21▪▪] (Table 2). She presented with a 10-day history of fever, shortness of breath, cough, sore throat, and myalgias, which began 10 days after exposure. Her respiratory condition rapidly deteriorated, requiring intubation and mechanical ventilation. The diagnosis was confirmed through serologic testing (including low IgG avidity), detection of *T. gondii* DNA in plasma cell-free DNA, antigen detection in liver biopsy, and positive PCR in whole blood, liver tissue, and bronchoalveolar lavage. These findings enabled timely initiation of appropriate treatment, which led to progressive clinical improvement. PCR testing of leftover venison also confirmed the presence of *T. gondii*[21▪▪]. Genotyping revealed an atypical strain belonging to haplogroup 12, the same haplogroup identified in previous outbreaks in Wisconsin and New York State, although notably, those cases did not present respiratory symptoms [20,28▪]. It remains unclear whether the severity of this case was due to a high parasite inoculum, an undiagnosed immune deficiency, or the enhanced virulence of the strain [21▪▪]. In brief, clinicians should inquire about recent game meat consumption, particularly in male patients presenting during the fall season with febrile illness accompanied by pulmonary, neurological, or ocular symptoms.

UPDATED STRATEGIES FOR PREVENTING TOXOPLASMA REACTIVATION IN HEMATOPOIETIC STEM CELL TRANSPLANTATION RECIPIENTS

In HSCT recipients, almost all human toxoplasmosis cases occur through reactivation of tissue cysts in patients who were seropositive prior to transplantation [4]. In contrast to solid organ transplants, the risk of acute transmission of *T. gondii* via the hematopoietic stem cell graft, from a seropositive donor to a seronegative recipient, is negligible [29▪▪]. Consequently, the incidence of human toxoplasmosis in HSCT recipients largely depends on the local *T. gondii* seroprevalence in the general population and, importantly, on the implementation of prophylactic measures in the transplant centers [30▪,31▪▪].

Whereas guidelines for preventing and managing human toxoplasmosis in people living with HIV have been regularly updated, recommendations for HSCT recipients have remained limited and less standardized for decades. In 2022, a panel of experts during the 9th European Conference on Infections in Leukaemia (ECIL-9) issued new guidelines for the management of *T. gondii* infection and human toxoplasmosis disease in HSCT recipients and patients with hematological malignancies, including revised definitions [29▪▪]. "Toxoplasma infection" is defined as a positive *T. gondii* PCR result in the blood without organ involvement, even if fever is present [29▪▪]. Quantitative PCR (qPCR) targeting the 529-bp fragment is preferred over qualitative PCR [29▪▪]. In a symptomatic patient with magnetic resonance imaging findings highly suggestive of central nervous system toxoplasmosis by a neuroradiologist, a diagnosis of "possible Toxoplasma disease" may be made if no laboratory confirmation of *T. gondii* infection is available and no alternative pathogen explaining the radiological findings is identified [29▪▪]. "Probable Toxoplasma disease" involves clinical and radiological signs of organ involvement plus at least one positive qPCR from any fluid sample or tissue, without histological confirmation [29▪▪]. Finally, "Proven Toxoplasma disease" requires histological or cytological detection of tachyzoites in tissue or fluids [29▪▪]. When histology is inconclusive or cytological evidence is of poor quality, a positive *T. gondii* qPCR from the same sample can confirm the diagnosis [29▪▪]. The growing availability of PCR in transplant centers has replaced the need for parasite culture,

Table 2. Recommendations for the prophylaxis and treatment of human toxoplasmosis after allogenic hematopoietic stem cell transplantation according to the ECIL 9 Guidelines [29▪▪]

