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Invited Review

Toxoplasma gondii infection in humans and animals in the United States

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Abstract

This paper reviews clinical and asymptomatic *Toxoplasma gondii* infection in humans and other animals in the USA. Seroprevalence of *T. gondii* in humans and pigs is declining. Modes of transmission, epidemiology and environmental contamination with oocysts on land and sea are discussed.
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Keywords: *Toxoplasma gondii*; Humans; Animals; Oocysts; Tissue cysts; USA

1. Introduction

Toxoplasma gondii infections are prevalent in humans and animals worldwide (Dubey and Beattie, 1988). Felids are the key animal species in the life cycle of this parasite because they are the hosts that can excrete the environmentally-resistant stage, the oocyst. Humans become infected post-natally by ingesting tissue cysts from undercooked meat, consuming food or drink contaminated with oocysts, or by accidentally ingesting oocysts from the environment. However, only a small percentage of exposed adult humans or other animals develop clinical signs of disease. It is unknown whether the severity of toxoplasmosis in immunocompetent hosts is due to the parasite strain, host variability or other factors. Recently, attention has been focused on genetic variability among *T. gondii* isolates from apparently healthy and sick hosts.

It has been 100 years since the discovery and naming of *T. gondii*. The parasite was first found in laboratory animals (for history see Dubey, 2007). Its medical importance remained unknown until 1939 when *T. gondii* was identified conclusively in tissues of a congenitally-infected infant in New York City, USA (Wolf et al., 1939), and its veterinary importance became known when it was found to cause abortion storms in sheep in 1957 in Australia (Hartley and Marshall, 1957). In the present paper, we summarize information on clinical and sub-clinical *T. gondii* infections in humans and animals in the USA, including transmission, epidemiology and control.

2. Clinical and asymptomatic *Toxoplasma gondii* infection in humans and animals

2.1. Infection in humans

2.1.1. Asymptomatic infection

Infection with *T. gondii* can occur pre- or post-natally. After birth, humans are usually infected with *T. gondii* by ingestion of oocysts in soil or water that have been contaminated with cat feces, or by ingestion of tissue cysts in undercooked meat (Dubey and Beattie, 1988; Bowie et al., 1997; Bahia-Oliveira et al., 2003; Dubey, 2004; Jones et al., 2005; de Moura et al., 2006). Transfusion or organ transplantation from an infected person can also transmit the organism (Shulman and Appleman, 1991; Schaffner,

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2001). Most persons infected after birth are asymptomatic (Montoya and Liesenfeld, 2004; Remington et al., 2006), however, some develop a mild disease or in rare cases, a more severe systemic illness (see Section 2.1.2). Once infected, humans are believed to remain infected for life. Unless immunosuppression occurs and the organism reactivates, people usually remain asymptomatic. However, there is ongoing research on whether chronic *T. gondii* infection has an effect on reaction time (Havlıček et al., 2001), tendency for accidents (Flegr et al., 2002), behavior (Flegr et al., 1996, 2000; Lafferty, 2005, 2006) and mental illness (Yolken et al., 2001; Flegr et al., 2003; Brachmann et al., 2005; Brown et al., 2005).

Selected serological surveys in humans in the USA are summarized in Table 1. Previous serological surveys were summarized by Dubey and Beattie (1988). A recent serosurvey using samples from the population-based National Health and Examination Nutrition Study (NHANES) found a decrease in the age-adjusted *T. gondii* prevalence in USA-born persons 12–49 years old from 14.1% in 1988–1994 to 9% in 1999–2004, a seroprevalence of 11% in USA-born women 15–44 years old in 1999–2004, and a seroprevalence of 28.1% in foreign-born women 1999–2004 (Jones et al., 2007). The overall seroprevalence (USA and foreign-born combined) increased with age and was higher among non-Hispanic black persons and Mexican Americans than among non-Hispanic white persons; however, among USA-born persons Mexican Americans had a lower seroprevalence than non-Hispanic white or black persons (age 12–49, 5.1% versus 8.8% and 11.5%, respectively). An earlier study evaluating NHANES III (1988–1994) sera for all persons $\leqslant$12 years of age (USA and foreign-born combined) showed an overall age-adjusted seroprevalence of 22.5%, a relatively linear increase in *T. gondii* infection with age, and a higher age-adjusted seroprevalence in the northeastern USA (29.2%) compared with the South (22.8%), Midwest (20.5%) or West (17.5%) (Jones et al., 2001). In this study, the risk for *T. gondii* infection was higher among persons who were foreign-born, had a lower education level, lived in crowded conditions and worked in soil-related occupations. In a separate study using NHANES III sera, the rate of *T. gondii* seropositivity among persons seropositive for the soil-transmitted helminth *Toxocara* spp. was nearly double the rate of *T. gondii* seropositivity among persons who were not seropositive for *Toxocara* spp., suggesting that sufficient soil exposure to lead to *Toxocara* spp. infection doubles the risk of *T. gondii* infection (Jones et al., 2008).

Prior studies have also shown a decrease in *T. gondii* seroprevalence in the USA over time. For example, in 1962 and 1989 *T. gondii* seroprevalence was examined among military recruits, showing rates of 14.4% and 9.5%, respectively (Feldman, 1965; Smith et al., 1996). Although not a complete sampling of the USA regional populations, the studies in military recruits (Feldman, 1965; Smith et al., 1996) and an earlier study (Feldman and Miller, 1956) found lower rates of *T. gondii* infection in the West. The western region of the USA is generally drier and oocysts may not survive as well in the soil in this climate. However, due to variations in weather, cat populations and human behavior, there is likely to be a wide variation in *T. gondii* prevalence within regions of the USA.

2.1.2. Symptomatic infection

A minority of healthy persons infected with *T. gondii* after birth develop symptoms, which are usually mild and include manifestations such as fever, malaise and lymphadenopathy (Montoya and Liesenfeld, 2004; Remington et al., 2006). However, in rare cases, humans who were previously healthy have developed severe and even fatal disease, including pulmonary and multivisceral involvement, possibly from more virulent types of the organism (Carme et al., 2002; Demar et al., 2007). In addition, up to 2% of healthy persons in the USA infected with *T. gondii* develop ocular disease (Holland, 2003), usually retinochoroiditis. A higher percentage of infected persons have been documented to develop ocular disease in other parts of the world, for example, one region of Southern Brazil (17.7% with ocular lesions) (Glasner et al., 1992). Retinochoroiditis can be due to congenital or post-natally acquired disease and can be associated with acute infection or reactivation (Montoya and Remington, 1996; Holland, 1999). Current thinking is that the majority of ocular toxoplasmosis comes from post-natally acquired disease (Holland, 1999, 2003). Acute toxoplasmic retinochoroiditis results in pain, photophobia, tearing and loss of vision.

Table 1
Selected USA human *Toxoplasma gondii* antibody prevalence studies

Year sampled	Age group	Source of sera	No. tested	% Positive	Reference
1962	U.S. young adult	Military recruits	2680	14	Feldman (1965)
1987	$\geqslant$18 years old	Maryland community	251	31	Roghmann et al. (1999)
1989	U.S. young adult	Military recruits	2862	9.5	Smith et al. (1996)
1992–1993	$\geqslant$18 years old	Illinois swine farm workers	174	31	Weigel et al. (1999)
1988–1994	U.S. age-adjusted $\geqslant$12 years old	NHANES[a]	17,658	22.5	Jones et al. (2001)
1999–2000	U.S. age-adjusted 12–49 years Women 12–49 years	NHANES	4234	15.8 14.9	Jones et al. (2003)
1999–2004	U.S. age-adjusted 12–49 years Women 15–44 years	NHANES	15,960	10.8 11.0	Jones et al. (2007)

[a] NHANES, National Health and Nutrition Examination Study.

Lesions tend to recur with progressive loss of vision over time, especially when the lesions are near the central structures of the eye (Holland, 2003). Considering the prevalence of *T. gondii* infection and the estimate that up to 2% of persons with *T. gondii* infection have ocular lesions in the USA (Holland, 2003), as many as 1.26 million persons in the USA may have ocular toxoplasmosis (based on the 2000 census, Holland, 2003). A national survey of ophthalmologists resulted in estimates that there were over 250,000 visits to ophthalmologists for active or inactive ocular toxoplasmosis in a 2-year period, a relatively large burden on the medical system (Lum et al., 2005).

2.1.2.1. Congenitally-infected children. Congenital toxoplasmosis generally occurs when a woman is newly infected with *T. gondii* during pregnancy (Remington et al., 2006), although rare exceptions have been reported in which women were infected just before pregnancy (Vogel et al., 1996). In addition, in immunosuppressed women reactivation of an infection acquired before pregnancy can lead to congenital toxoplasmosis (Mitchell et al., 1990; Minkoff et al., 1997). The risk of congenital infection is lowest when maternal infection is in the first trimester (10–15%) and highest when infection occurs during the third trimester (60–90%) (Dunn et al., 1999; Foulon et al., 1999; Remington et al., 2006). However, congenital infection usually leads to more severe disease when it occurs in the first trimester (Desmonts and Couvreur, 1974; Holliman, 1995; Remington et al., 2006). Congenital infection can lead to a wide variety of manifestations in the fetus and infant including spontaneous abortion, still-birth, a live infant with classic signs of congenital toxoplasmosis such as hydrocephalus or microcephalus, cerebral calcifications and retinochorioditis, an infant who fails to thrive or has CNS involvement or retinochoroiditis, or an apparently normal infant who develops retinochoroiditis or symptoms of CNS involvement later in life (McAuley et al., 1994; Remington et al., 2006). Most children are asymptomatic at birth (Guerina et al., 1994), but many will develop ocular or neurological manifestations (including learning disabilities) later in life (Wilson et al., 1980; Koppe et al., 1986; Guerina et al., 1994; Dunn et al., 1999; McLeod et al., 2006; Systemic Review on Congenital Toxoplasmosis Study Group, 2007).

