

Neglected Parasitic Infections in the United States: Toxoplasmosis

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Abstract. *Toxoplasma gondii* is a leading cause of severe foodborne illness in the United States. Population-based studies have found *T. gondii* infection to be more prevalent in racial/ethnic minority and socioeconomically disadvantaged groups. Soil contaminated with cat feces, undercooked meat, and congenital transmission are the principal sources of infection. Toxoplasmosis-associated illnesses include congenital neurologic and ocular disease; acquired illness in immunocompetent persons, most notably ocular disease; and encephalitis or disseminated disease in immunosuppressed persons. The association of *T. gondii* infection with risk for mental illness is intriguing and requires further research. Reduction of *T. gondii* in meat, improvements in hygiene and food preparation practices, and reduction of environmental contamination can prevent toxoplasmosis, but more research is needed on how to implement these measures. In addition, screening and treatment may help prevent toxoplasmosis or reduce the severity of disease in some settings.

INTRODUCTION

Toxoplasmosis is an infection caused by the protozoan parasite *Toxoplasma gondii*. Cats are the definitive host in which the organism can complete its sexual cycle. Cats usually shed the environmentally resistant oocyst form of the organism in their feces for 1–2 weeks after a new infection, although in specific situations related to strain types, co-infection with *Cystoisospora felis* (syn. *Isospora felis*), and immunosuppression, repeat shedding is possible.¹ Sporulation is required for oocysts to become infectious and occurs within 1–5 days in the environment. Sporulated oocysts are quite hardy; they can remain infective in a moist environment for a year or more.¹ Once ingested by humans or any other warm-blooded animal, the parasite transforms into a tissue-infective stage in the intestine, migrates through the intestinal wall, and is carried via the blood to other tissues including the central nervous system.

Humans are accidental hosts and can be infected through a variety of exposures. Food-borne transmission occurs with ingestion of raw or undercooked meat containing the parasite in tissue cysts (usually pork, lamb, goat, or wild game meat, although beef and field-raised chickens have been implicated in epidemiologic studies),² or through ingestion of food, soil, or water contaminated by cat feces (for example, from eating unwashed fruits and vegetables, gardening, or cleaning a cat's litter box). Mother-to-child transmission typically occurs when a pregnant woman is newly infected during, or just prior to, her pregnancy. The organism can also be transmitted when a previously uninfected person receives an organ or blood transfusion from an infected donor.

The proportion of human *T. gondii* infections acquired by eating meat containing infective cysts versus ingesting oocysts from cat feces contamination is not known for a representative sample of the general population. However, ingestion of oocysts from cat feces/soil and ingestion of tissue cysts in meat both are significant contributors to the disease burden in humans, although oocysts have recently been shown to play an important role.^{3–5} Modern confinement production has

decreased *T. gondii* contamination of meat but there is concern that a new trend in the production of free-range raised animals for meat could increase the risk of contamination.²

Three principal clonal *T. gondii* genotypes were originally detected, primarily in isolates from the United States and Europe. However, more recently using sequence-based technology 15 haplogroups that define 6 major clades have been described,⁶ and the new paradigm is that many atypical genotypes differ in pathogenicity and transmissibility from typical genotypes.⁷ Research supports the concept that *T. gondii* genotype may be related to disease severity.^{8–10} However, there is relatively little information about *T. gondii* genotypes infecting asymptomatic persons, and in general, the clinical implications of *T. gondii* strains are incompletely understood.

CLINICAL MANIFESTATIONS

A self-limited or mild illness characterized by fever, malaise and lymphadenopathy is often seen after *T. gondii* infection, but many infections are subclinical. However, regardless of initial symptoms, a chronic infection is established, and immunosuppression, such as occurs with advanced human immunodeficiency virus disease or use of immunosuppressive medications in cancer treatment or after organ transplant, can result in disease reactivation and severe morbidity including neurologic involvement, or mortality. In those with advanced human immunodeficiency virus-related immunosuppression, encephalitis is a common manifestation unless long-term prophylactic medication is taken.

