Intervention Strategies to Reduce Human *Toxoplasma gondii* Disease Burden

Marieke Opsteegh, Titia M. Kortbeek, Arie H. Havelaar, and Joke W. B. van der Giessen

1Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, and 2Faculty of Veterinary Medicine, Institute for Risk Assessment Sciences, Utrecht University, The Netherlands

Infection with *Toxoplasma gondii* is acquired through consumption of undercooked infected meat, or by uptake of cat-shed oocysts. Although congenital toxoplasmosis is generally considered to contribute most to the disease burden of *T. gondii*, ocular disease from acquired infection was recently shown to add substantially to the burden. In addition, toxoplasmosis in immune-compromised individuals usually results from reactivation of an infection acquired earlier in life. Nevertheless, prevention of toxoplasmosis commonly targets mainly pregnant women. We summarize current prevention strategies of congenital toxoplasmosis and evaluate options to improve protection of the general population (including pregnant women). To protect the general population, freezing of meat destined for raw or undercooked consumption is the most readily applicable option, especially when limited to meat from animals originating from nonbiosecure husbandry systems. In the long term, more health benefits are expected from cat vaccination; therefore, development of a cat vaccine and evaluation of its implementation is a research priority.

**Keywords.** *Toxoplasma gondii*; control; prevention; intervention; disease burden.

*Toxoplasma gondii* is best known as a cause of congenital disease, which can occur when a woman is primarily infected during pregnancy. Infection of pregnant women may lead to abortion or stillbirth, chorioretinitis, hydrocephalus or microcephalus, and intracerebral calcifications in live-born children [1]. Infected children who are healthy at birth may develop chorioretinitis later in life. In immunocompromised hosts with T-cell defects (eg, organ transplant recipients, persons with AIDS, and patients with hematologic malignancies or receiving immunosuppressive therapy), toxoplasmosis may manifest as potentially fatal encephalitis, pneumonitis, and myocarditis [1]. Toxoplasmosis in these patients is usually a consequence of the recrudescence of a latent infection acquired earlier in life. Toxoplasma *gondii* infection in immunocompetent individuals has long been perceived as harmless. Indeed, the acute phase of infection usually passes asymptomatically or with symptoms limited to a transient lymphadenopathy and mild flu-like symptoms. However, it is now recognized that ocular toxoplasmosis is not necessarily a (late) sequela of congenital infection, but may also result from postnatally acquired infection [1]. It has been estimated that at least two-thirds of prevalent human ocular toxoplasmosis cases in Europe have acquired the infection postnatally [2], thereby adding substantially to the total disease burden attributed to *T. gondii* [3]. Moreover, severe disseminated toxoplasmosis, associated with life-threatening pneumonia but also cardiac abnormalities and fatal multiple organ failure, was reported in immunocompetent individuals from French Guiana [4, 5], demonstrating that emerging strains potentially increase the severity of acquired toxoplasmosis. In addition, *T. gondii* infection has been associated with illnesses such as schizophrenia and other conditions that involve behavioral changes [6], but a causal relationship has not been established.

Recent estimations of the disease burden due to *T. gondii* infections in various countries (as outlined in
Toxoplasmosis is present in every country, and the global annual incidence of congenital toxoplasmosis has been estimated at 190,100 cases (1.5 per 1000 live births) [7]. The incidence of acquired toxoplasmosis is less well known. Country-specific estimates diverge widely (eg, 58 and 2.6 cases per 100,000 in the United States [8] and the Netherlands [3], respectively). However, incidence does not fully represent the true public health impact, as disease severity is not accounted for. Integrated metrics include quality-adjusted or disability-adjusted life-years (QALYs or DALYs, respectively) and cost of illness. In the United States, the annual burden of Toxoplasma gondii is estimated at 10,964 QALYs (third among 14 food-related pathogens after Salmonella enterica and Campylobacter species) and the cost of illness at $2.9 billion (second after Salmonella enterica) [9]. In the Netherlands, in 2009, the total burden of toxoplasmosis was estimated at 3620 DALYs, including 1350 DALYs attributed to acquired infections (first among 14 enteral pathogens) [3]. Globally, the burden of congenital toxoplasmosis was estimated at 1.20 million DALYs. High burdens were seen in South America and in some Middle Eastern and low-income countries [7]. Note that these results cannot be compared directly due to differences in assumptions and model parameters.