In the USA, the most complete data on the rate of congenital infection comes from the New England Regional Newborn Screening Program, which serves Massachusetts and New Hampshire. All infants born in the catchment area are screened for a variety of conditions including *T. gondii* infection. Of the 635,000 infants who underwent serological testing between 1986 and 1992, 52 were infected, resulting in an infection rate of approximately 1 per 10,000 births. Only two (4%) of these infants were recognized to have congenital toxoplasmosis before the screening results were known; however, follow-up examinations identified signs of disease in 40% of the infants (Guerina et al., 1994). A subsequent study on the epidemiology of congenital toxoplasmosis identified in the New England Regional Newborn Screening Program 1988–1999 reported a rate of approximately 1 per 12,000 live births (Jara et al., 2001). Older prospective studies in Alabama and New York reported in the 1970s found rates of congenital toxoplasmosis of 13 per 10,000 and seven per 10,000 births, respectively (Kimball et al., 1971; Alford et al., 1974).

2.1.2.2. Immunosuppression. Toxoplasmic encephalitis is the most common clinical presentation of toxoplasmosis among persons with AIDS. It is usually the result of reactivation of latent tissue cysts (Luft et al., 1983, 1984; Wong et al., 1984; Israelski et al., 1993) when persons become severely immunosuppressed, with the highest risk occurring when the CD4+ T-lymphocyte count drops below 50 cells per microliter (Luft et al., 1983, 1984; Wong et al., 1984; Porter and Sande, 1992; Jones et al., 1996; Leport et al., 1996). The clinical presentation often includes a focal encephalitis with headache, confusion, motor weakness and fever and, if not treated, can progress to seizures, stupor and coma (Luft et al., 1983, 1984; Wong et al., 1984). Speech abnormalities and hemiparesis are the most common focal neurological findings (Luft et al., 1993). The primary lesion is cerebral necrosis, particularly of the thalamus (Renold et al., 1992). Pneumonia, other disseminated systemic disease or retinochoroiditis can be seen but are not as common as toxoplasmic encephalitis in HIV-infected persons. Clinically severe toxoplasmosis can also occur in immunosuppressed persons with malignancies and after transfusions (rarely) or transplants with immunosuppressive therapy (Siegel et al., 1971; Shulman and Appleman, 1991; Schaffner, 2001).

In the era before highly active antiretroviral therapy (prior to the mid-1990s), the annual incidence of toxoplasmic encephalitis was up to 33% among *T. gondii* seropositive HIV-infected persons with advanced immunosuppression who were not receiving prophylaxis with drugs active against *T. gondii* (Benson et al., 2004. Treating opportunistic infections among HIV-infected adults and adolescents. AidsInfo, U.S. Department of Health and Human Services, accessed 1/10/08 http://aidsinfo.nih.gov/contentfiles/TreatmentofOI_AA.pdf, pp. 9–12). In another study, the annual incidence was 38% among *T. gondii* seropositive persons with AIDS who were studied over 2 years (Israelski et al., 1993). An analysis of 90 inpatient and outpatient facilities in nine USA cities from January 1990 through August 1995 found an incidence rate of toxoplasmic encephalitis of 4.0 cases per 100 person-years among HIV-infected persons with a CD4+ T-lymphocyte count less than 100 cells per microlitre (Jones et al., 1996). However, during the years that prophylaxis and highly active antiretroviral therapy became widely used (mid-1990s in most developed countries), the incidence and deaths associated with toxoplasmic encephalitis declined markedly (Jones et al., 1999, 2002; Kaplan et al., 2000; Hooshyar et al., 2007). A French study found that the rate of toxoplasmic encephalitis declined from 3.9 cases

per 100 person-years in the time before the availability of highly active antiretroviral therapy (1992–1995) to 1 case per 100 person-years after it was available (1996–1998) (Abgrall et al., 2001). A decline to a similar incidence level was shown during the same time period across 11 USA cities (Kaplan et al., 2000).

2.2. Toxoplasma gondii infections in other animals

2.2.1. Livestock

Poultry, pigs and cattle are the main species of livestock in USA. Clinical toxoplasmosis is not a major problem in these animals.

2.2.1.1. Pigs. Seroprevalence data are summarized in Table 2. Prevalence of *T. gondii* varies dramatically among the classes of pigs surveyed (market pigs versus sows, indoor pigs with a biosecurity system versus free-range). The pigs used for unprocessed pork consumption (feeder pigs, market pigs) are mostly raised indoors in well managed facilities to prevent access to rodents and cats. In these well managed facilities, prevalence of *T. gondii* has greatly declined in the last decade (Table 2). In a statistically valid population-based nationwide survey conducted in 1983–1984, seroprevalence was 23% in market pigs and 42% in breeder pigs (sows) (Dubey et al., 1991). When pigs from these same areas were tested in 1992, prevalence had dropped to 20.8% in breeders and 3.1% in finisher pigs (Dubey et al., 1995c). The institution of a National Animal Health Monitoring System (NAHMS) for swine now allows periodic surveillance of pigs for microbial infections. The prevalence of *T. gondii* in three NAHMS swine surveys in 1990, 1996 and 1998 showed a steady decline (Table 2). The prevalence of *T. gondii* in pigs is also influenced by management systems. In poorly managed non-confinement systems, prevalence runs as high as 68% (Table 2). Risk assessment studies indicated that exposure to cats (oocysts) and mice, and not outdoor housing, were associated with *T. gondii* infection in pigs (Weigel et al., 1995b).

Viable *T. gondii* was isolated from 0.3% to 92.7% of pigs surveyed, depending on the source of pigs, class of pigs and the type of pork tested (Table 3). Seropositivity in general is a good indicator of the presence of viable parasites. In one study of 1000 sows, 22% were seropositive and viable *T. gondii* was isolated from 17% of these using heart tissue for bioassays; the isolation rate would likely have been higher if additional tissues were sampled. In another study, viable *T. gondii* was isolated from 51 of 55 pigs when hearts and tongues were used for testing (Table 3).

As mentioned earlier, clinical toxoplasmosis in pigs is rare. Toxoplasmosis was first reported in pigs on a farm in Ohio, USA (Farrell et al., 1952; Sanger and Cole, 1955). Pigs on this farm were reported to have cough, lack of coordination, tremors and diarrhea, with a 50% mortality rate. There were still-births, premature births and deaths soon after birth. Viable *T. gondii* were found in colostrums and sows' milk. These findings have not been confirmed and it seems likely that the outbreak was complicated by other causes (Dubey and Beattie, 1988). Dubey et al. (1979) described acute toxoplasmosis in a pig-

Table 2
Prevalence of *Toxoplasma gondii* antibodies[a] in sera of pigs from the USA

Year sampled	Type	Source of sera	No. tested	% Positive	Reference
1983–1984	Market hogs	Nationwide	11,229	23[c]	Dubey et al. (1991)
	Sows		623	42	
1989–1992	Sows	Abattoir-Iowa	1000	22.2	Dubey et al. (1995a)
1989–1990	All ages	31 Farms-Hawaii	509	48.5	Dubey et al. (1992c)
1990	Sows	NAHMS[b]	3479	20	Patton et al. (1996)
1991–1992	Sows	Tennessee-343 herds	3841	36	Assadi-Rad et al. (1995)
1992	Market hogs	Illinois-179 herds	1885	3.1[c]	Weigel et al. (1995a)
	Sows		5080	20.8	
1992–1993	Market hogs	Illinois-47 herds	4252	2.3[c]	Dubey et al. (1995c)
	Sows		2617	15.1	
1994–1995	Market hogs	North Carolina-14 herds	2238	0.5[c]	Davies et al. (1999)
1994–1995	Market hogs	NAHMS	4712	3.2[c]	[d]
	Sows		3236	15	
1998	Various ages	Connecticut, Massachusetts, NewHampshire, Rode Island, Vermont	1897	47.5	Gamble et al. (1999)
2000	Market hogs	NAHMS	8086	0.9[c]	[e]
	Sows		5720	6	
2002	Market hogs	Massachusetts-1 herd	55	87.2	Dubey et al. (2002a)
2006	Market hogs	Maryland-1 herd	48	68.7	Dubey et al. (2008b)

[a] Modified agglutination test, 1:20 or higher dilution.
[b] National Animal Health Monitoring System.
[c] Declining seroprevalence in market pigs.
[d] Patton et al. (1998).
[e] Patton et al. (2000).