Primary prophylaxis for *T. gondii* seropositive recipients
First line: trimethoprim–sulfamethoxazole oral or i.v. 80–400 mg daily Alternative: trimethoprim–sulfamethoxazole oral or i.v. 160–800 mg three times weekly
Not recommended: less frequent dosing, lower doses, or alternatives such as pyrimethamine–sulfadiazine, atovaquone, dapsone, azithromycin, or clindamycin.
If trimethoprim–sulfamethoxazole cannot be used due to delayed engraftment or myelosuppression and PCR is unavailable use atovaquone 1500 mg q12h, oral until engraftment, then switch to trimethoprim–sulfamethoxazole
Duration: at least 6 months After two negative qPCRs, initiate secondary prophylaxis (see below).
Preemptive therapy for Toxoplasma infection
If already on trimethoprim–sulfamethoxazole prophylaxis, increase dose or switch therapy. If not on prophylaxis, start one of the following: pyrimethamine 200 mg loading dose, then 50–75 mg/day + folinic acid 10–25 mg/day + sulfadiazine 1000 mg (<60 kg) – 1500 mg (≥60 kg) q6h pyrimethamine 200 mg loading dose, then 50–75 mg/day + folinic acid 10–25 mg/day + clindamycin 600 mg q6h (up to 1200 q6h), oral or i.v. trimethoprim–sulfamethoxazole (prophylactic, intermediate, or therapeutic dose)
Duration: continue until 2 negative qPCRs (7 days apart). After 2 negative qPCRs switch to secondary prophylaxis (see below) and ongoing qPCR monitoring during immunosuppression or low $CD4^+$ cell counts.
Treatment for possible, probable, proven Toxoplasma disease
First choice: pyrimethamine 200 mg loading dose, then 50–75 mg/day + folinic acid 10–25 mg/day combined with: sulfadiazine 1000 mg (<60 kg) – 1500 mg (≥60 kg) q6h if intolerant: clindamycin 600 mg q6h (up to 1200 q6h), oral or IV if intolerant: atovaquone 1500 mg q12h, oral
Alternative regimes: trimethoprim–sulfamethoxazole 10–20 mg/kg/day + 50–100 mg/kg/day, oral or i.v. ± clindamycin 600 mg q6h (up to 1200 q6h), oral / i.v. or atovaquone 1500 mg q12h, oral + sulfadiazine 1000 mg (<60 kg) – 1500 mg (≥60 kg) q6h
Duration: Minimum 6 weeks, or until clinical resolution + Two negative blood PCRs (7 days apart), or One negative CSF qPCR if initially positive. Extend treatment if disease is extensive or if response is incomplete at 6 weeks. Reduce or discontinue immunosuppression when possible Consider steroids if: Severe ocular toxoplasmosis CNS disease with midline shift Progression within 48 h of treatment Elevated intracranial pressure
Secondary prophylaxis for recipients with a recent Toxoplasma infection or disease and risk for recurrence
Indications: active GVHD, immunosuppression, or low $CD4^+$ cell counts Regimen: based on previous prophylaxis, initial induction therapy, and patient tolerance.

i.v., intravenous; GVHD, graft-versus-host disease; CNS, central nervous system; CSF, cerebral spinal fluid.

which is now rarely used. Including any fluid sample in diagnostic criteria has also improved sensitivity, especially for sites such as pleural, pericardial fluid, and the eye, where biopsy is often impractical due to patient condition or procedural risk. Since prognosis depends on early intervention, prompt initiation of preemptive therapy is crucial, similar to the approach used for cytomegalovirus (CMV) infection in the same population, to reduce the risk of organ or disseminated disease [29▪▪].