Table 1. Ranking of Toxoplasmosis

<table>
<thead>
<tr>
<th>Rank</th>
<th>Pathogen</th>
<th>DALYs</th>
<th>QALYs</th>
<th>Cost (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Campylobacter jejuni</td>
<td>100,000</td>
<td>67,000</td>
<td>36.0 billion</td>
</tr>
<tr>
<td>2</td>
<td>Toxoplasma gondii</td>
<td>10,964</td>
<td>6500</td>
<td>2.9 billion</td>
</tr>
<tr>
<td>3</td>
<td>Salmonella enterica</td>
<td>9360</td>
<td>5400</td>
<td>2.0 billion</td>
</tr>
</tbody>
</table>

Table 1) demonstrate the overall public health impact of toxoplasmosis and warrant implementation of intervention measures. Prevention of toxoplasmosis currently focuses on pregnant women or immunocompromised and transplant patients. The effectiveness of the measures to prevent congenital toxoplasmosis is the subject of debate, and none of these measures aim to prevent acquired infections in the general population. Improvement of current T. gondii intervention strategies is highly needed to reduce the T. gondii disease burden on a population level. In this paper, 12 potential intervention strategies aimed at both congenital and acquired toxoplasmosis are evaluated (Table 2).

**TOXOPLASMA GONDII TRANSMISSION ROUTES**

The routes of T. gondii transmission to humans have been clear since the discovery of sexual development in cat intestines in the late 1960s and early 1970s [10]. People can become infected through consumption of raw or undercooked meat containing tissue cysts or via the environmental route by ingestion of oocysts (eg, during gardening or playing in the sandbox), or from eating contaminated raw seafood, vegetables, or fruit (Figure 1) [11]. Drinking water is considered safe when treatment includes coagulation, flocculation, and settling prior to filtration [12], but can be a risk when these treatments are not in place. Congenital transmission can occur when a woman becomes primarily infected during pregnancy. Toxoplasma gondii transmission by a transplanted organ can be prevented by serological screening and prophylactic treatment [1].

**PREVENTION OF CONGENITAL TOXOPLASMSOSIS**

Current intervention is predominantly aimed at preventing congenital toxoplasmosis. This can be done by educating pregnant women about the sources of infection to encourage them to change their behavior and thus reduce their risk of T. gondii infection (primary prevention). The information should cover proper heating of all meat and avoiding raw meat products, hand hygiene for gardening and other soil contact, washing of vegetables and fruits consumed raw, and precaution measures for cleaning of the cat litter box. Although health education for pregnant women has existed for decades, its effectiveness has not been evaluated adequately [13, 14]. Randomized cohort studies in which the effect of different health education programs on the incidence of T. gondii infections are studied are needed. Secondary prevention of congenital toxoplasmosis is based on prenatal or neonatal screening and treatment. In France and Austria, prenatal screening consists of a first serological test before or early in pregnancy and serological follow-up for those who tested negative [15]. In France, when seroconversion is demonstrated, spiramycin treatment is initiated and amniotic fluid is tested to check for transmission to the fetus. If amniotic fluid is positive for T. gondii, spiramycin will be replaced by pyrimethamine-sulfadiazine treatment until delivery. In addition, the fetus is checked by ultrasound or magnetic resonance imaging, and if severe lesions are demonstrated, the pregnancy may be terminated. The effectiveness of prenatal treatment is the subject of debate and large-scale randomized clinical control studies are lacking. Initially, a large European study showed only weak evidence for reduction of mother-to-child transmission, and no effect on the risk of clinical manifestations at birth could be demonstrated [16]. Later, a reduction of serious neurological sequelae was demonstrated [17]. Recently, French data demonstrated that mandatory monthly prenatal screening has decreased transmission rates, and implementation of polymerase chain reaction analysis of amniotic fluid in 1995 coincided with improved clinical outcomes at age 3 years [15]. In neonatal screening, as carried out in Poland and some states in the United States and Brazil, dried blood spots are tested for anti-T. gondii immunoglobulin M. If initial and confirmatory test results are positive, treatment is initiated and such a child will be examined regularly. There is variation in therapeutics used and duration of treatment. The neonatal screening program in Denmark was terminated because of the lack of a demonstrable benefit of treatment [18]. Consensus about the usefulness of secondary prevention is still absent.