Table 3
Isolation of *Toxoplasma gondii* from various food animals in the USA

Species	Source	No. bioassayed and tissue	% Positive	Reference
Pigs	Abattoir-Maryland	50 diaphragms	24	Jacobs et al. (1960)
	Abattoir, Iowa	1000 sow hearts	17	Dubey et al. (1995a)
	Massachusetts-1 herd	55 market hogs Hearts and tongues	92.7	Dubey et al. (2002a)
	Retail meat, nationwide	2094 pork	0.3	Dubey et al. (2005b)
	Maryland-1 herd	36 hearts	36.8	Dubey et al. (2008b)
Sheep	Abattoir-Maryland	86	9.2	Jacobs et al. (1960)
	Retail meat	50 lamb chops	4	Remington (1968)
	Abattoir-Maryland	68 lamb hearts	77.9	Dubey et al. (2008c)
Cattle	Abattoir-Maryland	60 diaphragms	0	Jacobs et al. (1960)
	Abattoir-Ohio	350 mixed tissues	0	Dubey and Streitel (1976)
	Retail meat, nationwide	2094 beef	0	Dubey et al. (2005b)
Chickens	Retail meat, nationwide	2094 breast meat	0	Dubey et al. (2005b)
Deer	Alabama	19	21	Lindsay et al. (1991)
	Mississppi	73	28.7	Dubey et al. (2004b)
	Iowa, Minnesotta	88	17	Dubey et al. (2008)
Black bear	Pennsylvania	28	35.7	Dubey et al. (1995b)
	Pennsylvania	10	70	Dubey et al. (2004b)

let on a farm in Indiana, USA. This piglet had necrosis of intestine, lymphadenitis, pneumonia and encephalitis; tachyzoites were demonstrable in lesions. This piglet and 15 littermates were apparently normal at birth, but developed diarrhea within 1–2 weeks, and eight of those died within 3–4 weeks. Epidemiological data indicated that the piglets probably became infected with *T. gondii* oocysts after birth (Dubey et al., 1979). Although congenital toxoplasmosis can be induced in pigs (Dubey et al., 1990a), we are not aware of a documented case of toxoplasmic abortion in pigs in the USA or elsewhere.

2.2.1.2. Cattle. Cattle are considered a poor host for *T. gondii.* Although cattle can be successfully infected with *T. gondii* oocysts, the parasite is eliminated or reduced to undetectable levels within a few weeks (Dubey, 1983, 1986), perhaps due to innate resistance. In one experiment, four steers weighing 100–150 kg were each fed 10,000 oocysts and killed 350, 539, 1191 and 1201 days p.i. (Dubey and Thulliez, 1993). At necropsy, many tissues from each animal were bioassayed (100 g each for bioassay in mice and 500 g each for bioassay in cats) for viable *T. gondi.* Viable *T. gondii* were isolated from steers killed 350 to 1191 days p.i. by bioassays in cats but not by bioassays in mice. The fourth steer became seronegative 15 months p.i. and viable *T. gondii* was not isolated from any tissue either in cats or mice. In another study, an attempt was made to isolate *T. gondii* from a naturally-exposed beef cow (Dubey, 1992). This 500 kg cow was killed and 100–500 g portions of its tissues were bioassayed in cats (500 g of each tissue) and mice (100 g of each tissue). None of the 12 cats fed approximately 6 kg of beef shed oocysts. Viable *T. gondii* was not isolated from any of the edible tissues of the cow by bioassays in mice but was isolated from a homogenate of intestine of the cow. Results of these experiments highlight the difficulties in detecting *T. gondii* infection in cattle. Other attempts to isolate *T. gondii* from beef are given in Table 3.

Little is known about the specificity and sensitivity of serological diagnosis of *T. gondii* infection in cattle because several tests that are used to diagnose toxoplasmosis in humans give erratic results with cattle sera (Dubey et al., 1985b), and it is difficult to verify specificity using naturally-infected cattle. The dye test, which is the most specific test for humans, gives false or erratic results with cattle sera (Dubey et al., 1985b; Dubey and Thulliez, 1993). Among all serological tests evaluated, a titer of 1:100 or higher in the modified agglutination test (MAT) appears to be indicative of *T. gondii* infection in cattle. In one serological survey of *T. gondii* in cattle from Montana, 3.2% of 2539 cattle had MAT titers of 1:128–1:512 (Dubey, 1985). In a study of beef from retail grocers, antibodies to *T. gondii* were not found by ELISA in meat juice from any of the 2049 samples of beef bioassayed during the National Retail Meat Survey for *T. gondii*, nor were viable organisms detected (Dubey et al., 2005b).

There are no confirmed reports of clinical toxoplasmosis in cattle (Dubey, 1986). Before the discovery of *Neospora caninum* as a cause of abortion in cattle (Thilsted and Dubey, 1989) it is likely that this parasite in cattle was misdiagnosed as *T. gondii*; *T. gondii* and *N. caninum* are morphologically similar parasites (Dubey et al., 1988c). Viable *T. gondii* was isolated from an aborted fetus from a cow in Washington State, USA (Canada et al., 2002). Whether the cow had aborted due to toxoplasmosis could not be determined because a histological examination of the fetus was not made. These authors reviewed other attempts to isolate *T. gondii* from bovine fetuses in the USA (Canada et al., 2002).

2.2.1.3. Poultry. In a recent survey, viable *T. gondii* was not isolated from chicken breast meat samples obtained from

retail meat stores (Table 3), however, meat juice from 1.4% of chickens had antibodies to *T. gondii* (Dubey et al., 2005b). There is no other serological survey for *T. gondii* in chickens raised in large-scale confinement operations. Jacobs and Melton (1966) isolated viable *T. gondii* from ovaries and oviducts of three and leg muscle of one of 108 chickens from a slaughter house in Maryland; the source of these chickens was not known.

Unlike chickens raised in confinement, backyard raised chickens are commonly infected with *T. gondii*. Viable *T. gondii* was isolated from 27% to 100% of chickens from backyard operations on small farms in Mississippi, Montana, Texas, Ohio, Illinois, Georgia and Louisiana (Gibson and Eyles, 1957; Eyles et al., 1959; Foster et al., 1969; Dubey, 1981, in press; Dubey et al., 2003a, 2007b); these chickens were primarily kept for egg production.

There are three reports of clinical toxoplasmosis in chickens from the USA. Ostendorf and Henderson [Ostendorf and Henderson, 1962. Toxoplasmosis in chickens. Proc. XII World Poultry Congress, Sydney, Australia, Section paper 385, pp. 385–387] reported that chickens with toxoplasmic encephalitis and chorioretinitis died on chicken farms in Indiana. Goodwin et al. (1994) reported peripheral neuritis in three chickens from Georgia and the diagnosis was made immunohistochemically, however herpes virus infection (Marek's disease) could not be ruled out. More recently, in a group of 14 backyard chickens in Illinois, three birds died suddenly (Dubey et al., 2007b). Torticollis, an inability to stand, and lateral recumbancy were the only clinical signs. One of these birds was necropsied. Marked lesions were limited to the brain which had multiple areas of necrosis, perivascular lymphocytic cuffs and gliosis. An unusual finding was the presence of numerous tissue cysts and tachyzoites in lesions. The remaining 11 chickens remained asymptomatic and all contained viable *T. gondii* (Dubey et al., 2007b).

2.2.1.4. Sheep. The prevalence of *T. gondii* in adult sheep and lambs in the USA is high (Tables 3 and 4). *Toxoplasma gondii* causes abortion and neonatal mortality in sheep worldwide. Isolated occurrences and epidemics of abortion and neonatal mortality have been reported in sheep in the USA (Dubey et al., 1981a, 1986b, 1990b; Dubey and Kirkbride, 1989a, 1990; Dubey and Welcome, 1988). Congenitally-infected lambs that survive the first week after birth usually grow normally and can be a source of infection for humans. An example is given here. Dubey and Kirkbride (1989b) isolated *T. gondii* from eight of eight naturally-infected lambs from a flock in South Dakota, USA. The lambs were from a flock that had aborted due to toxoplasmosis. *Toxoplasma gondii* was found histologically in 11 of 30 lambs that were born dead. Lambs that survived the first week after birth remained asymptomatic and were bled at 3–4 months of age; antibodies (MAT 1:1024 or higher) were found in 67 of 112 lambs. Eight of these lambs with MAT titers of 1:4096 or higher were slaughtered when they were 7 months old. *Toxoplasma gondii* was isolated from the hearts of three, tongues of seven, leg of lamb in eight, and lamb chops of seven by bioassays of 100 g of each tissue in mice (Dubey and Kirkbride, 1989b). There is no documented case of clinical toxoplasmosis in adult sheep in the USA or elsewhere. The case of encephalomyelitis in an adult sheep in New York, USA by Olafson and Monlux (1942) is now considered to have been due to a *Sarcocystis*-like parasite (Dubey and Beattie, 1988).

2.2.1.5. Goats. The number of goats in the USA is small and they are often raised in small operations. Most of the goats raised in the USA are dairy goats and females are used to produce milk and cheese. Although abortion and neonatal mortality are the main clinical signs, adult goats can develop clinical toxoplasmosis involving liver, kidneys and brain (Dubey and Beattie, 1988). Abortion and neonatal mortality was reported in dairy goats in Montana, Connecticut, and Maryland (Dubey, 1981; Dubey et al., 1981a, 1986a) in the USA.

2.2.1.6. Horses. Horses are resistant to *T. gondii*. Two recent surveys indicate a low prevalence of *T. gondii* in horses (Table 4). We are not aware of any confirmed report of clinical toxoplasmosis in horses anywhere in the world.

2.3. Pets and other animals

2.3.1. Domestic cats (*Felis domesticus*)

Toxoplasma gondii infection in cats is both of epidemiological and clinical significance. There has been no nationwide survey of the prevalence of *T. gondii* in cats in the USA and the available data were summarized by Conrad et al. (2005). In the largest survey using convenience samples from sick cats submitted for diagnosis to a clinical laboratory, antibodies to *T. gondii* were found in 31% of 12,628 cats (Vollaire et al., 2005). The seroprevalence of *T. gondii* varies with the age and lifestyle of the cat (Dubey, 1973).