Congenital infection can cause pregnancy loss (miscarriage or stillbirth) or severe disease in the newborn, including developmental delays, blindness, and epilepsy.¹¹ However, many newborns with congenital toxoplasmosis are asymptomatic at birth. Nevertheless, even if asymptomatic at birth, illness will develop in many infected infants later in their life, most often ocular disease, but also neurologic symptoms and developmental disabilities.¹¹ For example, 82% of congenitally infected children (9 of 11, including 4 who received treatment) were shown to have ocular lesions by age 20 in one small prospective series.¹² Other studies confirm the risk for severe illness among congenitally infected children but have found a somewhat lower risk in treated children. For example, in a group of 127 treated children followed-up to 16 years in France, ocular lesions were present in 18.9%.¹³ In another

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series of 130 treated children followed-up 12 years in France, ocular involvement was found in 30%,¹⁴ and in a third series of French adults (median age = 22 years) who had congenital toxoplasmosis that was treated pre- and post-natally, 59% had ocular lesions but only 13% had reduced vision.¹⁵ A comparison of cohorts of children with congenital toxoplasmosis in Brazil with those in Europe found that *T. gondii* causes more severe ocular disease in congenitally infected children in Brazil.⁹ The authors suggested that the increased frequency and severity of ocular disease in Brazil compared with that in Europe may be caused by more virulent type 1 and atypical strains found there.⁹ In general, infants born to women who were infected with *T. gondii* more than a few weeks before conception are not at risk for congenital infection, although congenital infection from women with chronic *T. gondii* infection has occurred with reactivation in immunosuppression or with infection by atypical genotypes.⁷

Although *T. gondii* infection appears to be lifelong, for most healthy persons infected outside of infancy it has long been believed that further clinical manifestations after acute infection are rare. However, studies have now revealed associations between *T. gondii* antibody seropositivity (indicating infection) and the presence of various psychiatric disorders in humans (e.g., schizophrenia,¹⁶ bipolar illness,¹⁷ suicide attempts,¹⁸ episodes of self-directed violence,¹⁹ and memory impairment in elderly persons²⁰). Although these results are intriguing and potentially signal a new and compelling reason to redouble efforts to prevent toxoplasmosis, additional studies are needed to fully elucidate the relationship between *T. gondii* infection and mental illness, and how the strain and stage of *T. gondii* (oocyst versus tissue cyst) affects this relationship.²¹

DIAGNOSIS AND TREATMENT

Toxoplasma gondii infection can be diagnosed by testing for antibodies against *Toxoplasma*, as well as by direct testing or visualization of the parasite in body tissues or fluids. Basic antibody tests (e.g., IgG and IgM) are available commercially. Detection of IgG against *Toxoplasma* indicates previous exposure, but does not indicate when infection occurred. Detection of IgM against *Toxoplasma* is suggestive of acute infection, but IgM can persist for months or even years after infection and false-positive IgM test results can occur in persons who are chronically infected or not infected with *T. gondii*.²² Therefore, when clinical action depends on test results, IgM test results should be verified at a reference laboratory, especially for pregnant women and newborns.²³ Antibody avidity testing can be used to help distinguish between recent and distant infection,²⁴ an important consideration for pregnant women when IgM is detected and the risk for congenital toxoplasmosis is being assessed. Avidity testing is available in many countries including the United States.²⁵

Treatment recommendations vary with the type and severity of infection. Mild disease in adults with normally functioning immune systems rarely requires treatment, whereas severe disease, including disease in immunosuppressed persons, requires treatment with a combination of anti-parasitic medications (e.g., pyrimethamine and sulfadiazine).^{26,27} Clinical management of pregnant women and infants with congeni-

tal infection is complex and consultation with a specialist is advised.²⁸

PUBLIC HEALTH SIGNIFICANCE OF TOXOPLASMOSIS IN THE UNITED STATES

Toxoplasmosis is responsible for considerable morbidity and mortality in the United States. Serologic evidence of infection is more frequently seen in black and Hispanic persons, and among persons who are foreign-born, have low educational levels or socioeconomic status, or have occupations involving exposure to soil.^{29,30} Serologic evidence of *Toxocara* (dog or cat roundworm) infection, which is soil-borne, is more commonly seen among those with *T. gondii* infection, suggesting common risk factors for acquiring the two infections.³¹