The ECIL-9 guidelines not only offer a more standardized framework for classifying human toxoplasmosis infection and disease in HSCT recipients, but they especially aim to improve monitoring strategies for early detection of *T. gondii* reactivation and timely treatment of the infection or disease to reduce toxoplasmosis-related mortality [29▪▪]. Pretransplant assessment of *T. gondii* risk in HSCT recipients should include serologic testing for both the recipient and the donor [29▪▪]. Individuals with isolated *T. gondii* IgG positivity are considered seropositive. Positive IgM antibodies may suggest a recent infection, but they can persist for over a year, complicating its utility [6]. Instead of relying solely on additional serologic tests, qPCR testing on blood is now recommended, as it can detect *T. gondii* infection days to weeks before the onset of clinical disease [29▪▪]. A positive qPCR result should be confirmed with a repeat test within 48–72 h, and prompt imaging is recommended to differentiate asymptomatic infection from human toxoplasmosis disease, enabling timely initiation of appropriate treatment (Table 2). The transplant should be postponed until treatment is completed and two PCR tests, at least seven days apart, are negative [29▪▪]. Persistent positivity beyond two weeks is associated with poorer outcomes [32▪▪]. In the study by Aerts *et al.* [32▪▪], evaluating weekly HSCT patients with human toxoplasmosis infection or disease, the median time from treatment initiation to the first negative qPCR result was seven days, with no significant difference between patients who received prophylactic or therapeutic doses. Notably, higher 30-day mortality rates were observed when qPCR remained positive beyond 10 days, leading the authors to conclude that earlier qPCR conversion to a negative test is associated with improved survival [32▪▪].

Given that over 95% of human toxoplasmosis cases occur in seropositive HSCT recipients, all seropositive individuals should receive primary toxoplasmosis prophylaxis (Table 2) [29▪▪]. This new recommendation is particularly important, as not all transplant centers routinely provide prophylaxis to seropositive recipients [4,30▪,32▪▪]. In a recent multicenter study across four European transplant centers, 84.7% of HSCT recipients who developed *T. gondii* infection or human toxoplasmosis disease had not received prophylaxis [32▪▪]. Similarly, in a retrospective study conducted in Texas, 51% of seropositive recipients, and 91% of those who experienced human toxoplasmosis reactivation, had not received any prophylaxis [30▪]. Due to marrow toxicity risk, trimethoprim–sulfamethoxazole prophylaxis is not suggested before engraftment but should be initiated early after transplant. This is particularly critical, as 41–56% of reactivations occur within the first month, and up to 90% occur within 6 months [29▪▪]. In a retrospective study conducted in France, 4.1% of patients undergoing weekly qPCR screening tested positive: 57.7% of the cases occurred before day 100 without prophylaxis, 26.9% occurred despite prophylaxis, and 15.4% were detected after day 100 [31▪▪]. These findings underscore that human toxoplasmosis can still develop despite prophylaxis, particularly in the early posttransplant period [31▪▪]. Aerts *et al.* [32▪▪] reported that 16.5% of their patients with *T. gondii* reactivation experienced breakthrough infections despite prophylaxis. Also, based on their findings, the same dose may be continued, unless there is a high parasitic load, persistent qPCR positivity after 10 days, or development of human toxoplasmosis disease, in which case the dose should be increased or alternative therapy considered [32▪▪].

Based on this evidence, the ECIL-9 guidelines recommend combining qPCR screening with prophylaxis, when feasible, as a complementary strategy to enhance early detection of *T. gondii* infection [29▪▪]. qPCR screening should begin prior to engraftment, be repeated on the day of transplant, then performed weekly until day 100 and biweekly until day 180 [29▪▪]. qPCR screening plays a critical role, particularly during the preengraftment period when prophylaxis is not administered, and in situations involving safety concerns with trimethoprim–sulfamethoxazole, uncertain adherence, or impaired drug absorption, such as in cases of gastrointestinal GVHD. Treatment success can be confirmed by weekly blood qPCR demonstrating two consecutive negative results, along with one negative result from any previously positive body fluid. Once confirmed, secondary prophylaxis and continued qPCR monitoring are recommended for the duration of immunosuppression [29▪▪]. These guidelines were developed based on evidence that pretransplant serologic screening, molecular monitoring, and prophylaxis with trimethoprim/sulfamethoxazole in seropositive recipients can reduce human toxoplasmosis related mortality from rates as high as 66 to 5.9% or even negligible levels in transplant centers where these measures are routinely applied [4,30▪,31▪▪,32▪▪,33].