The prevalence of *T. gondii* was higher in feral than pet or owned cats (Table 5). These data are comparable among different categories of cats because results are based on 1:25 serum dilution tested by the MAT and most of those were performed in one laboratory.

Cats can suffer from clinical toxoplasmosis (Meier et al., 1957; Dubey and Carpenter, 1993a,b; Dubey and Lappin, 2006). Affected cats may appear depressed and anorexic and die suddenly with no obvious clinical signs. Pneumonia is the most important clinical manifestation of feline toxoplasmosis. Other common clinical manifestations are hepatitis, pancreatic necrosis, myositis, myocarditis, uveitis, dermatitis and encephalitis. Clinical toxoplasmosis is most severe in congenitally infected kittens. Among 100 histologically confirmed cases of toxoplasmosis in cats, 36 were considered to have generalized toxoplasmosis, 36 pulmonary, 16 abdominal, two hepatic, one pancreatic, one cardiac, two cutaneous and seven neurologic; in 14 cats

Table 4
Serological prevalence of *Toxoplasma gondii* in selected species of animals in the USA

Species	Locality and source	Year	Number tested	% Positive	Serologic test	Cut-off value	Reference
Sheep	New Jersey, New York, Pennsylvania	Not stated	Adults-309[a] Lambs-345[a]	62.4:55.0	ELISA	?	Malik et al. (1990)
	California, Idaho, New England, Oregon	1974–1976	Ewes-2164[a] Lambs-1056[a]	24:8	IHAT	1:64	Riemann et al. (1977)
	Idaho	Not stated	Ewes-250[b]	20.8	IHAT	1:64	Huffman et al. (1981)
	Maryland	1984	Sheep-78[b]	41	MAT	1:16	Dubey et al. (1986b)
	New York	1987	Ewes-592[b]	73.8	MAT	1:16	Dubey and Welcome (1988)
	Iowa, Minnesotta, South Dakota, Kansas	1983–1987	Ewes-1564[b]	65.8	MAT	1:64	Dubey and Kirkbride (1989a)
	Maryland, Virginia	2006	Lambs-383[a]	27.1	MAT	1:25	Dubey et al. (2008c)
Goats	California	1974–1977	Dairy goats-1054[b]	23	IHAT	1:64	Ruppanner et al. (1978)
	Washington	1982–1984	Dairy goats-1000	22.1	MAT	1:40	Dubey and Adams (1990)
Horses	Nationwide	1973	1294	20	IHAT	1:64	Riemann et al. (1975c)
	Midwest	1976–1977	500[a]	10	DT	1:2	Al-Khalidi and Dubey (1979)
	24 states	1998	1054[a]	6.9	MAT	1:20	Dubey et al. (1999)
	Wyoming	2002	276[b]	0.2	MAT	1:25	Dubey et al. (2003c)
Wild pigs	California	1982–1983	135	17	LAT	1:32	Clark et al. (1983)
	Georgia (mainland)	1979–1980	170	18.2	MAT	1:25	Dubey et al. (1997a)
	(Ossawa island)	1992–1994	1,064	0.9	MAT	1:25	Dubey et al. (1997a)
	South Carolina	1990	180	31	MAT	1:32	Diderrich et al. (1996)
White-tailed deer	Pennsylvania	1991	583	60	MAT	1:25	Humphreys et al. (1995)
	Minnesotta	1990–1993	1367	30	MAT	1:25	Vanek et al. (1996)
	Mississippi	2002–2003	73	46.5	MAT	1:25	Dubey et al. (2004b)
	Iowa	2007	84	64.2	MAT	1:25	Dubey et al. (2008d)
Black bear (*Ursus americanus*)	Pennsylvania	1989–1992	665	80	MAT	1:25	Briscoe et al. (1993)
	Pennsylvania	1993	28	78.5	MAT	1:25	Dubey et al. (2004b)
	Pennsylvania	1998	80	80.5	MAT	1:25	Dubey et al. (2004b)
	Pennsylvania	2007	37	75.6	MAT	1:25	Dubey, J.P., unpublished data
	North Carolina	1996–1997	143	84	MAT	1:25	Nutter et al. (1998)
Raccoon (*Procyon lotor*)	Iowa, New Jersey, Ohio, South Carolina, Pennsylvania	Not stated	427	50.3	MAT	1:25	Dubey et al. (1992b)
	Kansas	1989–1993	20	70	MAT	1:25	Brillhart et al. (1994)
	Illinois	1992–1993	188	67	MAT	1:25	Dubey et al. (1995c)
	Iowa	1984–1988	885	15	MAT	1:32	Hill et al. (1998)
	Illinois	1989–1993	379	49	MAT	1:25	Mitchell et al. (1999)
	Florida, New Jersey, Pennsylvania, Massachusetts	1993–1996	99	46	MAT	1:50	Lindsay et al. (2001)
	Virginia	2000–2001	256	84.4	MAT	1:25	Hancock et al. (2005)
	Wisconsin	2006	54	59.2	MAT	1:25	Dubey et al. (2007a)

[a] Abattoir.
[b] Farms.

concurrent microbial or other conditions were identified (Dubey and Carpenter, 1993a).

Cats, like humans, suffer from an immunodeficiency virus (FIV). Although FIV infection can experimentally predispose cats to generalized toxoplasmosis (Davidson et al., 1993), this phenomenon appears to be rare in naturally-infected cats as there are only a few reports of fulminating toxoplasmosis in cats with FIV (Heidel et al., 1990; Dubey and Lappin, 2006). The interaction between *T. gondii* and FIV is intriguing because both the seroprevalence and the magnitude of titers were higher in dually infected cats (Witt et al., 1989).

Table 5
Seroprevalence of *Toxoplasma gondii* in domestic cats (*Felis domesticus*) from the USA according to the type and habitat of the cat

Cat type	Locality	No. tested	% Positive	Reference
Goat farm	Marland	4	100	Dubey et al. (1986a)
Sheep farm	Maryland	16	100[b]	Dubey et al. (1986b)
Pig farms	Iowa	74	41.9	Smith et al. (1992)
Pig farms	Illinois	391	68.3	Dubey et al. (1995c)
Feral	Iowa	20	80	Hill et al. (1998)
Rural	Ohio			Dubey et al. (2002b)
Barn		94	50	
Outside		80	38	
Feral		78	62	
	Rhode Island			DeFeo et al. (2002)
Shelter		84	50	
Owned		116	36	
	North Carolina			Nutter et al. (2004)
Feral		100	63	
Owned		76	34	

[a] Data based on modified agglutination test.
[b] Viable *T. gondii* isolated from tissues of nine of 16 cats.

2.3.2. Dogs

Primary toxoplasmosis in dogs is rare. Most cases of acute toxoplasmosis in the USA were observed in dogs not vaccinated against the immunosuppressive canine distemper virus (CDV) (Capen and Cole, 1966; Dubey and Beattie, 1988; Dubey et al., 1989; Rhyan and Dubey, 1992). The most severe disease occurs in pups but to our knowledge there is no documented case of congenital toxoplasmosis in dogs. Common clinical manifestations of toxoplasmosis in dogs are pneumonia, hepatitis and encephalitis (Dubey and Lappin, 2006).

2.3.3. Other pets

Sporadic cases of clinical toxoplasmosis occur in rabbits (Leland et al., 1992; Dubey et al., 1992a), squirrels (van Pelt and Dieterich, 1972; Soave and Lennette, 1959; Dubey et al., 2006; Bangari et al., 2007), mink (Frank, 2001) and pet birds, especially in canaries and finches (Dubey, 2002; Dubey et al., 2004a). Toxoplasmosis in squirrels can simulate signs of rabies (Soave and Lennette, 1959). Reported clinical signs in squirrels were anorexia, diarrhea, lethargy, viciousness, labored breathing and in two cases squirrels had bitten children. An unusual clinical presentation of toxoplasmosis in canaries is blindness with almost complete destruction of the eyes (Dubey, 2002).

2.4. Wild animal species, including game

Among wild animals, *T. gondii* infections in deer, bears and raccoons are of epidemiological significance and prevalence data are summarized in Table 4. Deer are strictly herbivores and the high prevalence of *T. gondii* in deer suggests widespread contamination of the environment with oocysts. Bears and raccoons are omnivores and infections in those indicate cumulative contamination with oocysts and intermediate hosts in the environment. In one survey, antibodies to *T. gondii* were found in 85.9% of red foxes (*Vulpes vulpes*) and gray foxes (*Urocyon cinereoargenteus*) in Kentucky, Indiana, Michigan and Ohio, and viable *T. gondii* was isolated from both of these hosts (Walton and Walls, 1964; Dubey et al., 2004b).

2.5. Captive zoo animals and endangered species

Certain species of zoo animals, especially New World primates, wallabies and kangaroos, are highly susceptible to toxoplasmosis (Ratcliffe and Worth, 1951; Dubey and Beattie, 1988). Acute toxoplasmosis has been described in ring-tailed lemurs, *Lemur catta* (Dubey et al., 1985a; Spencer et al., 2004), squirrel monkeys, *Saimiri sciureus* (McKissick et al., 1968; Anderson and McClure, 1982), marmoset, *Oedipomidus oedipus* (Benirschke and Richart, 1960), and wooley monkey, *Lagothrix* sp. (Hessler et al., 1971). These animals can die suddenly, often with visceral toxoplasmosis, before the lesions develop in the brain. Enteritis characterized by necrosis of the cells of lamina propria and mesenteric lymphadenitis suggest oral infection with food and water contaminated with oocysts. Old World primates are generally resistant to clinical toxoplasmosis but there is a report of toxoplasmosis in macaques, *Macacca mulata* (Wong and Kozek, 1974).