**REDUCTION OF MEAT-BORNE TRANSMISSION**

Tissue cysts can be present in all warm-blooded animals including food animals and wildlife. Options to reduce the risk of infection from consumption of meat include prevention of infection in animals and decontamination of meat. The overall effectiveness of these measures largely depends on the relative attribution of meat-borne transmission, which is uncertain. In a European case-control study, depending on the center, 30%–63% of new infections in pregnant women were attributed to...
meat and 6%–17% to soil [19]. In the United States, the proportion of human cases that are food-borne (including vegetables) was estimated to be around 50% [8]. More recently, a serological assay to specifically detect oocyst-acquired infections in recently infected individuals has been developed, and use of this test in selected populations has shown a high rate of oocyst-acquired infections in the United States (78%) and Chile (45%) [20].

**PREVENTION OF INFECTION IN FOOD ANIMALS**

Herbivorous animals become infected by ingestion of oocysts while grazing, drinking contaminated water, or eating contaminated

---

**Table 2. Potential Health Benefits, Implementation Issues, and Main Bottlenecks for Intervention Measures to Reduce the *Toxoplasma gondii* Disease Burden in Humans**

<table>
<thead>
<tr>
<th>Option</th>
<th>Potential Health Benefits</th>
<th>Implementation</th>
<th>Main Bottlenecks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prenatal screening and treatment</td>
<td>Reduce congenital transmission, reduce symptoms of congenital toxoplasmosis</td>
<td>Requires much organization and is costly</td>
<td>Effectiveness of treatment is subject to debate and depends on frequency of screening; method is costly; causes anxiety in pregnant women; amniocentesis poses a small risk of abortion</td>
</tr>
<tr>
<td>2. Neonatal screening and treatment</td>
<td>Reduce symptoms of congenital toxoplasmosis</td>
<td>Requires much organization, less costly than prenatal</td>
<td>Effectiveness of treatment is unclear</td>
</tr>
<tr>
<td>3. Health education of pregnant women</td>
<td>Reduce congenital infections</td>
<td>Often in place, but needs improvement</td>
<td>Effectiveness depends on completeness of and adherence to advice</td>
</tr>
<tr>
<td>4. Health education of general population</td>
<td>Reduce acquired infections</td>
<td>Relatively easy to extent health education to the general public</td>
<td>Adherence to advice is likely to be very limited</td>
</tr>
<tr>
<td>5. Exposure reduction for food animals</td>
<td>Reduce infections acquired through meat</td>
<td>Measures can be included in already existing biosecurity programs</td>
<td>Effectiveness depends on relative attribution of meat-borne infection; possibilities for risk reduction very limited for outdoor-reared animals</td>
</tr>
<tr>
<td>6. Vaccination of food animals</td>
<td>Reduce infections acquired through meat</td>
<td>No vaccine currently licensed</td>
<td>Effectiveness depends on relative attribution of meat-borne infection and vaccine efficiency in field situation</td>
</tr>
<tr>
<td>7. Decontaminate all meat</td>
<td>Reduce infections acquired through meat</td>
<td>Complicates logistics at slaughterhouse</td>
<td>Effectiveness depends on relative attribution of meat-borne infection; some methods may not be accepted by consumers and may be expensive</td>
</tr>
<tr>
<td>8. Decontaminate meat products destined for undercooked consumption</td>
<td>Reduce infections acquired through meat</td>
<td>Complicates logistics in meat processing plants</td>
<td>See 7, but to a lesser extent</td>
</tr>
<tr>
<td>9. Decontaminate meat from infected animals or animals from high-risk farms</td>
<td>Reduce infections acquired through meat</td>
<td>Requires setup of logistics for screening and decontamination</td>
<td>Effectiveness depends on relative attribution of meat-borne infection and sensitivity of the detection method; screening is costly, no feasible detection method available for cattle</td>
</tr>
<tr>
<td>10. Reduce stray cat population</td>
<td>Reduce acquired infections</td>
<td>Investigation into the most effective method is required before large-scale implementation, requires much organization</td>
<td>Effect is delayed as infectious oocysts remain; effectiveness depends on the contribution of stray cats to the total cat population; depending on the chosen method, animal protection agencies may object</td>
</tr>
<tr>
<td>11. Education of cat owners (timely neutering, limiting hunting opportunities, no raw meat, stimulating use of the litter box and proper disposal)</td>
<td>Reduce acquired infections</td>
<td>Relatively easy to implement</td>
<td>Delayed effect as infectious oocysts remain; effectively influencing cat behavior is difficult and subsequent effect on oocyst shedding is uncertain; no effect on stray cats</td>
</tr>
<tr>
<td>12. Vaccination of cats</td>
<td>Reduce acquired infections</td>
<td>No vaccine currently available</td>
<td>Delayed effect as infectious oocysts remain; vaccine efficiency in field situation requires high vaccination coverage, which depends on willingness of cat owners and feasibility of vaccination of stray cats</td>
</tr>
</tbody>
</table>
feedstuff. Omnivorous animals such as pigs can also be infected through consumption of rodents, birds, or meat harboring tissue cysts [21]. Measures to prevent infection of food animals include keeping the animals indoors; keeping cats away from farms, feed, and bedding production and storage; providing clean drinking water and blocking access to surface water; implementing strict rodent control; and refraining from feeding offal and raw goat whey. Controlled indoor husbandry has drastically reduced the prevalence of T. gondii infection in pigs and is considered an important factor in the decrease of seroprevalences observed in human populations [22, 23]. However, the current tendency toward organic pig husbandry is likely to increase the risk of human infection, as a higher prevalence in organic pigs has been demonstrated [24, 25]. For outdoor-reared animals (eg, organic pigs and sheep), it is unlikely that prevention measures can substantially reduce the prevalence of infection. For these animals, vaccination would be a more feasible option; however, a vaccine aimed at preventing tissue cyst formation is currently not on the market. Toxovax, a vaccine licensed only for prevention of T. gondii abortions in sheep, is available. As this vaccine prevents dissemination of parasites to the placenta, it is likely to also prevent dissemination to