CHRONIC TOXOPLASMA INFECTION: IMPACTS ON PREGNANCY AND DEBATED LINKS TO NEUROPSYCHIATRIC ILLNESS

During pregnancy, acute *T. gondii* infection in seronegative women can result in spontaneous abortion, intrauterine growth restriction, preterm birth, congenital toxoplasmosis, or late-onset ocular toxoplasmosis [6]. The severity of outcomes is greatest when infection occurs in the first trimester, involves

T. gondii Type I strain and atypical genotypes, and is left untreated [6]. Traditionally, immune competent pregnant women with a chronic infection, evidenced by stable titers of *T. gondii* IgG prior to conception, were considered protected against vertical transmission and, consequently, adverse pregnant outcomes and congenital toxoplasmosis. However, growing evidence from recent years indicates that vertical transmission can still occur in seropositive, immune competent women, either infected months before conception or experiencing reactivation or reinfection during pregnancy [34▪,35▪▪,36,37▪,38▪▪]. This is not unexpected, as also pre conceptional CMV immunity may fail to prevent fetal infection with a new strain in a new pregnancy or allow reactivation, leading to congenital disease. Similar concerns have been raised for chronic *T. gondii* infection, particularly due to the circulation of more virulent *T. gondii* genotypes and the persistence of bradyzoites in seropositive women through cycles of cyst rupture, host cell reinfection, new cyst formation [39].

Although it is well established that congenital transmission can occur following acute *T. gondii* infection within 6 months before conception, the precise time window considered absolutely well tolerated for a subsequent pregnancy remains uncertain. The most emblematic case supporting the possibility of vertical transmission due to an infection acquired beyond the 6-month risk window before conception involves an HIV-seronegative mother who gave birth to two infants with congenital toxoplasmosis, two years apart [40]. She seroconverted between the 10th and 33rd week of her first pregnancy and gave preterm birth to a symptomatic infant with both ocular and neurological involvement [40]. Two years later, she delivered a second infant with similar signs of congenital toxoplasmosis. The identification of the same *T. gondii* type II strain in the mother and both siblings supports hypothesis of reactivation as the cause of transmission [40]. A recent cohort study of 137 pregnant women in Brazil, assessed during their first or second prenatal visit, found a significant inverse association between maternal *T. gondii* IgG titers and neurodevelopmental outcomes in their one-year-old children [34▪]. Specifically, among women with chronic infection, each unit increase in maternal IgG was associated with a 0.08-point decrease in Bayley III composite scores [34▪]. *T. gondii* IgG antibodies typically appear 2–3 weeks after a new infection, peak at 6–8 weeks, and then gradually decline to stable levels. Thus, variations in IgG titers may suggest recent immune stimulation, but the timing of infection remains unclear due to the lack of IgG avidity assessment in the study.

Recent evidence suggests that reactivation of chronic *T. gondii* infection during pregnancy may be associated with adverse pregnancy outcomes also in immune-competent women [35▪▪,37▪,38▪▪]. In a cohort of 740 Hispanic pregnant women in the USA, *T. gondii* seropositivity (83% had high IgG avidity) was associated with a higher incidence of adverse outcomes, including preterm births and spontaneous abortion, with an adjusted odds ratio (OR) of 1.7 (95% CI: 1.06–2.73) [38▪▪]. The adjustment accounted for variables potentially influencing these outcomes, including socioeconomic status, smoking, and hypertension. Preterm birth occurred in 18.4% of seropositive mothers compared to 11.2% of seronegative, and spontaneous abortion in 9.2 vs. 6.3%, respectively. Although newborns of seropositive mothers were smaller for gestational age (6.4 vs. 2.1%, $P=0.014$), this association was not significant after adjustment, with preeclampsia, twinning, and smoking emerging as stronger predictors [38▪▪]. However, another study of 136 Brazilian pregnant women and their newborns also reported an association between chronic infection and small for gestational age (OR 9.4; 95% CI: 1.18–88.1), though the analysis was adjusted only for maternal height and prenatal weight [37▪]. It remains uncertain whether inflammation-mediated placental damage, direct pathogenic effects of *T. gondii*, or a combination of both plays the most critical role in driving these adverse outcomes [41]. The involvement of the parasite is further supported by several case reports describing severe congenital toxoplasmosis in infants born to mothers with chronic infection, confirmed through PCR detection of *T. gondii* and the presence of hallmark clinical signs. The most recent study reported two cases of severe congenital toxoplasmosis in infants who were asymptomatic at birth, except for being small for gestational age [35▪▪]. Although it was not possible to definitively distinguish between reactivation and reinfection with a different genotype, the detection of IgM antibodies postpartum in one case suggests reinfection as the more likely cause [35▪▪]. Taken together, these findings challenge the long-held assumption that chronic *T. gondii* infection confers complete protection against adverse pregnancy outcomes and congenital transmission.