There are many reports of severe toxoplasmosis in wallabies and kangaroos in zoos worldwide, including from the USA (Boorman et al., 1977; Dubey et al., 1988b; Miller et al., 1992; Adkesson et al., 2007). Among marsupials, macropodids are highly susceptible to acute toxoplasmosis. Clinical signs include pneumonia, myocarditis, hepatitis and blindness, and they can die even after treatment with sulfonamides and pyrimethamine (Dubey and Crutchley, 2008).

Toxoplasmosis in the endangered Hawaiian crow (*Corvus hawaiiansis*) is of particular interest because there are few (<25) animals left and four animals in the wild died of clinical toxoplasmosis (Work et al., 2000).

2.6. Marine mammals

Recent findings of *T. gondii* infection in marine mammals in the USA are most intriguing. In a preliminary report Thomas and Cole (1996) reported protozoal encephalitis in 8.5% of sea otters. Before this, there were isolated reports of *T. gondii*-associated encephalitis in other marine mammals including seals, sea lions and dolphins, and these were summarized by Dubey et al. (2003b). The sea otter is listed as an endangered species (Conrad et al., 2005). Two groups of researchers made detailed studies of causes of mortality in sea otters. Of the 105 otters necropsied at the Californian laboratories from 1998 to 2001, *T. gondii* was considered to be the primary cause of death in 17 and a related parasite, *Sarcocystis neurona* in seven otters (Kreuder et al., 2003). Otters with preexisting *T. gondii* encephalitis were considered prone to shark attack (Kreuder et al., 2003). In another investigation involving otters that died in California and Washington State but necropsied at the National Wildlife Health Center in Wisconsin, protozoal encephalitis was considered the cause of death in 39 of 334 (11.3%) sea otters; of these 22 were infected with *S. neurona*, five with *T. gondii* and 12 had dual infections (Thomas et al., 2007). Thus, *T. gondii* was not a major cause of mortality in these sea otters.

Antibodies to *T. gondii* were found in a variety of marine mammals including sea otters, dolphins, seals and walruses (Table 6). Prevalence of *T. gondii* in sea otters was high but varied between 47% and 100%, depending on the category (live versus dead), source (California versus Washington), and the serological test used. Prevalence in sea otters from California was higher than in Washington otters. Although *T. gondii* were not found in 65 sea otters from Alaska (Miller et al., 2002a), antibodies were found in other marine mammals from Alaska (Table 6). Both antibodies and clinical toxoplasmosis were found in the Hawaiian monk seal (*Monachus schauinslandi*), indicating water in the Pacific Ocean is infected (Honnold et al., 2005; Aguirre et al., 2007).

The high seroprevalence of *T. gondii* antibodies in sea otters has been verified parasitologically. Viable *T. gondii* was isolated from 85 sea otters from California and Washington (Cole et al., 2000; Miller et al., 2002b; Conrad et al., 2005; Sundar et al., 2008).

A very high seroprevalence of *T. gondii* was found in the bottlenose dolphin (*Tursiops truncatus*) from California, Florida, North Carolina and South Carolina, indicating that marine mammals on both coasts of the USA are exposed to *T. gondii* (Table 6). Recently, viable *T. gondii* was isolated from bottlenose dolphins (Dubey et al., in press c). Transplacental toxoplasmosis is considered rare in marine mammals (Dubey et al., 2003b; Miller et al., 2008).

2.7. Pathogenesis of toxoplasmosis including T. gondii genotype

Only a small percentage of exposed adult humans or animals develop clinical toxoplasmosis. It is unknown whether the severity of toxoplasmosis in immunocompetent individuals is due to the parasite strain, host variability or other factors. Experimentally, oocyst-induced infections are more severe than those induced by tissue cysts and bradyzoites by the natural oral route, irrespective of the dose (Dubey and Frenkel, 1973; Dubey and Beattie, 1988; Dubey, 1997; Dubey et al., 1997b). Severe clinical toxoplasmosis was reported in humans and was linked epidemiologically to ingestion of *T. gondii* oocysts in food or water (Teutsch et al., 1979; Benenson et al., 1982; Bowie et al., 1997; de Moura et al., 2006). Little is known about the effect of race or geography on clinical toxoplasmosis in humans, except that there is a high prevalence of eye dis-

Table 6
Prevalence of *Toxoplasma gondii* antibodies in marine mammals in the USA

Species	Source	No. tested	% Positive	Test	Titer	Reference
Sea otters (*Enhydra lutris*)	California – live	80	36	IFAT	1:320	Miller et al. (2002a)
	Dead	77	61	IFAT		Miller et al. (2002a)
	Live	100	82	MAT	1:25	Dubey et al. (2003b)
	Dead	25	52	MAT	1:25	Sundar et al. (2008)
	Washington live	21	38	IFAT	1:320	Miller et al. (2002a)
	Dead	10	100	MAT	1:25	Sundar et al. (2008)
Walruses (*Obobenus rosmarus*)	Alaska	53	5.6	MAT	1:25	Dubey et al. (2003b)
Sea lions (*Zalophus californianus*)	Alaska	27	29.6	MAT	1:25	Dubey et al. (2003b)
	California	18	61.1	MAT	1:25	Dubey et al. (2003b)
Harbor seals (*Phoca vitulina*)	Washington	380	7.6	MAT	1:25	Lambourn et al. (2001)
	Alaska	311	16.4	MAT	1:25	Dubey et al. (2003b)
Ringed seal (*Phoca hispida*)	Alaska	32	15.6	MAT	1:25	Dubey et al. (2003b)
Bearded seals (*Erignathus barbatus*)	Alaska	8	50	MAT	1:25	Dubey et al. (2003b)
Spotted seals (*Phoca largha*)	Alaska	9	11.1	MAT	1:25	Dubey et al. (2003b)
Hawaiian monk seal (*Monachus schauislandi*)	Hawaii	117	1.7	MAT	1:25	Aguirre et al. (2007)
Bottlenosed dolphin (*Tursiops truncatus*)	California	94	96.8	MAT	1:25	Dubey et al. (2003b)
	Florida	47	100	MAT	1:25	Dubey et al. (2003)
	Florida, South Carolina	146	100	MAT	1:25	Dubey et al. (2005a)
	South Carolina	49	53	MAT	1:25	Dubey et al. (2008e)

ease in southern Brazil (Glasner et al., 1992; Silveira et al., 2001; Holland, 2003).

Recently, attention has been focused on genetic variability among *T. gondii* isolates from apparently healthy and sick hosts. *Toxoplasma gondii* isolates have been classified into three genetic Types (I, II, III) based on restriction fragment length polymorphism (RFLP) (Howe and Sibley, 1995) and until recently, *T. gondii* was considered to be clonal with very little genetic variability. Based on newer markers for genetic characterization and using recently isolated strains, a higher genetic variability has been revealed than was previously reported (Ajzenberg et al., 2002; Ajzenberg et al., 2004; Khan et al., 2006; Lehmann et al., 2006).

Circumstantial evidence suggests that certain genetic types of *T. gondii* may be associated with clinical toxoplasmosis in humans in the USA (Howe et al., 1997; Grigg et al., 2001; Boothroyd and Grigg, 2002; Khan et al., 2005, 2006). It has been suggested that Type I isolates or recombinants of Types I and III are more likely to result in clinical toxoplasmosis (see Khan et al., 2005, 2006 and references contained therein), but genetic characterization has essentially been limited to isolates from patients with toxoplasmosis. In France, of the 86 *T. gondii* isolates obtained from patients with clinical toxoplasmosis, 73 (84.8%) were Type II, two (2.3%) were Type III, seven (8.1%) were Type I and four (4. 6%) were atypical; there was no apparent association between severity of disease and genotype (Ajzenberg et al., 2002). In humans in French Guiana and Suriname, severe cases of toxoplasmosis in immunocompetent patients have been related to *T. gondii* strains with atypical genotypes (Ajzenberg et al., 2004; Demar et al., 2007).

There is very little information regarding the genetic diversity of *T. gondii* isolates circulating in the general human population. Therefore, we must be cautious in claiming a linkage between parasite genotypes and disease presentations without more complete knowledge of the *T. gondii* genotypes in human populations and the environment. Mouse-virulent strains with atypical genotypes, similar to strains from clinical cases of humans in Brazil (see Khan et al., 2006) have been found in asymptomatic chickens and cats from Brazil (Dubey et al., 2002; Dubey et al., 2007; Pena et al., 2008).

Two new genotypes (Types A and X) of *T. gondii* have been found in sea otters from California and Washington (Miller et al., 2004; Conrad et al., 2005; Sundar et al., 2008). Miller et al. (2004) observed localized clustering of genotype Type X near Morro Bay and reported Type X *T. gondii* as the primary cause of meningoencephalitis in nine of 12 otters. However, in another study, *T. gondii* was considered a contributing cause of death in only three of 37 (25 from California and 12 from Washington) sea otters; these three otters also had other potentially fatal conditions (Sundar et al., 2008). In the remaining 34 otters *T. gondii* infection was considered incidental (Sundar et al., 2008). Whether these new *T. gondii* genotypes (Types A and X) are host- or region-specific, and their association with mortality, needs further investigation.