Figure 1. Sources of Toxoplasma gondii infection in humans. Reproduced from Clin Microbiol Rev, 2012, 25: 264–96, DOI: 10.1128/CMR.05013-11, with permission from the American Society for Microbiology.
other tissues and thereby reduce tissue cyst development [26], but this has not been tested experimentally. Even so, a different type of vaccine would be favorable, as the current vaccine is based on an attenuated live strain of *T. gondii* (S48), which limits production and shelf life, demands cold chain administration, and is potentially hazardous to the person administering the vaccine [26].

To increase the feasibility of preventing infection in food animals, screening to identify farms with infected animals (see Table 3) can be used to limit the interventions to farms with infected animals. This could be useful in pig production, as infected pigs are usually only found at a limited number of farms [24, 25], whereas almost all sheep farms have infected animals (eg, [32]).

### DECONTMATION OF MEAT

Several methods can be applied to decontaminate infected meat. Freezing meat at −12°C (a properly functioning home freezer) for 2 days will render tissue cysts nonviable, as can γ-irradiation and high-pressure processing [21]. Consumer acceptance may be a problem because of actual or perceived effects on color, texture, and taste of the meat. In addition, the use of γ-irradiation and high-pressure processing may be restricted by legislation, and may incur high costs. Again, it is possible to increase the efficiency of decontamination by limiting measures to high-risk meat products. In a quantitative microbial risk assessment including 50 meat products, 9 unheated meat products contributed 40% of the predicted *T. gondii* infections [33]. High-risk meat products could be defined as (1) meat destined for preparation of raw meat products (such as raw sausages, carpaccio, or steak tartare) and products that are more likely to be eaten undercooked (eg, beef steak, lamb chops); (2) meat from animals with outdoor access; or after implementation of screening on animal or farm level, (3) meat from animals infected with *T. gondii*; or (4) meat from animals originating from farms with a high *T. gondii* prevalence. These definitions could also be combined—for example, focusing on decontamination of meat to be eaten raw or partially undercooked from high-risk farms.

### REDUCTION OF ENVIRONMENTAL CONTAMINATION

Felids are the only definitive hosts for *T. gondii*, and primary infection results in shedding of millions of unsporulated oocysts within a period of 2 weeks on average. Oocysts become infectious within 1–5 days, depending on temperature and humidity [12], and can be dispersed from defecation sites mechanically and transported to water by runoff. Infectious oocysts are very resistant to environmental conditions including freezing and can survive up to 54 months in cold water and up to 18 months after deposition in soil [12]. The amount of infectious oocysts in the environment thus depends on feline population size, incidence of *T. gondii* infection in felines, amount of oocysts shed by an infected feline, fraction of oocysts that end up in the environment and sporulate, and survival of infectious oocysts [34]. Possibilities to intervene follow from these factors.

To regulate the cat population, cat owners need to have their cats spayed or neutered in a timely manner. In addition, control strategies for stray cat populations must be implemented.