In the United States, studies examining data from the mid to late 2000s estimated toxoplasmosis to be the second leading cause of deaths attributable to foodborne illness (an estimated 327 deaths), the fourth leading cause of hospitalizations attributable to foodborne illness (an estimated 4,428 hospitalizations), and a leading contributor to loss of quality-adjusted life years.^{32,33} *Toxoplasma gondii* infects an estimated 1.1 million persons each year in the United States.³⁴ Chorioretinitis caused by infection with *T. gondii* develops in an estimated 21,000 persons each year, and symptomatic chorioretinitis, leading to vision loss, develops in more than 4,800 of these persons.³⁴ Because symptoms in the eye recur over time and new lesions commonly develop, these calculations are likely to be minimum estimations of the incidence of symptomatic ocular toxoplasmosis. Ocular toxoplasmosis creates a significant burden on the healthcare system, with an estimated 250,000 visits to ophthalmologists for active or chronic disease over a two-year period.³⁵

Serologic surveys over past decades indicate that rates of infection with *T. gondii* have decreased in the United States. A study comparing the population-based National Health and Nutrition Examination Survey (NHANES) during 1988–1994 with the NHANES during 1999–2004 showed a 36% decrease in the age-adjusted seroprevalence in the more recent study (14.1% to 9.0% in persons 12–49 years of age).³⁰ Preliminary results from the NHANES 2009–2010 show further decreases (Jones J, unpublished data). Because in the older study (NHANES 1988–1994) all persons ≥ 12 years of age were tested, an estimate could be made for the overall population in this age range. The age-adjusted *T. gondii* antibody seroprevalence was 22.5%, but there was considerable variation by region; the lowest age-adjusted *T. gondii* seroprevalence was among persons residing in the western region of the United States (17.5%) and highest in the North-east (29.2%).²⁹

An estimated 400–4,000 infants are born with congenital toxoplasmosis each year in the United States.^{36–38} Overall, approximately 30% of women who acquire infection during pregnancy transmit the infection to the fetus; the risk of transmission from mother to child is lowest when infection occurs during the first trimester (10–15%) and higher as pregnancy progresses to the third trimester (60–90%).³⁹ However, injury to the fetus is usually greatest when acute infection occurs early in pregnancy,³⁹ although some atypical genotypes can cause severe congenital toxoplasmosis in the third trimester.⁷

Estimates of the incidence of congenital infections vary in the United States. The most recently published population-based estimate is derived from the New England Newborn Screening program in the late 1980s and early 1990s,^{38,40} a region shown to have the highest prevalence of *T. gondii* infection in the United States.²⁹ Analysis of newborn IgM blood spot screening tests in Massachusetts and New Hampshire yielded an estimate of 1 case per 12,212 live births.⁴⁰ More recent data from the New England Newborn Screening Program showed that congenital toxoplasmosis rates during 2000–2010 ranged from approximately 1.3 to 6.8 per 100,000 live births (Eaton R, unpublished data). Newborn screening filter paper blood spot IgM test sensitivity is low (approximately 50–75%).^{41–43} In addition, because false-positive IgM test results also occur, serum samples from the mother and infant must be followed-up to verify true positive test results.⁴⁰ Older local studies in the United States found congenital toxoplasmosis rates of approximately 1 per 1,000 newborns.^{44,45} Similar to seroprevalence estimates among adults, rates of congenital infection are likely to vary by region of the United States.