3. Epidemiology and transmission of *T. gondii*

Congenital infection, ingestion of infected tissues and ingestion of oocysts are the three main modes of transmission of *T. gondii*. Overall, less than 1% of humans and livestock acquire *T. gondii* infection transplacentally. The proportion of the human population that becomes infected by ingesting *T. gondii*-infected meat, food or water contaminated with oocysts is unknown and currently there are no tests to distinguish meat- versus oocyst-acquired infections. Most of the evidence is based on epidemiological investigations and prevalence studies in animals. The surge of infections in teenage and low prevalence in young children suggests that transmission by meat is important in the USA.

3.1. Role of infected meat

In the USA poultry, pork and beef are the main meat types consumed. Approximately 100 million pigs, 30 million cattle and 8.5 billion chickens are killed annually for human consumption in the USA. Serological or parasitological surveys based on slaughterhouse samples do not provide a true assessment of risk to humans because nearly half of the pork and a substantial amount of chicken in retail meat is injected with salts and water (Dubey et al., 2005). Some of the salt treatments (labelled as "enhanced" meat) kill *T. gondii* tissue cysts (Hill et al., 2004). Further, most of the retail chicken sold in the USA is frozen, which also kills *T. gondii*. In a recent nationwide study of the prevalence of *T. gondii* in retail meat, viable organisms were isolated from only seven of 2094 pork samples and none of 2094 beef or 2094 chicken meat samples (Dubey et al., 2005b). Thus, while the scope of human infection resulting from meat sources remains undetermined, the low prevalence of *T. gondii* infection in market pigs alone cannot account for the 10–40% seroprevalence in humans in the USA (Jones et al., 2003, 2007). We are not aware of a risk assessment study in the USA but in a retrospective study of 131 mothers who had given birth to children infected with *T. gondii*, 50% recalled having eaten uncooked meat (Boyer et al., 2005). In a multicentre European study of pregnant women, ingestion of inadequately cooked meat (lamb, beef or game) was identified as the main risk (Cook et al., 2000). *Toxoplasma gondii* is one of three pathogens (together with *Salmonella* and *Listeria*) which account for >75% of all deaths due to foodborne disease in the USA and economic cost to care for congenitally-infected children are high (Roberts et al., 1994; Mead et al., 1999). In the following section we will discuss meat sources of *T. gondii* for humans.

3.1.1. Pigs

Currently, there is no national identification system for individual pigs destined for human consumption and pigs are not tested for *T. gondii* infection at slaughter. Therefore, the routes by which *T. gondii*-infected pigs from

highly endemic areas enter the market and the role these pigs have in the overall epidemiology of *T. gondii* in humans remain unknown. Meat from breeder pigs is generally processed for sausages and it is highly unlikely that *T. gondii* survives the processing procedures. Thus, breeders are probably not important with respect to transmission of *T. gondii* to humans. Although the prevalence of *T. gondii* is declining, even a 1% infection rate would amount to 1 million infected pigs going to market for human consumption. Any part of infected pork can be a source of infection because *T. gondii* has been found in most edible tissues or cuts of meat, both in experimentally- and naturally-infected pigs (Dubey et al., 1986c). A 50 kg market pig would account for over 300 servings of meat.

We are not aware of any report of toxoplasmosis in humans directly linked to eating infected pork in the USA but clinical toxoplasmosis and blindness were linked to the ingestion of undercooked pork in Korea (Choi et al., 1997).

3.1.2. Cattle

The ingestion of beef or dairy products is not considered important in the epidemiology of *T. gondii* because cattle are not a good host for this parasite. However, we cannot be sure that beef does not play a role in *T. gondii* transmission as only relatively small amounts of beef have been tested for viable *T. gondii* parasites. Epidemiologically, two small outbreaks of toxoplasmosis were linked to ingestion of infected beef. Five medical students developed symptoms of acute toxoplasmosis characterized by headache, fever, lymphadenopathy, myalgia and splenomegaly during the second week after eating rare hamburgers at a university snack bar (Kean et al., 1969). The restaurant had bought the meat from a local butcher who insisted that the meat was unadulterated beef; he never ground lamb in the same grinder and when pork was ground it was at the end of the day and the grinder was washed thoroughly after use. In another instance, three persons developed symptomatic toxoplasmosis linked to eating Kibee Nayee (a meat dish made with raw beef) at a Syrian restaurant (Lord et al., 1975).

3.1.3. Chickens

In the USA, the per capita yearly consumption of poultry is estimated to be 37.2 kg and approximately 8.5 billion chickens are killed annually for human consumption. In a recent survey, *T. gondii* was not isolated from any of the 2094 chicken meat samples obtained from retail meat stores in the USA (Dubey et al., 2005b). There are several reasons why the results of this study do not negate the possibility that infected chickens may be important sources of infection for humans. In this study, chicken breasts were selected for sampling because of the experimental design that required testing of 1 kg of boneless meat for each sample, although the authors were aware that that the prevalence of *T. gondii* in chicken breast is lower than in other tissues. For example, *T. gondii* was isolated from breast meat of only 18.6% of infected chickens (Dubey, in press). Further, many of the chicken breasts had been injected with enhancing solutions that have a deleterious effect on *T. gondii*. Finally, some of the samples collected might have been frozen or hard chilled, although the labels indicated otherwise. Standards of hard chill are vague and *T. gondii* is highly susceptible to freezing. In contrast to the bioassay results, antibodies to*T. gondii* were found in 1.3% of the juice extracted from the breast meat using an ELISA, with values six times higher than in control chicken sera (Dubey et al., 2005b). These data suggest that *T. gondii* does occur in commercially marketed chickens in the USA but processing and handling procedures inactivate the organisms prior to sale to consumers. The recent trend of consumers demanding meat from organically grown free-range poultry will increase the prevalence of *T. gondii* in chickens consumed by humans and it will be necessary to cook the meat properly to protect consumers from infection.

The prevalence of *T. gondii* in chicken eggs is extremely low and the ingestion of uncooked eggs is not considered an important risk for toxoplasmosis (Dubey, in press). However, eggs should be cooked thoroughly before human consumption.

3.1.4. Sheep

According to U.S. Department of Agriculture regulations, sheep <1 year old (without permanent teeth) are classified as lambs and slaughtered for human consumption, while older animals are classified as sheep and their meat (mutton) is sold for pet food and export. In the USA lambs and sheep are slaughtered in separate commercial slaughter facilities. Between 3 and 3.5 million lambs are slaughtered in the USA for food each year, and the per capita consumption of lamb meat in the USA is approximately 0.5 kg per year (NASS Agricultural Statistics, 2005 www.usda.gov/nass/pubs/agr05/agstats2005.pdf). Results of a recent study and previous surveys indicate the prevalence of *T. gondii* in lambs can be high (Tables 3 and 4) but the role of ingestion of infected lamb in the epidemiology of toxoplasmosis in humans remains to be determined.

Symptomatic toxoplasmosis in a family in New York City was circumstantially linked to eating rare lamb (Masur et al., 1978).

3.1.5. Goats

The amount of goat meat consumed in the USA is unknown but goat meat is popular with several ethnic groups, especially from Asia. In addition to infected meat, milk from goats has been implicated in human toxoplasmosis (Riemann et al., 1975; Sacks et al., 1982). Milk from goats is more easily digested than cow's milk by children. Riemann et al. (1975a) reported on an infant that developed toxoplasmosis after drinking raw milk from goats; four of the 10 goats had antibodies to *T. gondii*. A small outbreak of toxoplasmosis in humans was attributed to drinking goat milk; one 39-year-old woman had chorioretinitis (Sacks et al., 1982).

3.1.6. Horses

Although viable *T. gondii* has been isolated from horses slaughtered for export, horse meat is not used for human consumption in the USA (Al-Khalidi and Dubey, 1979).

3.1.7. Venison and other game

Deer are popular game animals in the USA and the deer population is estimated in millions. During the 2006 deer hunting seasons in Iowa and Minnesota, 150,552 and 270,778 deer were harvested in the respective states (http://files.dnr.state.mn.us/outdoor_activities/hunting/deer/2006_harvestreport.pdf). Antibodies to *T. gondii* are prevalent in white-tailed deer in the USA. Using a titer of 1:25 in MATs as a positive cut-off, antibodies to *T. gondii* were found in 30–60% of deer (Table 3) and viable *T. gondii* was isolated from 17% to 28% (Table 4). Cases of clinical toxoplasmosis (Sacks et al., 1983), including ocular manifestations (Ross et al., 2001), have been documented in humans who had consumed undercooked venison.

Hundreds of bear, elk, moose, wild pig and other game are harvested in the USA each year. The prevalence of *T. gondii* in black bears is very high (Tables 3 and 4). In addition to the possibility of transmission to humans, eviscerated tissues of these animals left in the field are a source of infection for carnivores, including cats.

3.2. Role of oocysts

Environmentally-resistant oocysts are essential in the life cycle of *T. gondii.* Only felids are known to excrete *T. gondii* oocysts (Miller et al., 1972). Both domestic cats (*F. domesticus*) and other felids may shed oocysts. Congenital transmission of *T. gondii* can occur but is rare in domestic cats and congenitally-infected kittens can shed oocysts (Dubey and Carpenter, 1993b; Dubey et al., 1995d). Most cats become infected with *T. gondii* post-natally, by ingesting either infected tissues or sporulated oocysts. *Toxoplasma gondii* transmission is more efficient through ingestion of infected tissues than ingestion of oocysts (Dubey, 2001, 2006).

