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Congenital toxoplasmosis in humans: an update of worldwide rate of congenital infections

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Review

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Abstract

The morbidity due to congenital toxoplasmosis in humans is very high. Most of these infected children are likely to develop symptoms of clinical toxoplasmosis. Sequelae in fetus resulting from *Toxoplasma gondii* infections in women who become infected with this parasite during pregnancy can be devastating and enormous efforts are directed in some countries to prevent these consequences. Here, an update on congenital toxoplasmosis in humans, especially the rate of congenital infections in humans worldwide, is provided. Although several countries have surveillance programmes, most information on the rate of congenital transmission is from France and Brazil. Because of compulsory national screening programme in France to detect and treat women with recently acquired *T. gondii* infection with anti-toxoplasma therapy, the rate of congenital transmission and the severity of disease in children are declining. Infections by this parasite are widely prevalent in Brazil. The severity of clinical toxoplasmosis in Brazilian children is very high and may be associated with the genetic characteristics of *T. gondii* isolates prevailing in animals and humans in Brazil. Virtually little or no information is available on this topic from China, India and other countries in Asia.

Introduction

Toxoplasmosis, caused by the protozoan parasite, *Toxoplasma gondii*, is a worldwide zoonosis, and infections are widely prevalent in humans and animals (Dubey and Beattie, 1988; Dubey, 2010). Toxoplasmosis can cause serious illness in humans of all ages, and in particular immunosuppressed patients and neonates (Robert-Gangneux and Dardé, 2012; Torgerson and Mastroiacovo, 2013; Peyron *et al.*, 2016; Dardé *et al.*, 2020; McLeod *et al.*, 2020). Although seroprevalence in Europe has declined in the past 2 decades, a very high prevalence is still prevalent in many countries (McLeod *et al.*, 2020).

Sequelae in fetus resulting from *T. gondii* infections in women who become infected with this parasite during pregnancy can be devastating and enormous efforts are directed in some countries to prevent these consequences. Here an update on congenital toxoplasmosis in humans is provided, especially on the rate of congenital infections in humans worldwide.

Background of congenital toxoplasmosis

After the ingestion of food or water contaminated with *T. gondii*, there is parasitemia, and tachyzoites can invade the placenta if the woman is pregnant. Humans have haemochorial placenta. Nearly half of fetuses whose mothers become infected during pregnancy escape *T. gondii* infection. The global rate of transmission during pregnancy is 29% (Dunn *et al.*, 1999). The stage of gestation at the time of mother's infection may determine the transmission of *T. gondii* to fetus. In general, the transmission of *T. gondii* is more efficient in the later half of gestation, mostly related to the anatomy and immune factors. For example, the thickness of the placenta varies with gestation; in early pregnancy, placental barrier of humans is 50–100 μM thick and progressively decreases to 2.5–5 μM at the end of pregnancy, allowing tachyzoites to more easily invade trophoblasts by the end of the gestational course (Blaszkowska and Góralska, 2014). Additionally, the internal cytotrophoblast layer is discontinuous, with its cells number decreasing during the gestational period. Infection early in gestation is clinically more severe, as reduced expression of Toll-like receptors in trophoblast cells during the first trimester of pregnancy may indicate a reduced ability of early placental cells to engage the immune response to intrauterine infection (Blaszkowska and Góralska, 2014).

Transplacental transmission of *T. gondii* infection generally occurs when a woman becomes infected during pregnancy. Rarely, congenital transmission occurs in women infected just before pregnancy or during chronic infection (Villena *et al.*, 1998; Elbez-Rubinstein *et al.*, 2009). In addition, in immunosuppressed women, reactivation/reinfection of an infection

Table 1. Rate of congenital *Toxoplasma gondii* transmission according to the gestational age of maternal seroconversion in France[a]

Reference	Desmonts and Couvreur (1984)	Hohlfeld *et al.* (1994)	Pratlong *et al.* (1994)	Dunn *et al.* (1999)	The SYROCOTT (2007)	Villena *et al.* (2010)	Wallon *et al.* (2013)
Gestational age (weeks)	$n = 489$[b]	$n = 2081$[b]	$n = 187$[b]	$n = 603$[b]	$n = 1438$[b]	$n = 235$[b]	$n = 1624$[b]
<16	9.1	3.7	3.9	6	15	7.2	10.0
16–28	28.2	16.5	17.1	40	44	35.3	20.0
>28	59.3	28.9	53.1	72	71	57.4	55.8

[a]Women who seroconverted during pregnancy were treated with anti-*T. gondii* drugs to prevent fetal transmission and damage to the fetus.
[b]No. of women who seroconverted during pregnancy.

acquired before pregnancy can lead to congenital toxoplasmosis but is rare (Peyron *et al.*, 2016).