PREVENTION STRATEGIES

The devastating impact of congenital infection has led to great interest in reducing risk through screening. In one economic analysis, an approach comprised of monthly prenatal *T. gondii* screening and treatment of women infected in pregnancy coupled with one year of treatment of infected newborns with pyrimethamine and sulfonamides was estimated to be cost saving if the rate of congenital infection was greater than 1 per 10,000 live births.⁴⁶ However, the cost savings were based on an ideal program with all prenatal visits conducted on time, all tests validated at a highly expert reference laboratory, and when required, treatment given soon after maternal seroconversion. The efficacy of treatment of pregnant women and infants has not been determined by well-controlled randomized trials, either for the ability to prevent congenital infection or reduce sequelae in infected infants. Treatment is thought to be most effective if given within days to weeks of seroconversion in pregnant women. Even in France, where routine screening has been recommended for decades, a study found late initial testing and poor compliance with recommended screening intervals (the first test was performed later than the recommended first 12 weeks of pregnancy in 25% of women, and only 40% of women had the recommended number of screening tests in pregnancy).⁴⁷ In Austria, where prenatal screening every trimester has been recommended and conducted for three decades, only 30% of seronegative women were found to be tested at least three times during their pregnancies.⁴⁸ These findings imply that in a real-world setting it can be challenging to screen and treat newly seroconverted pregnant women soon after infection. Nevertheless, the societal and economic costs of care for developmental disabilities such as congenital toxoplasmosis, estimated to be from approximately 500,000 to 3.3 million U.S. dollars per case according to the severity,⁴⁶ are considerable for symptomatic cases.

Although there has been some enthusiasm within the medical community for prenatal or neonatal screening programs, others, including the United Kingdom National

Screening Committee, have argued that there is currently no evidence from randomized placebo-controlled trials demonstrating efficacy for screening and treatment of congenital toxoplasmosis.^{49–51} In recent years, prenatal or neonatal toxoplasmosis screening has been evaluated but not adopted in numerous countries in Europe, including the United Kingdom, Switzerland, and Denmark^{50–53}; and in Canada and Israel.^{54,55} Screening in these countries was not adopted because of a low incidence of *T. gondii* infection (similar to that of the United States), concerns about the lack of well-controlled studies documenting benefit, and concerns about potential costs and harms of the programs outweighing benefits in a practical setting. In addition, the American College of Obstetricians and Gynecologists did not recommend universal screening of pregnant women for *T. gondii* infection in their practice guidelines.⁵⁶ Studies and systematic reviews have yielded conflicting results on the benefits of prenatal screening and treatment of congenital toxoplasmosis.^{57–66} There is a need for well controlled studies to help determine the effectiveness these interventions.

Preventing infection of pregnant women through education is another potentially beneficial strategy. A study of pregnant women in the United States found that they often lack knowledge about how to prevent *T. gondii* infection, especially the risks associated with eating or handling raw or undercooked meat.⁶⁷ Although numerous studies have provided some evidence that education of pregnant women may be beneficial,^{68–72} one review of toxoplasmosis-related health education called for more rigorously designed research on prevention of toxoplasmosis through education, and questioned the validity of results from published studies.⁷³ In addition, a recent Cochrane systematic review found very little rigorous scientific evidence that prenatal education is effective in reducing congenital toxoplasmosis and called for randomized controlled trials to confirm the potential benefits and quantify the impact of educational interventions.⁷⁴

Vaccination of cats for toxoplasmosis has also been proposed as a control method and an oral live vaccine prevented cats from shedding oocysts in clinical trials.⁷⁵ However, the commercial production of toxoplasmosis vaccine for cats was discontinued because of its high cost, the need to keep the vaccine frozen, its short shelf life, and lack of interest among cat owners.¹ A live toxoplasmosis vaccine for sheep that produces protective immunity for 18 months is available in some countries (but not in the United States) to reduce loss of lambs.⁷⁶ Vaccination with killed *T. gondii* preparations has been unsuccessful. For humans, development of a live mutant or avirulent strain vaccine has not been pursued because these strains may pose a risk to the fetus and there is insufficient data on the risk of reversion to *T. gondii* strains that could cause disease, particularly in immunosuppressed persons.