Approximately one-third of households in the USA own a cat and this number is steadily increasing. There are approximately 78 million domestic cats and 73 million feral cats (reviewed by Conrad et al., 2005). It is probable that every farm in the USA has cats. In one study of pig farms in Illinois, 366 cats were trapped on 43 farms, a mean of 8.5 cats per farm, with a mean of six seropositive cats on each farm (Weigel et al., 1999). *Toxoplasma gondii* oocysts were detected in cat feces, feed, soil or water samples on six farms (Dubey et al., 1995c; Weigel et al., 1999). Thus, there is strong potential for *T. gondii* transmission in rural settings.

At any given time, approximately 1% of cats are expected to shed oocysts, based on the observation that most cats only shed oocysts for about 1 week in their life (Dubey, 1995, 2004). We are aware of only a few surveys for *T. gondii* oocysts in cats in the USA (Table 7). In two large surveys (Wallace, 1971; Dubey et al., 1977), *T. gondii* oocysts were found in of only a few (<1%) cats. Recently, Dabritz et al. (2007b) detected *T. gondii*-like oocysts in feces of three of 326 cats from the Morrow Bay area of California; whether these oocysts were *T. gondii* could not be determined by PCR and bioassays were not performed. These surveys are time consuming and expensive, because bioassays are needed to distinguish *T. gondii* oocysts morphologically from oocysts of related parasites in cat feces. Most cats seroconvert after they have shed oocysts (Dubey and Frenkel, 1972). Thus, it is a reasonable assumption that most seropositive cats have already shed oocysts. For epidemiological studies, seroprevalence data are more meaningful than determining the prevalence of *T. gondii* oocysts in feces.

Under laboratory conditions, cats can shed as many as 500 million oocysts after ingesting one *T. gondii*-infected mouse (Dubey and Frenkel, 1972). Millions of oocysts were shed by cats fed even a few bradyzoites (Dubey, 2001). The number of oocysts shed by naturally-infected domestic cats is largely unknown. In the most extensive study performed to date, Schares et al. (2008) found *T. gondii*-like oocysts in feces of 48 of 24,106 cats from Germany and other European countries; of these 26 (0.11%) were identified as *T. gondii* and 22 (0.09%) as *Hammondia hammondi.* Up to 13 million *T. gondii* oocysts were present per gram of cat feces (Schares et al., 2008). This study also demonstrates the importance of proper identification of *T. gondii* oocysts in cat feces because half of the cats were shedding *H. hammondi* oocysts which have no zoonotic significance. In one reported case, 10,000 viable oocysts were found in rectal contents of an asymptomatic cat on a sheep farm in Maryland (Dubey et al., 1986b).

If one assumes a 30% seropositivity of 151 (78 domestic and 73 feral) million cats and a conservative shedding of 1 million oocysts per cat then there will be enormous numbers of oocysts (50 million × 1 million) in the environment. Dabritz et al. (2007a,b) estimated an annual burden of 94 to 4671 oocysts/m^2 in California. However, more data are needed on the actual numbers of oocysts/g of feces in naturally-infected cats in the USA.

Table 7
Isolation of *Toxoplasma gondii* oocysts from feces of naturally-exposed cats in the USA

Cat type	Locality	No. tested	No. positive (%)	Reference
Homes	Kansas	510	0	Dubey (1973)
Shelter	Hawaii	1604	12 (0.7)	Wallace (1971)
Shelter	Ohio	1000	7 (0.7)	Dubey et al. (1977)
Sheep farm	Maryland	16	1 (6.2)	Dubey et al. (1986b)
Pig farms	Illinois	274	5 (1.8)	Dubey et al. (1995c)

Cats bury or hide their feces and unless they are ill, they clean their feet and body by licking. This washing is apparently very effective in removing dirt and feces from their body hair (Dubey, 1995). Although cats can be reinfected with *T. gondii* they are considered to shed oocysts only once in their life based on short-term experiments in the laboratory (Davis and Dubey, 1995). In one long-term experiment four of nine cats reshed oocysts after challenge (Dubey, 1995). However, coinfection with a related coccidian, *Isospora felis*, can cause reshedding of large numbers of *T. gondii* oocysts from chronically infected cats (Chessum, 1972; Dubey, 1976). Coinfection with FIV does not cause reshedding of *T. gondii* oocysts (Lappin et al., 1992; Dubey, 1995).

The bobcat (*Lynx rufus*) and cougar (*Felis concolor*) are the two main wild cats in continental USA. The number of bobcats in the USA is thought to be millions and one study estimated thousands of cougars (Conrad et al., 2005). Bobcats fed with tissue cysts shed *T. gondii* oocysts (Miller et al., 1972). In a recent survey in Pennsylvania, 83% of 131 bobcats were found to have *T. gondii* antibodies (Mucker et al., 2006) and viable *T. gondii* was isolated from five of six bobcats from Georgia (Dubey et al., 2004b). Young and weak white-tailed deer and small mammals are common prey for bobcats and 60% of white-tailed deer in Pennsylvania, USA were seropositive for *T. gondii* (Table 8). In addition to live prey, eviscerated tissues (gut piles) from hunted deer and black bears would be a source of infection for wild cats. Thus, a sylvatic cycle of *T. gondii* in rural USA is feasible and appears to be efficient.

The role of cougars in the sylvatic cycle of *T. gondii* has not been established in the USA. A large waterborne outbreak of toxoplasmosis in humans was epidemiologically linked to oocyst contamination of a water reservoir in British Columbia, Canada (Bowie et al., 1997). Although oocysts were not detected in drinking water taken from the reservoir after the outbreak (Isaac-Renton et al., 1998), viable oocysts were detected in rectal contents (sample A) of a wild trapped cougar (*Felis concolor vancouverensis*) and in a fecal pile (sample B) in the vicinity of the reservoir (Aramini et al., 1998). It is noteworthy that 12.5 million oocysts were present in sample A and 250,000 in sample B (Aramini et al., 1998). Genotyping data on the *T. gondii* isolates from these cougars now suggest that both faecal samples might be from the same cougar (Dubey et al., 2008a).

Assessing environmental contamination with *T. gondii* oocysts is technically difficult. Ideally, domestic cats like to bury their feces in soft and moist soil but one can find cat feces on street pavements, grass, grain or hay. Little is known of the sporulation or survival rate of oocysts openly exposed to sun and other environmental conditions. Oocysts survived outdoors in Texas (6–36 °C) in native cat feces, uncovered, for 46 days, for 334 days when covered (Yilmaz and Hopkins, 1972) and outdoors in soil buried at the depth of 3–9 cm in Kansas for 18 months (Frenkel et al., 1975). *Toxoplasma gondii* oocysts are highly resistant to disinfectants but are killed by temperatures above 60 °C (Dubey et al., 1970; Dubey, 2004; Wainwright et al., 2007a). Ultraviolet rays also have a deleterious effect on oocysts, depending on the dose (Wainwright et al., 2007b; Dumètre et al., 2008).

Direct detection of viable oocysts in drinking water in the USA has not been achieved, but oocysts have been isolated from animal feed and soil from pig farms (Table 7). The fate of cat feces disposed of in the toilet or in domestic trash destined for landfills is unknown. It is anticipated that the heat generated and lack of oxygen will kill some or all oocysts, depending on the conditions. It is likely that oocysts are carried into our homes on shoes contaminated with oocysts on street pavements.

3.2.1. Contamination of sea water with *T. gondii* oocysts

Freshwater runoff has been suggested as a risk factor for *T. gondii* infection in California sea otters (Miller et al.,

Table 8
Serological prevalence of *Toxoplams gondii* in large wild cats in the USA

	No. examined	Test	Titer	% Positive	Locality	Reference
Bob cats (*Lynx rufus*)	15	DT	1:4	73	Georgia	[a]Walton and Walls (1964)
	12	IHAT	1:64	72	California	Riemann et al. (1975b)
	86	IHAT	1:64	69	California	Franti et al. (1975)
	27	DT	1:8	44	New Mexico	Marchiondo et al. (1976)
	150	IHAT	1:16	18	Georgia, West Virginia	Oertley and Walls (1980)
	3	IHAT	1:64	66	Florida	Burridge et al. (1979)
	6	MAT	1:25	83.3	Georgia	[b]Dubey et al. (2004b)
	131	MAT	1:25	83	Pennsylvania	Mucker et al. (2006)
	25	MAT	1:25	88	California	Riley et al. (2004)
	52	LAT	1:64	50	USA	Kikuchi et al. (2004)
Cougars (*Felis concolar*)	36	LAT	1:64	58	California	Paul-Murphy et al. (1994)
	320	LAT	1:64	19.1	USA	Kikuchi et al. (2004)
Lynx (*Felis lynx*)	255	MAT	1:25	15	Alaska	Zarnke et al. (2001)
Panther (*Felis concolor coryi*)	56	ELISA	1:48	9	Florida	Roelke et al. (1993)

DT, dye test; ELISA, kinetic enzyme linked immunosorbent assay, IHAT, indirect hemagglutination test; LAT, latex agglutination test; MAT, modified agglutination test.

[a] Viable *T. gondii* isolated from brain of one of 16 bobcats.

[b] Viable *T. gondii* isolated from hearts of the five seropositive bobcats.