Transplacental infection can lead to a wide variety of manifestations in the fetus and infant including spontaneous abortion, stillbirth; it can also cause severe disease in live infant, but most children are asymptomatic at birth. Although *T. gondii* may sometimes cause sporadic abortion, there is no evidence that it causes habitual abortion. Most severe cases of prenatally acquired toxoplasmosis were reported first with the predominant manifestation of encephalomyelitis. Historically, the first confirmed case of congenital toxoplasmosis was in an infant girl who was delivered full term by Caesarean section on 23 May 1938 at Babies Hospital, New York (Wolf *et al.*, 1939). The girl developed convulsive seizures at 3 days of age and lesions were noted in the maculae of both eyes through an ophthalmoscope. She died of toxoplasmosis when 1-month-old and an autopsy was performed. At postmortem, brain, spinal cord and right eye were removed for examination. Free and intracellular *T. gondii* were found in the lesions of encephalomyelitis and retinitis, and viable *T. gondii* was isolated in mice, rats and rabbits inoculated with tissues from the girl (Wolf *et al.*, 1939).

In early 1950s, Dr Albert Sabin proposed a triad of signs: hydrocephalus or microcephalus, intracranial calcification and retinochoroiditis. This triad has been useful in drawing attention to prenatal toxoplasmosis. A better understanding came from the work of Eichenwald (1960), who found asymptomatic and clinical toxoplasmosis in many children in 1950s in Austria. Although the study by Eichenwald (1960) from selected cases before treatment (prenatal and postnatal) of infected children became a routine, it pointed that toxoplasmosis can cause serious illness in children including both generalized and neurological disease (Dubey and Beattie, 1988). As stated earlier, the most common manifestation of prenatal toxoplasmosis is ocular disease, sometimes presented as microphthalmy, cataracts, strabismus or nystagmus and even total blindness.

Hydrocephalus is the most dramatic sign of congenital toxoplasmosis, and occurs in approximately 4% of symptomatic children (Hutson *et al.*, 2015). Initially, it was considered to be due to the blockage of aqueduct of Sylvius. Recently, 4 anatomical patterns of hydrocephalus were reported: (i) obstruction of aqueduct of Sylvius, occurring in 43% of cases, (ii) obstruction of foramina of Monroe occurring in 25% of cases, (iii) mixed aqueductal and foraminal obstruction, occurring in 11% of cases, and (iv) with no obstructive pathogenesis, and was seen in 21% of cases (Hutson *et al.*, 2015). Ocular symptoms are the most common signs of congenital toxoplasmosis.

Most prenatal infections are sub-clinical at birth. Disease, if present in the neonatal period, is likely to be severe, invariably with neurological signs and often with signs of generalized infection. Such patients rarely recover without serious sequelae. Disease appearing in the first few months of life is usually less severe and is manifested by nystagmus, convulsions, bulging fontanelle and abnormal increase in skull circumference. Such patients sometimes develop normally.

It is likely that many cases of prenatal toxoplasmosis are missed because of difficulty in diagnosis. Couvreur *et al.* (1984), who diagnosed prenatal toxoplasmosis in 210 babies aged 0–10 months, found premature birth, intrauterine growth retardation or both in 17%, hyperbilirubinemia in 10%, hydrocephaly or microcephaly in 9%, intracranial calcification in 11% and retinochoroiditis in 22%. Infection was fatal in 2 of the 210, severe in 10%, mild without neurological signs in 34% and subclinical in 55%. It is noteworthy that over half of the babies born with *T. gondii* infection had no clinical manifestations. As noted by Eichenwald (1960) earlier, in congenitally infected children, virtually all organ systems may be affected (Peyron *et al.*, 2016).

An important question concerns the subsequent fate of subclinically infected babies. Many of them develop retinochoroiditis, although it may not manifest until later in childhood, or even in adult life. In a follow-up of 11 congenitally infected children without symptoms at birth, 9 (82%) developed lesions within 20 years; 4 (36.6%) of them developed retinal scars that impaired vision, 5 (45.5%) developed scars without affecting vision (Koppe *et al.*, 1986). In a 14-year follow-up of 327 congenitally infected children in Lyon, France, 95 (29%) had lesions despite treatment for toxoplasmosis. At the final examination, 60 (18%) had lesions only in the eyes, 35 (11%) had CNS lesions (intracerebral calcification in 31, hydrocephalus in 6 and microcephalus in 1) (Wallon *et al.*, 2004). In a study in the USA, 11 of 120 congenitally infected children (many with obvious symptoms) recruited in a treatment programme died within 4 years despite treatment (McLeod *et al.*, 2006*a*).

The morbidity of congenital toxoplasmosis in children is very high and true suffering may be underestimated (Havelaar *et al.*, 2007; Bénard *et al.*, 2008; Stillwaggon *et al.*, 2011; Torgerson and Mastroiacovo, 2013; El Bissati *et al.*, 2018; Binquet *et al.*, 2019; Picone *et al.*, 2020). One study estimated 1.2 million disability-adjusted life years and an estimated 190 100 cases globally (Torgerson and Mastroiacovo, 2013).