GAPS IN CURRENT KNOWLEDGE AND PROGRAMATIC INTERVENTIONS

Despite limited data on the incidence and prevalence of infection and illness caused by *T. gondii*, toxoplasmosis is clearly an important public health problem in the United States and globally. Much remains to be learned about toxoplasmosis to improve our knowledge of the disease, as well as to decrease infection rates through prevention and treatment.

Further insight into the number of children infected by mother-to-child transmission could be gained by conducting a pilot prenatal screening and treatment program with active surveillance for congenital toxoplasmosis. However, the benefits of treatment remain uncertain and treatment trials with placebo treatment groups might be problematic from an ethical standpoint. In addition, because the congenital toxoplasmosis rate is low in the United States, appropriately controlled studies of treatment efficacy would require millions of study participants and be extremely expensive. Given these limitations, a monitored pilot evaluation of prenatal screening and treatment in a high-risk country or geographic region may be the best practical option, even if only a subset of the population undergoing prenatal screening is monitored for outcomes (e.g., randomly selected healthcare facilities, or sentinel sites).

There are numerous potential *T. gondii* maternal screening program pitfalls that include: lack of confirmation of positive screening test results before taking clinical actions, such as amniocentesis to assess fetal infection or implementing treatment; risk of amniocentesis to verify fetal infection;^{77,78} and late initial testing and poor compliance with screening intervals that lead to delayed initiation of therapy, as has been a problem in France and Austria.^{47,48,79} Because routine prenatal *T. gondii* infection screening would be new in low-incidence countries such as the United States, and the practicalities of its implementation in such countries are unknown, assessments of such screening and treatment programs should include 1) the proportion of *T. gondii* testing in pregnancy performed at correct intervals, and 2) the appropriate use of reference laboratories to validate test results, 3) evaluation of elective pregnancy terminations in women who show positive test results but who have not had their tests results confirmed, 4) the outcome and side effects of amniocentesis used to verify fetal infection, 5) the side effects of medications used in pregnant women and infants, 6) the time after maternal seroconversion that treatment is initiated, 7) the regimen used for treatment, 8) patient compliance with the treatment, 9) the outcome in infants, and 10) the costs and benefits. In the United States, if large numbers of tests were performed for screening, it is not certain that confirmatory testing could be limited to one expert reference laboratory, or even to several commercial laboratories, and in the past *T. gondii* tests at some commercial laboratories have not been accurate.²²

The diagnosis of toxoplasmosis can be difficult, especially in immunosuppressed patients and in persons with congenital disease. Diagnostic tools for toxoplasmosis, including polymerase chain reaction, more sensitive and specific IgM tests, Western blots for comparison of maternal and infant antibody response, and strain typing tests, would benefit from further development.^{11,80–82} In addition, relatively little is known regarding treatment efficacy for ocular disease.^{83,84} Improvements in treatment could potentially be achieved through 1) trials to establish the efficacy for preventing congenital transmission and sequelae in infants, as well as the optimal medications and duration of therapy; and 2) collaboration with those in the ophthalmologic community to improve detection and treatment of ocular disease and to create standardized, evidence-based practices for ocular disease designed to minimize morbidity and to prevent recurrent disease.

The reduction in prevalence of *T. gondii* infection in the United States suggests that efforts to improve quality control

by meat producers and improved cat-care hygiene, as well as efforts to increase knowledge about toxoplasmosis among physicians and the public, have been successful in reducing toxoplasmosis risk.³⁰ Further reductions in infection could be achieved through identification and mitigation of risk factors for *T. gondii* infection, including 1) encouraging good production practices by meat producers, 2) developing methods to minimize environmental contamination of soil and water with *T. gondii*, and 3) improving patient education and public health messages to reduce ingestion of undercooked meat and improve cat feces-related and soil-related hygiene.^{67,85,86} Further understanding of the impact of toxoplasmosis on health, including mental health, is needed to help keep public health resources focused on prevention efforts. Continued evaluation of *T. gondii* infection using population-based studies to monitor the prevalence and temporal trends in infection will be essential to measure the impact of prevention efforts and guide adjustments in prevention strategies.

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