In contrast to the data on pregnancy, the association between chronic *T. gondii* infection and neuropsychiatric disorders remains more debated and less well established. Several studies have explored a potential link between chronic *T. gondii* infection and schizophrenia, bipolar disorder, and epilepsy supported by evidence that the parasite alters rodent behavior to increase predation by cats [42,43]. However, many of these studies are case–control or cross-sectional in design, lack formal statistical analyses,

and fail to adjust for key confounding factors such as genetic susceptibility and environmental influences. As a result, even systematic reviews on this topic, which are typically considered the highest level of evidence, are difficult to interpret due to the inconsistent quality of most included studies [44,45]. A recent case–control study involving 115 individuals with bipolar disorder and 115 from the general population found that patients had significantly higher proportion of *T. gondii* IgG positivity (24.3 vs. 8.7%, $P=0.001$) [46▪]. However, the bipolar disorder group included a greater proportion of men, older individuals, and people with lower educational attainment, factors that are themselves associated with a higher risk of *T. gondii* infection. However, the authors performed a multivariate logistic regression adjusting for demographic and socioeconomic variables, which yielded an OR of 2.89 (95% CI: 1.08–7.73), indicating a potential association [46▪]. Another case–control study involving 98 patients with schizophrenia and 98 age-matched healthy blood donors found that patients had significantly higher odds of *T. gondii* IgG positivity (69.4 vs. 51%; OR 2.18, 95% CI: 1.21–3.90) [47▪]. The prevalence was higher among individuals with lower educational attainment, and this, as well as other potential confounders, were not accounted for in a multivariate analysis. Nevertheless, due to the inherent limitations of the case-control design, these two studies cannot establish causality. It is, for example, possible that patients who tested positive for *T. gondii* acquired the infection because of behaviors due to their underlying neuropsychiatric condition. Behavioral changes associated with certain psychiatric disorders may increase the likelihood of engaging in riskier eating habits, such as consuming undercooked or contaminated food, which could elevate the risk of alimentary acquisition of *T. gondii*. Furthermore, both chronic infection and neuropsychiatric conditions may arise from shared environmental exposures, rather than a direct causal relationship. Patients living in disadvantaged environments may face greater exposure to *T. gondii* through poor food safety and hygiene, while simultaneously being more vulnerable to the development of psychiatric disorders due to chronic stress, trauma, or limited access to healthcare. This highlights the need for well designed prospective cohort studies, that can clarify temporal relationships, reduce reverse causation bias, and account for behavioral and lifestyle confounders.

CONCLUSION

Venison-associated outbreaks underscore the need for heightened clinician awareness. Although new guidelines for managing HSCT recipients with chronic *T. gondii* infection have reduced mortality, chronic infection is increasingly recognized as a broader health concern. Emerging evidence highlights risks for pregnant women, particularly adverse pregnancy outcomes, while associations with neuropsychiatric disorders remain uncertain. Well designed, large-scale prospective studies are clearly needed to better guide clinical management and public health strategies for this ubiquitous pathogen.

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Conflicts of interest

There are no conflicts of interest.

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- ▪▪ of outstanding interest

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