The risk of congenital infection is lowest when mother becomes infected in the first trimester (10–15%) and highest when mother acquires infection during the third trimester (Table 1). If maternal infection occurs early in pregnancy, it results in fewer infected babies, but they are more severely affected than the greater number of infected babies born when infection is acquired later in pregnancy. The highest risk to the fetus is when infection is acquired at 10–24th week of gestation. As will be seen in Table 1, most of this information on the transmission of congenital toxoplasmosis is derived from studies in France. In their pioneering study, Desmonts and Couvreur (1974*a*, *b*) reported congenital toxoplasmosis in 210 children born at 1 hospital in Paris; approximately 26% were subclinically infected at birth.

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Only about 10% were clinically affected – 6% mildly and 4% severely, and up to 3% died in the neonatal period. In a subsequent study from the same hospital, Daffos *et al.* (1994) reported clinical outcome in 148 infected fetuses of 2030 mothers who seroconverted during pregnancy. Based on ultrasound examinations, they found that 48, 12 and 3% of fetuses had cerebral ventricular dilatations when mothers became infected in early (<16 weeks), middle (17–23 weeks) and late (after 24 weeks) gestation, respectively (Daffos *et al.*, 1994). In a multicentre European study of 255 congenitally infected children, gestational age at the time of seroconversion in mothers was correlated with cerebral lesions but not retinochoroiditis (Gras *et al.*, 2005). In this study, 51 of 255 infants had 1 or more lesions, and 9 had both intracranial and ocular lesions. Of these, 4 of 55 children died (at 13 months, 11 months, 3 months and 7 days of age). The mother of the baby that died at 1 week of age had seroconverted between 5 and 31 days of gestation and she had received spiramycin prophylaxis from 32nd week until delivery (Gras *et al.*, 2005). The frequency and severity of clinical disease in congenitally infected children in France and Austria has decreased dramatically in the last decade, perhaps because of improved early detection and treatment. Ultrasound sonography can aid the determination of severity of lesions in the fetus (Codaccioni *et al.*, 2020).

A recent study in France retrospectively evaluated 88 cases of congenital toxoplasmosis with ultrasound anomalies diagnosed by fetal medicine experts, 45 (51.1%) had one or more cerebral lesions, the most common lesion being intracranial hyperechogenic cerebral nodular foci (Codaccioni *et al.*, 2020). In Table 2, initial data from screening studies are listed; at that time only a few follow-up studies on infected children were undertaken. Subsequently, many of these children were followed clinically for 4 or more years, and data included in the study were reported (The SYROCOT, 2007). Of 691 congenitally infected children from Europe, Brazil, Colombia and the USA, 24% had at least 1 clinical manifestation, 185 had ocular lesions and 13% had intracerebral calcification (The SYROCOT, 2007).

As stated earlier, 60–70% of babies born from infected mothers escape infection. The severity of toxoplasmosis in the fetus or the infant is not related to the degree of symptoms of *T. gondii* infection in the mother. In 1 study that retrospectively examined risk factors among women who gave birth to infected children, 52% could not recall being sick (Boyer *et al.*, 2005). In another study from a hospital in Lyon, France, of 603 women who seroconverted during pregnancy, only 36 (5%) had clinical symptoms (Dunn *et al.*, 1999). In 161 of these 603 women (504 were treated for toxoplasmosis), infection was transmitted to their fetuses; 5 of them aborted, 3 were stillborn. Most of the 153 live born children were followed for 54 months after birth; 41 (27%) developed clinical signs (33 had retinochoroiditis, 14 had intracerebral calcification, 8 had combinations of signs, 1 child died when 8 days old) (Dunn *et al.*, 1999).

The severity of symptoms is primarily related to the trimester of pregnancy when the mother becomes infected with *T. gondii* (Table 1). However, *T. gondii* genotype might be another factor, and this topic was reviewed recently (Dardé *et al.*, 2020; Mcleod *et al.*, 2020). *Toxoplasma gondii* strains are grouped into clonal Type I, II, III and atypical, based on different systems of genotyping (Dardé *et al.*, 2020). Type II and III *T. gondii* strains predominate in Europe and North America, and Type I is rare. A different situation prevails in South America. The *T. gondii* strains from Brazil are mostly atypical and clonal strains are rare. In France, most strains isolated from congenital infections are Type II and the severity of congenital toxoplasmosis is related to the trimester of pregnancy when mother becomes infected (Dardé *et al.*, 2020). However, in Brazil, women who became infected during the third trimester of pregnancy during oocyst-associated outbreaks of *T. gondii* had congenitally infected children with severe toxoplasmosis (Conceição *et al.*, 2021). The severity of congenital toxoplasmosis in Brazil in comparison with France is thought to be associated with atypical *T. gondii* genotypes (Dubey *et al.*, 2012). However, compared with France, relatively few strains from congenitally infected children in Brazil have been isolated and fully genotyped; 14 genotypes were reported (Carneiro *et al.*, 2013). There was no association of genotype with the severity of ocular lesions. However, in the USA, by using a serotyping assay, ocular toxoplasmosis and different anatomical patterns of hydrocephalus were associated with *T. gondii* Type II than in non-Type II (McLeod *et al.*, 2012). It should be noted that serotyping has limited efficiency in distinguishing genotypes.