2002b; Conrad et al., 2005). Based on an estimate of 10 million oocysts shed by each cat and a 36% defecation rate outdoors, a burden of 36 oocysts/m^2 over the region was calculated by Dabritz et al. (2007a). These authors considered this level of land contamination is likely to be high enough for oocysts to reach marine waters (Dabritz et al., 2007). Sea otters eat approximately 25% of their body weight in invertebrate prey each day (Conrad et al., 2005). Cold blooded animals, including fish, are not a host for *T. gondii* (Omata et al., 2005). Before the discovery of the oocyst stage of *T. gondii*, numerous experiments were done to infect various invertebrates including arthropods with *T. gondii* tachyzoites and although the parasite survived for various amounts of time, there was no evidence that it multiplied in cold blooded animals (Dubey and Beattie, 1988). With respect to oocysts, it is not known if the sporozoite excysts after ingestion by cold blooded animals. Molluscs, however, can act as transport hosts for *T. gondii* oocysts (Arkush et al., 2003; Lindsay et al., 2004). In addition, sea otters might ingest oocysts directly from marine water. How much marine water is cycled through the gut of sea otters in a day is unknown but it is likely to be large volumes.

Toxoplasma gondii infection of other marine mammals that mainly eat fish is even more intriguing. Seroprevalence of *T. gondii* in bottlenose dolphins from both coasts of the USA is very high (Dubey et al., 2003b, in press c).

3.2.2. Contamination of zoos with oocysts shed by Pallas cats and other felids

Transmission of *T. gondii* in zoos is of special importance because many species of captive animals are highly susceptible to clinical toxoplasmosis and there is the possibility of transmission to zoo visitors. Certain species of macropodids (e.g. wallabies), canaries and finches, and New World monkeys (e.g. squirrel monkeys) die of acute toxoplasmosis (Dubey and Beattie, 1988; Dubey, 2002). In addition to bobcats, cougars and panthers (Table 7) which are native to the USA, many other felids are kept captive in zoos throughout the USA (de Camps et al., 2008), and all those are potential shedders of *T. gondii* oocysts. Of particular interest is the housing of Pallas cats (*Felis manul*) in zoos. The natural habitat of Pallas cats is the high mountains of Tibet, western Siberia, Turkestan and Mongolia. There are a few Pallas cats in USA zoos, mostly descendents of cats imported from Russia in 1994 (Kenny et al., 2002). Pallas cats can shed *T. gondii* oocysts (Dubey et al., 1988a; Basso et al., 2005) and acute toxoplasmosis is a leading cause of mortality in Pallas cats (Riemann et al., 1974; Dubey et al., 1988; Kenny et al., 2002). Unlike humans, Pallas cats infected with *T. gondii* before pregnancy can repeatedly transmit *T. gondii* to their kittens (Basso et al., 2005).

3.2.3. Atlanta stable outbreak of human toxoplasmosis

In October 1977, an outbreak of acute toxoplasmosis occurred in patrons of a riding stable in Atlanta, Georgia, USA (Teutsch et al., 1979). Several aspects of this episode are epidemiologically and biologically interesting and therefore recalled here. Thirty-five of 37 patrons of the stable had clinical toxoplasmosis characterized by headache, fever, lymphadenopathy and abortion in one of three pregnant patrons. That woman was in her first trimester at the time of the outbreak. She aborted in December, 1977 and viable *T. gondii* were isolated from the fetus's amniotic fluid (Teutsch et al., 1980; Dubey et al., 1981b). An epidemiological investigation suggested that the patrons acquired *T. gondii* from oocysts aerosolized during the riding activity, although attempts to isolate oocysts from 29 samples of soil, sand and sawdust from different parts of the stable were unsuccessful (Dubey et al., 1981b). Attempts were made to isolate *T. gondii* from animals trapped in and around stable. Viable *T. gondii* were isolated from tissues of two of four kittens, three of three adult cats, and four of four mice trapped in the stable in November, 1977 (sample 1) but not from 12 mice, three rats and four cotton rats trapped in the stable in December, 1977 (sample 2). All four mice and the five cats from whose tissues viable *T. gondii* were isolated had no detectable antibodies to *T. gondii* at a 1:2 serum dilution (prozone was excluded) of serum tested using a dye test. Bulldozing of the arena between collection of samples 1 and 2 might have contributed to differences in results obtained with these two samples. Seronegativity of the five cats and the four mice with demonstrable *T. gondii* might be related to insensitivity of the dye test for cat sera. Unusual aspects of the outbreak were: a very high rate (95%) of clinical toxoplasmosis in exposed persons, and the first documented outbreak linked to inhalation or ingestion of oocysts. With respect to pathogenicity of the *T. gondii* isolates, an isolate from one cat was as mouse-virulent as the isolate from the human fetus; doses of one tachyzoite, one bradyzoite and one oocyst were lethal to mice (Dubey et al., 1981b). These results indicated that asymptomatic animals can harbor mouse-virulent *T. gondii*. At that time, there were no genetic markers available and those isolates were not cryopreserved. Results also indicated that timing for sampling is important in an epidemiological investigation because different results were obtained with samples 1 and 2. Historically, this was the first large outbreak in humans linked to ingestion of oocysts.

4. Control, prevention and future developments

Cats are key to the transmission of *T. gondii* as illustrated by the following two studies. The prevalence of *T. gondii* in pigs from a remote island (Ossabaw Island, Georgia) was very low (0.9% of 1264 pigs) compared with 18.2% of 170 feral pigs from mainland Georgia, and this difference was attributed to the absence of cats on Ossabaw island (Dubey et al., 1997a). The seroprevalence of *T. gondii* in pigs and mice on pig farms in Illinois, USA was greatly reduced when cats on these farms were vaccinated orally with a strain of *T. gondii* that does not produce

oocysts in cats but immunizes them against shedding of oocysts (Mateus-Pinilla et al., 1999). Because *T. gondii* is transmitted by multiple modes and sources, it is difficult to establish the definite modes of transmission on an individual basis. Risk assessment researchers should bear in mind that cats are everywhere in the USA and owning a cat does not directly relate to *T. gondii* transmission risk because feral cats can spread oocysts in any suitable location. There is currently no non-viable, effective vaccine to prevent *T. gondii* infection in animals and humans, with none on the horizon. Therefore, practicing good hygienic measures appears to be the best option to minimize transmission of *T. gondii* to humans. Although oocysts are almost indestructible, tissue cysts in meat are easily killed by freezing meat in a household freezer (Kotula et al., 1991) and by cooking until the internal temperature reaches 66 °C (Dubey et al., 1990c). Prevalence of *T. gondii* in wild game and venison in the USA is very high and hunters need to be aware of the risk of transmission of infection to humans and, more importantly, spread of infection in the environment. The viscera of hunted animals need to be buried to prevent scavenging by animals, especially cats.

Educational programs directed at reducing environmental contamination with *T. gondii* would eventually curtail the cost of treating humans for clinical toxoplasmosis. To screen for congenital toxoplasmosis is controversial (Kim, 2006). Pre-natal screening for *T. gondii* infection and treatment of the mother and infant has been conducted in countries with a higher prevalence of *T. gondii* infection than the USA, for example, France (monthly if seronegative) (Thulliez, 1992) and Austria (each trimester if seronegative) (Aspock and Pollak, 1992). However, a recently reported large European multicenter cohort study found no evidence that pre-natal treatment with either spiramycin or sulphonamide combined with pyrimethamine had an effect on maternal transmission (Gilbert and Gras, 2003). A meta-analysis of 22 European cohorts found weak evidence that treatment started within 3 weeks of seroconversion reduced mother-to-child transmission compared with treatment started after 8 weeks or more (Thiebaut, 2007). One current practice is to start a woman on spiramycin if she becomes newly infected during pregnancy in the first trimester, and then perform amniocentesis to detect fetal infection. If fetal infection is detected, then medication is switched to pyrimethamine and sulfadiazine (Montoya and Liesenfeld, 2004). Pyrimethamine and sulfadiazine may be used initially in the late second and third trimesters when acute infection is detected. However, it is important to note that maternal screening and treatment are not without risk. Bader et al. (1997) determined that in countries with low *T. gondii* prevalence such as the USA, even with a relatively low amniocentesis complication rate (0.36% fetal death), with a limited pre-natal screening program there would be 18.5 fetal losses for each congenital toxoplasmosis case avoided. In addition, because most women of childbearing age in the USA (89%, Jones et al., 2007) are susceptible to *T. gondii* infection, most would need to be screened repeatedly during pregnancy, resulting in a relatively high cost compared with costs in countries with a higher prevalence of *T. gondii* infection in women before they reach childbearing age (and therefore fewer women susceptible to acute infection during pregnancy). There is still a need for cost–benefit studies to evaluate pre-natal screening for toxoplasmosis in the USA.

Newborn screening for *T. gondii* is conducted in Massachusetts (started in1986) and New Hampshire (started in 1988) (Guerina et al., 1994). Infant heel stick filter paper blood spots are tested, with confirmatory testing in the mother when *T. gondii*-positive infants are identified. Infants are treated for 1 year. Early results suggested that treatment of infants in this program may be beneficial, but follow-up results for more than 6 years (as in Guerina et al., 1994) are needed to determine outcomes. In another series of infants referred for care, initiating treatment for congenital toxoplasmosis after birth produced results which suggest a benefit from infant treatment compared with historical controls (McLeod et al., 2006). Although there have been neonatal screening programs for toxoplasmosis in Denmark and Brazil, there are no randomized, controlled trials demonstrating the effectiveness of neonatal screening and treatment (Petersen, 2007). However, randomized studies of newborn screening and treatment would be costly because of the large population needed for evaluation.

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