Cats become infected mainly through hunting or by eating raw meat [35]. To reduce the number of prey animals caught, the cat can be kept indoors, especially at night [36], or equipped with a bell or electronic sonic device [37], but the effect of these measures on the incidence of *T. gondii* infection has not been studied directly. Vaccination of cats may be a more effective way of reducing oocyst shedding by cats. However, no vaccine is currently commercially available. Experimental vaccination using the attenuated T-263 strain demonstrated that oocyst shedding after challenge infection could be prevented in 31 of 37 kittens [38]. This live vaccine has disadvantages similar to those described for Toxovax, and development of different vaccination approaches taking into account potential coverage rates should be considered a research priority. Sufficient vaccination coverage may be a challenge; although 85% of Dutch cat owners who visited a veterinarian were willing [35], they may present a biased sample of the total population of cat owners. Vaccination of stray cats is only feasible when a capture program is in place.

To prevent oocysts from ending up in the environment, cats should be stimulated to use the litter box, and specific areas with high soil contact for humans (eg, sandboxes and vegetable gardens) should be kept free of cats. Cat litter should be disposed of with normal household waste, as this route is most likely to result in effective heat treatment of oocysts. Disposal for composting can lead to contamination of the garden, and oocysts flushed down the toilet may contaminate surface waters.

### CONCLUSIONS AND RECOMMENDATIONS

The potential health benefits, implementation issues, and main bottlenecks for the major intervention measures introduced in the previous sections are summarized in Table 2.

Because pregnant women constitute a specific risk group that is seen by healthcare professionals, educating them about the

---

**Table 3. Screening for *Toxoplasma gondii*-Positive Animals or Farms**

<table>
<thead>
<tr>
<th>Screening Methods</th>
<th>Purposes</th>
<th>Coverage May Be a Challenge</th>
<th>Main Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology, PCR, and bioassay</td>
<td>Detect <em>T. gondii</em> infection in animals</td>
<td>85% of Dutch cat owners who visited a veterinarian were willing</td>
<td>Potential coverage rates should be considered a research priority. Sufficient vaccination coverage may be a challenge.</td>
</tr>
<tr>
<td>PCR-based detection or development of new serological methods</td>
<td>Get an indication of the risk of beef for consumption</td>
<td>85% of Dutch cat owners who visited a veterinarian were willing</td>
<td>Possibilities to intervene follow from these factors.</td>
</tr>
<tr>
<td>Serology</td>
<td>Identify farms with infected animals</td>
<td>85% of Dutch cat owners who visited a veterinarian were willing</td>
<td>Control strategies for stray cat populations must be implemented.</td>
</tr>
</tbody>
</table>

---

**FOOD SAFETY • CID 2015:60 (1 January) • 105**
risks (Table 2, option 3) should be part of any prevention strategy, even though effectiveness has not been demonstrated. Protection of pregnant women can be extended by prenatal or neonatal screening (Table 2, options 1 and 2), but this is costly and the effectiveness of treatment is still subject to debate.

To reduce acquired infections, health education can be extended to the general population (Table 2, option 4); however, the effectiveness is expected to be very limited. Instead, the sources of infection can be targeted. In that case, options that reduce oocyst contamination of the environment (Table 2, options 10–12) are preferable over options targeting meat-borne transmission alone (Table 2, options 5–9). However, considering the bottlenecks for stray cat control and the limited possibilities to influence cat behavior, targeting meat-borne transmission is more feasible in the short term. Reducing the risk of infection is probably only feasible for indoor-reared food animals such as conventionally reared pigs and chickens. Additional *T. gondii*-related measures, especially limiting cat access to farm, feed, and bedding, are relatively easy to implement when an intensive biosecurity program is in place. For sheep, a *T. gondii* vaccine is commercially available. If the vaccine is demonstrated to also reduce oocyst contamination of the environment (Table 2, options 10–12), screening could be implemented for pigs. However, this requires much organization, and, as there is no screening method available for cattle (see Table 3), limiting decontamination to raw meat products and meat products that are more likely to be consumed raw or undercooked is probably more feasible.

Although a cost-benefit analysis is the preferred method to evaluate the different intervention measures, quantitative data are currently lacking. Based on this summary of options with identification of bottlenecks, a *T. gondii* prevention strategy that includes education of pregnant women and decontamination of raw and undercooked meat products of unvaccinated animals from nonbiosecure husbandry systems is recommended until an effective cat vaccine becomes available and widely implemented. Development of an effective cat vaccine and evaluation of its implementation is a research priority, and would eventually eliminate the need for decontamination of meat once the environmental contamination with infectious oocysts decreases.

Notes

Acknowledgments. We thank the Health Council of the Netherlands for critical comments.

Financial support. This work was supported by the Ministry of Health, Welfare and Sports, The Hague, The Netherlands.

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