Estimates of congenital transmission

An estimate of the incidence of clinically manifest prenatal toxoplasmosis may be obtained in 3 ways: first, from reports of observed cases and, second, from calculations based on the infection rate during pregnancy, and third, from screening of babies at birth. Representative examples of estimates of congenital infections based primarily on screening of mothers during pregnancy are given in Table 2. Many countries have some surveillance programmes (van der Giessen *et al.*, 2021). Congenital infections noted during acute outbreaks of toxoplasmosis summarized recently (Dubey, 2021) were excluded from Table 2. Data from the National Collaborative Chicago-based Toxoplasmosis Study in the USA (Boyer *et al.*, 2005, 2011; McLeod et al., 2006*a*, *b*, 2009, 2020) are not included in Table 2.

More information is available from countries that have screening (prenatal or postnatal) programmes (Tables 2 and 3).

Most of the estimates of congenital infections are from studies that are 10–40 years old, but they are listed in Table 2 to provide perspective. Only Austria and France have compulsory screening of pregnant women for *T. gondii* infection. Rates of congenital transmission are difficult to compare among countries because of the different methodology used. In some studies, only seroconversion during pregnancy was reported (Sagel *et al.*, 2011). One could guess/estimate congenital infection based on the assumption of 50% rate of transmission from mother to fetus. Although there is no national screening for toxoplasmosis in Brazil, valuable information has been obtained from testing of children at few hospitals; these studies were reviewed in detail previously (Dubey *et al.*, 2012) and summarized here in Table 2.

France

Much of the information on congenital toxoplasmosis is derived from studies in France (Tables 1–3). Mass screening of women during pregnancy was initiated by Georges Desmonts in Paris, France in the 1960s looking at seroconversion in women during pregnancy and the transmission of *T. gondii* to the fetus (Desmonts and Couvreur, 1974*a*, *b*); the screening programme became mandatory in France in 1992. France has a population around 65 million, with less than 900 000 pregnancies. All women are screened for *T. gondii* antibodies at their first prenatal visit and those with IgG antibodies are not tested further. Seroconversion data are sought through monthly screening and seroconverted women are followed clinically by ultrasound examinations and treated with anti-*T. gondii* therapy to prevent transmission to the fetus or fetal damage. In Lyon, in a cohort of 603 pregnant women with confirmed toxoplasmosis, the overall maternal–fetal transmission rate was 29% (95% CI 25–33), which marked a sharp increase in risk with the duration of gestation from 6% at 13 weeks to 72% at 36 weeks (Dunn *et al.*, 1999).

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Table 2. Congenital *T. gondii* infection in humans based on prenatal or postnatal screening[a]

Country	No. screened (years)	Infected children	Incidence rate	Symptomatic children[b]	Reference
Australia	18 908 (1986–1989)	3	1:6300	0	Walpole *et al.* (1991)
Austria	63 416 pregnant women (2000–2007)	66 pregnant with primoinfection	Seroconversion rate in mothers 0.17%; no data on congenital infection	No data	Sagel *et al.* (2011)
Austria	5545	4[c]	1:1386	No data	Prusa *et al.* (2013)
Austria	1 387 680 (1992–2008)	141	1: 10 000	7 died/terminated (4 spontaneous abortion, 2 hydrocephalus terminations, 1 porencephaly). Of the 17 live infants all had ICC, including microphthalmos in 2; 12 had neurological deficits within the first year of life	Prusa *et al.* (2015*b*)
Brazil	>364 130 (1995–2009)	>195 (newborn screening)	5–23/10 000	Data summarized in Dubey *et al.* (2012)	Neto *et al.* (2004); The SYROCOT (2007); Gilbert *et al.* (2008)
Brazil (Minas Gerais)	146 307 (2006–2007)	190 (newborn screening)	13: 10 000	>142 (142 RC, 39 ICC, 12 hydrocephalus, 10 microcephaly, 46 hearing loss, 4 died)	Vasconcelos-Santos *et al.* (2009); de Resende *et al.* (2010)
Brazil (Sergipe)	15 204 (1999) newborns	6 (newborn screening)	4: 10 000	4 (3 RC, 1 ICC)	Inagaki *et al.* (2012)
Brazil (Goiás)	246-newborns (2003–2011)	162 (prenatal screening)	No data	128 (50 RC, 51 ICC, 19 brain ventriculomegaly or hydrocephalus, 66 severe generalized disease, 13 blinds, 7 died)	Avelino *et al.* (2014)
Brazil (Paraná)	31 (2000–2010)	29 (prenatal or postnatal screening)	No data	26 symptomatic at 1 month (16 RC, 13 ICC, 6 hydrocephalus, 2 microphthalmia, 1 microcephaly, 3 hearing loss)	Capobiango *et al.* (2014)
Brazil (Rio Grande do Sul)	41 305 (2004–2014)	24 (prenatal screening)	6: 10 000	19 (13 RC, 9 ICC, 1 hydrocephalus, 5 microcephaly, 5 hearing loss, 1 cataract, 1 spastic). Of 5 children born asymptomatic, 3 remained IgG at 12 months, 1 became IgG negative at 15 months, and 1 lost to follow-up	Bischoff *et al.* (2016)
Brazil (Rondônia)	102 963 (4 years)	126 (newborn screening)	12: 10 000	126 newborns with symptoms suggestive of congenital toxoplasmosis	Paraguassú-Chaves *et al.* (2019)
Brazil (Paraná)	65 375 (2002–2016)	39 (29 prenatal screening)	6: 10 000 (15-year average)	15 without clinical data, 12 of 24 symptomatic (12 RC, 3 ICC, 2 hydrocephalus)	Takahashi *et al.* (2019)
Brazil (Rio Grande do Sul)	77 follow-up neonates, infants or children (1996–2017)	77 infected children followed up to a median of 10 years (2–25) (65 prenatal or postnatal screening)	No data	62 (55 RC, 44 ICC, 18 brain ventriculomegaly, 4 hydrocephalus, 9 microcephaly, 3 hearing loss) new RC lesions after the first year in 29 patients, with peaks at 4–5 and 9–14 years	Lago *et al.* (2021)
Colombia	937	1	No data	RC	Gomez-Marin *et al.* (1997)
Colombia	2786 women + 522 newborns	17[d]	14:2786	4 RC, 4 ICC, 3 RC	Gómez (2005); Gallego-Marín *et al.* (2006); Gomez-Marin *et al.* (2007); The SYROCOT (2007)
Colombia	15 333 (2003–2008)	15	No data	7 symptomatic, 3 died in first month after birth. Hydrocephalus in 1, ICC in 3, RC in 3	Gómez-Marin *et al.* (2011)
Denmark	89 873	27	1:3328	5 (hydrocephalus and RC in 1, ICC and RC 1, ICC and retarded in 1, blind and retarded in 1)	Lebech *et al.* (1999); Gilbert and Peckham (2001)
Finland	16 733 (1988–1989)	4	1:4481	2 (ICC and RC in 1), no additional cases in 5-years follow-up	Lappalainen *et al.* (1995)
France	30 768	36	1:854	7 (RC 7, CNS 1)	Philippe *et al.* (1988)

(*Continued*)

Table 2. (*Continued.*)

Country	No. screened (years)	Infected children	Incidence rate	Symptomatic children[b]	Reference
France	Children from 1206 infected mothers (1987–2000)	366	No data	65 (ICC 24, RC 46)	The SYROCOT (2007)
France	818 700 (2007)	272[e]	3.4: 10 000	11 prenatal (6 abortions, 5 fetal deaths), 28 symptomatic (ICC 21, 3 hydrocephalus, 4 macular chorioretinitis)	Villena *et al.* (2010)
France	Children from 1,624 infected mothers (1992–2008)	207[f]	No data	32 (RC), 22 (ICC), 5 hydrocephalus, 2 hepatosplenomegaly	Wallon *et al.* (2013)
Germany	262 912 (1999–2002)	55	1:4762	12 (ICC 5, RC 2, ICC and RC 4, hydrocephalus, ICC and RC 1)	Schmidt *et al.* (2006)
Greece	63 suspected (2006–2009)	21	4.5–5.1 per 100 000 births	14 confirmed and 7 probable cases. 10 symptomatic at birth (RC in 5)	Aptouramani *et al.* (2012)
Hungary	17 735 (1987–1994)	0	No data	No data	Szénási *et al.* (1997)
Italy	28 247 (1996–2000)	2	1: 14 123	0 at birth, new RC in 3 in 1-year follow-up	Valcavi *et al.* (1995)
Italy	Children from 43 infected mothers (1996–2000)	15	No data	3 (ICC 3, RC 3)	The SYROCOT (2007)
Morocco	48 890 (2015)	21	4–8/10 000 births	No data	El-Bissati *et al.* (2018)
The Netherlands	28 049 (1987–1988)	12	No data	3 (ICC 1, RC 3)	Gilbert and Peckham (2001), The SYROCOT (2007)
The Netherlands	10 008 (2006)	18	No data	No follow-up	Kortbeek *et al.* (2009)
Norway	35 940 (1992–1993)	11		1 (RC with loss of vision)	Jenum *et al.* (1998)
Norway	Children from 33 infected mothers (1992–1994)	17	No data	6 (ICC 4, RC 3)	The SYROCOT (2007)
Panama	2,326 pregnant women screening and newborn babies testing (2017–2018)	9	3.8/1000 live births	No data	Flores *et al.* (2021)
Poland	>27 516 (1998–2000)	20	No data	5 (ICC 5, RC 1)	Paul *et al.* (2000, 2001*a*, *b*); The SYROCOT (2007)
Spain	16 362 women surveyed (1999)	5[g]	No data	4 born asymptomatic	Muñoz Batet *et al.* (2004)
Sweden	35 000 (1992–1993; 1997–1998)	3	No data	1 (ICC, RC)	Evengård *et al.* (1999, 2001)
USA	>635 000 (1986–1992)	50 + 5	1: 10 000	19 (14 CNS, 9 RC), 1–6-year follow-up in 39 children, new eye lesions in 4	Guerina *et al.* (1994); Guerina (1994)

[a]Modified from Dubey (2010).
[b]CNS, central nervous system signs; ICC, intracerebral calcification; NS, not stated; RC, retinochoroiditis.
[c]Of 3708 mothers, 7 seroconverted during pregnancy. One infected fetus with abnormal prenatal ultrasound identified by prenatal screening, and infections in 3 babies were found by cord blood screening.
[d]Of 2786 screened, 19 mothers seroconverted during pregnancy and 14 children were born infected. Three children were found infected by screening of 532 newborns; 8 of these infected children were selected for The SYROCOT analysis because diagnosis of cerebral lesion was done with tomography; those studies based on ultrasound were discarded (personnel communication from Gomez-Marin to J.P.D-February 25, 2021).
[e]In 2007, there were 818 700 live births in France through the national screening programme; 272 congenital *T. gondii*-infections were recognized; 160 infections were diagnosed postnatally (130 at the age of 2 months, 22 between 2 months and 1 year). Of 235 cases, infection was acquired in first trimester in 17 (7%), 83 (35%) in the second trimester and 135 (58%) in third trimester.
[f]Of 1624 mothers who seroconverted during pregnancy. Lesions *in utero* in 5, 20 at birth, 21 after birth. RC lesions discovered at birth in 2, in the first year in 20 and third year in 5.
[g]In a multicentre retrospective study of 16 362 women in Barcelona in 1999, seroprevalence was 28.6% with primary infection of 1.02 per 1000 susceptible women; 9 of 12 susceptible women seroconverted during pregnancy. Out of 5 infected children, 4 were asymptomatic at birth; outcome of fifth infant was not stated.

Table 3. Congenital toxoplasmosis (CT) in children, based on cases reported at national level in the surveillance system (Toxosurv/National Reference Centre on Toxoplasmosis)[a]

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Total CT cases (%)	272 (0.031)	268 (0.030)	266 (0.032)	244 (0.029)	188 (0.022)	204 (0.025)	179 (0.022)	216 (0.026)	246 (0.030)	195 (0.024)	153 (0.019)	151 (0.020)
Prevalence CT diagnosed at birth	160	153	158	135	132	107	122	152	158	122	89	80
Children born with CT	234	233	228	207	173	176	165	205	225	172	128	120
Prevalence CT symptomatic at birth	26	27	25	18	26	15	17	15	20	15	12	12
Prevalence severe forms CT at birth	8	8	8	5	9	7	5	4	5	2	5	3
Mortality	12	17	25	12	5	13	9	7	5	5	4	9
Number of pregnancies	867 308	866 810	824 641	832 799	822 621	790 290	811 510	818 565	798 948	783 640	783 640	719 737

[a]Courtesy of Toxosurv/National Reference Centre on Toxoplasmosis.

Most complete data on the estimates of congenital toxoplasmosis were recently made available from France; 2 or 3 infants were infected per 10 000 live births (Table 3). Based on 12-year data, the number of congenitally infected children decreased from 272 (0.031%) in 2007 to 151 (0.018%) in 2018, including the severe congenital infections (Table 3).

Austria

Austria has a population of around 9 million and is one of the first countries to establish a screening programme for *T. gondii* infection during pregnancy (Thalhammer, 1973, 1978). During 1992–2008, 1 387 689 women/infants were tested for *T. gondii* infection by serology, molecular tests and cord blood screening (Prusa *et al.*, 2013, 2015*a*, *b*, 2017). Annually 8.5% per 10 000 women acquired *T. gondii* infection during pregnancy with an estimated 1 congenitally infected infant per 10 000 pregnancies (Prusa et al., 2015*b*). Data regarding clinical outcome are summarized in Table 2. Rationale was provided by the Austrian Government concerning the cost savings because of prenatal screening (Prusa *et al.*, 2017).

Other European countries

There are no recent data on congenital transmission. Data in the past 2 decades are summarized in Table 2. The national screening programme in Denmark was discontinued because of low rate of congenital transmission and the cost-effectiveness (Table 2).

Africa

Little information is available from Africa. A review paper stated 21 cases of congenital toxoplasmosis from 6 hospitals in 3 geographic areas of Morocco (El Bissati *et al.*, 2018). Based on the number of live births annually in these 6 centres, 4–8 congenitally infected children were born per 10 000 births but details are lacking (El Bissati *et al.*, 2018). There are many unconfirmed reports of congenital toxoplasmosis and spontaneous abortion associated with toxoplasmosis in Egypt; these were recently reviewed by Abbas *et al.* (2020). Most of these reports are based on serological results on single samples from pregnant women, and detection of DNA in the placenta.

USA

A neonatal screening was initiated in Massachusetts, USA in 1980s (Guerina *et al.*, 1994). Prenatal screening is based on testing mothers for *T. gondii* seroconversion during pregnancy and postnatal screening is often sampling of cord blood or heel pricks of the newborn combined with phenylketonuria testing (Guthrie cards). However, most of these data were based on prevalence at birth without a follow-up. The 1994 study revealed a low rate of congenital transmission (Table 2).

As stated earlier, through the National Collaborative Chicago-based Toxoplasmosis Study, information has been gained concerning epidemiology, clinical presentation, treatment of congenitally infected children in the USA (Boyer *et al.*, 2005, 2011; McLeod *et al.*, 2006*a*, 2009, 2020).

Brazil

Brazil has a population of around 213 million. Although there is no national screening of *T. gondii* in pregnant women or children in Brazil, several centres are performing screening based on convenience and affordability. Data summarized by Dubey *et al.* (2012), up to 2011, indicated 5–23 congenital infections per 10

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000 births. Often the sampling was based on who could pay for the tests, and under these circumstances, there will be lower representation of samples from low economic groups. There is also the possibility of false negativity based on IgM testing because many infants with congenital toxoplasmosis are negative for IgM antibodies at birth. There is no national reference laboratory for the confirmation of *T. gondii* serological testing in Brazil.

The most comprehensive study on congenital toxoplasmosis in children is from the State of Minas Gerais, Brazil (Vasconcelos-Santos *et al.*, 2009; de Resende *et al.*, 2010; Carneiro *et al.*, 2013). In this study, blood samples were collected from 146 307 newborns at 1560 public health care centres in 853 cities in the state of Minas Gerais. All serological testing was performed in one laboratory initially using an IgM-ELISA capture test kit (Toxo IgMQ-Preven, Symbiosis, Leme, Brazil) and results were confirmed on further testing for IgA antibodies by ELISA, and IgG and IgM anti-*T. gondii* (enzyme-linked fluorometric assay, VIDAS, BioMérrieux SA, Lyon, France), using blood samples from infants and their mothers. Additionally, infected children were followed clinically months after delivery (Vasconcelos-Santos *et al.*, 2009; de Resende *et al.*, 2010). Congenital toxoplasmosis was suspected in 235 infants (1 in 622), and confirmed in 190 children (1 in 770 live births); this figure of 1 per 770 live births does not include *in utero* mortality due to toxoplasmosis nor infants negative for IgM antibodies at birth (Dubey *et al.*, 2012).

Of the 106 infected children identified early in screening programme, 46 (43.4%) had hearing loss; 4 of these had sensorineural hearing loss and 13 had conductive hearing loss (de Resende *et al.*, 2010). Most of these children had ophthalmic lesions (Vasconcelos-Santos *et al.*, 2009). One hundred and forty-two (79.8%) out of 178 children that underwent ophthalmic examination at 2 months of age had ocular lesions. In 113 of these children, lesions were bilateral; 46.3% of them had macular lesions (de Resende *et al.*, 2010). Viable *T. gondii* was isolated by mouse bioassay from peripheral blood in 27 (15.2%) out of 178 children when they were 4 months or older (Carneiro *et al.*, 2013). To our knowledge, this is the highest rate of parasitemia demonstrated in congenitally infected children. Genetically, 14 of the 24 isolates tested by 10 PCR-RFLP markers revealed 14 genotypes, distinct from those in Europe (Dardé *et al.*, 2020).

A recent study from a hospital in Porto Alegre, Brazil reported long-term follow-up of 77 congenitally infected children from a retrospective investigation of patients 1996–2017 (Lago *et al.*, 2021). The children were followed for 2–25 years (Table 2). Most children had ocular lesions (55 children) and 44 had intracerebral calcification, a hallmark of congenital toxoplasmosis. Fewer ocular lesions were detected in children who were treated before they were 4 months old (35.2%) *vs* those treated after they were 12 months old (77.8%), clearly revealing the benefit of early treatment. Two peaks of retinochoroiditis were detected between 4–5 and 9–14 years (Lago *et al.*, 2021). Other lesions in these children were hydrocephalus in 4, microcephalus in 9 and hearing loss in 3 (Lago *et al.*, 2021).

Based on limited studies, both the rate of congenital infection and the severity of disease in congenitally infected children are higher in Brazil than in Europe. This topic was discussed by Dubey *et al.* (2012) and is repeated here. This conclusion was based on a comparison of ocular lesions in 30 children in Brazil with 281 children in Europe using a similar methodology. In these 30 Brazilian children, the ocular lesions were more extensive and more likely to involve the area of the retina affecting the central vision than in the European children, despite the fact that most of the Brazilian children had been treated for toxoplasmosis for 12 months (Gilbert *et al.*, 2008). This study also concluded that the Brazilian children had a 5 times higher risk of severe toxoplasmosis than children in Europe. In another report, the risk of intracranial lesions detected by computed tomography scan was much higher in Brazilian children than in children in Europe (The SYROCOT, 2007). Some of these differences are thought to be related to the genetic makeup of the *T. gondii* strains in humans in Brazil. Indeed, the *T. gondii* strains from the Minas Gerais study had atypical genotype compared with most of the strains from congenitally infected children in France that were mostly Type II (Ajzenberg *et al.*, 2002; Dardé *et al.*, 2020). In addition to genotype, several other factors should not be ignored including the host genetics, the environment, cultural and economic factors.

Other South American and Central American countries

More data have been reported from Colombia, and the pattern of clinical manifestations and prevalence is like from Brazil (Table 2). In a selected survey, 15 congenital infections were identified among 15 333 women sampled (Gómez-Marin *et al.*, 2011). No information is available from other countries in this region.

China, India and other Asian countries

There is little or no information on the rates of congenital transmission of *T. gondii* in these countries.

Prophylactic treatment during pregnancy and prenatal screening

Prevention of infection of the fetus by prophylactic treatment of the mother depends on the delay between maternal infection and its transmission to the fetus. It is also hoped that if infection is already present in the fetus, treatment may limit its ill effects. Treatment is begun as soon as possible during the prenatal period. In Austria and France, it is by spiramycin before the 20th week of pregnancy and thereafter by pyrimethamine and sulfonamide (Picone *et al.*, 2020).

A large European multicentre cohort study found no evidence that pre-natal treatment with either spiramycin or sulphonamide combined with pyrimethamine influenced maternal transmission (Gilbert *et al.*, 2001). The relative risk of mother-to-child transmission of *T. gondii* compared to Lyon, France (women treated) was 1.24 in Austria (women treated), 0.59 in Denmark (no treatment) and 0.65 in the Netherlands (50% treated, 50% not treated) (Gilbert *et al.*, 2001). 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 (The SYROCOTT, 2007). On the other hand, the number of congenital infections, based on the mothers testing screening in Lyon, France, decreased after 1992 (46.6% after 1992 *vs* 59.4% from 1987–1991) when screening of susceptible women became mandatory and antenatal treatment was initiated as soon as the diagnosis was made (Wallon *et al.*, 2013). In a recent randomized multicentre trial of sulfadiazine plus pyrimethamine (SzP), and spiramycin (Sp) in 143 mothers (73 SzP group, 70 Sp group) who seroconverted during pregnancy, the transmission rate of congenital toxoplasmosis was 2-fold lower in the SzP group (18.5%) than the Sp group (30%) (Mandelbrot *et al.*, 2018). Cerebral lesions were noted in 0/73 in the SzP group *vs* 6 of 70 in the Sp group, indicating the effectiveness of therapy in reducing damage to fetal tissues.

One current practice is to start treatment with spiramycin if the woman becomes infected in the first or early second trimester of pregnancy, and then perform amniocentesis to detect

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fetal infection (Montoya, 2018). If fetal infection is detected, then therapy is switched to pyrimethamine and sulfadiazine. Pyrimethamine and sulfadiazine may be used initially in the late second and third trimesters when acute infection is detected.

French *T. gondii* programme is based on serological screening of mothers to give prophylactic measures to seronegative women to avoid maternal infection. When seroconversion occurs during pregnancy, in complement to prophylactic treatment, a prenatal diagnosis is recommended. This prenatal diagnosis is based on monthly ultrasonography examination and molecular testing for *T. gondii* DNA on amniotic fluid. Amniocentesis must be performed after 18 amenorrhea weeks and 4 weeks after maternal infection. In case of detection of DNA (PCR positive) in amniotic fluid, diagnosis of congenital toxoplasmosis is made. However, if the PCR is negative, this does not mean that the fetus is free of congenital infection. Children must be followed at birth to detect congenital infection. In France, since surveillance of congenital toxoplasmosis by the National Reference Centre for Toxoplasmosis (beginning in 2007), approximately 10% of false-negative diagnoses are identified annually (data from NRC for toxoplasmosis). One explanation for these observations is that *T. gondii* is arrested in the placenta and crosses the barrier a few days to weeks later.

Each country needs to evaluate the cost of screening pregnant women, treatment of congenitally infected children and human suffering based on resources and the prevalence of *T. gondii* in general population (Scallan *et al.*, 2011; Jones *et al.*, 2018; Suijkerbuijk *et al.*, 2018; Binquet *et al.*, 2019; Bobić *et al.*, 2019). Stillwaggon *et al.* (2011) provided an extensive guideline for estimating the costs of preventive maternal screening for and the social costs resulting from toxoplasmosis based on studies in Europe and the USA. While estimating these costs, the value of all resources used or lost should be considered, including the cost of medical and non-medical services, wages lost, cost of in-home care, indirect costs of psychological impacts borne by the family for lifetime care of a substantially cognitively impaired child; cost of fetal death was estimated to be 5 million dollars (Stillwaggon *et al.*, 2011). A study on the cost-effectiveness of screening from Austria estimated a lifetime cost of 103 Euros per birth under prenatal screening compared with 323 Euros without screening (Prusa *et al.*, 2017). Although it is unethical to value human life in terms of dollars, each nation must balance public funding for all the needs of its people, including the prevention of crippling ailments.

Where it has been carried out with thoroughness, persistence and determination, as in France, education appears to have contributed to a reduction in the incidence of *T. gondii* infection during pregnancy. It should be included in the instructions given in antenatal clinics and by obstetricians and midwives dealing with individual patients. Individual instruction given in person is likely to be most effective but should be supplemented by booklets printed in the various languages of the patients and by videos in the waiting rooms of antenatal clinics.

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