Congenital toxoplasmosis in France in 2007: first results from a national surveillance system

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When immunocompetent people become infected with the parasite *Toxoplasma gondii*, the disease is generally asymptomatic. However, transplacental transmission of *T. gondii* may lead to severe congenital infection including *in utero* abortion, foetal death, or neurological or ocular damage of the foetus. France has had a national programme to prevent congenital toxoplasmosis since 1978. However, although estimated seroprevalence in pregnant women has fallen from 84% in the 1960s to 44% in 2003, no reliable data have been available on the annual number of cases of congenital toxoplasmosis or the severity of infection. In 2006, the French National Institute for Public Health Surveillance (Institut de Veille Sanitaire) and the National Reference Centre for Toxoplasmosis recommended that a national laboratory-based surveillance system be used for the surveillance of the disease. In 2007, 31 laboratories reported at least one congenital case through the surveillance system, giving a total of 272 cases. A total of 11 terminations of pregnancy were reported (six abortions and five foetal deaths). Of the live-born cases, 206 were asymptomatic, 28 were symptomatic and seven had a severe form of the disease. As there were 818,700 births in France and French overseas departments in 2007, the overall prevalence of congenital toxoplasmosis observed that year was 3.3 (95% confidence interval (CI): 2.9 to 3.7) per 10,000 live births and the incidence rate of the disease at birth was 2.9 (95% CI: 2.5 to 3.2) per 10,000 live births; the estimated incidence rate of symptomatic congenital toxoplasmosis was 0.34 (95% CI: 0.2 to 0.5) cases per 10,000 live births.

Introduction

Toxoplasmosis is caused by the protozoan parasite *Toxoplasma gondii*, which is widely distributed in the environment. When immunocompetent people become infected, the disease is generally asymptomatic. However, transplacental transmission of *T. gondii* may lead to severe congenital infection including *in utero* abortion, foetal death, or neurological or ocular damage of the foetus [1]. In France, estimated seroprevalence among pregnant women fell from 84% in the 1960s to 54% in 1995 to 44% in 2003. Models estimating the incidence of toxoplasmosis by age showed that between 1995 and 2003 the incidence rate fell by 17.6% for 20-year-old women and by 8.3% for women aged 40 years [2,3]. The number of women who seroconverted during pregnancy was estimated in 1995 to be approximately 2,700 per year [4]. The risk of transplacental transmission increases with gestational age at the time of maternal infection: in 1999, Dunn estimated an overall global transmission rate of 29% during pregnancy [5].

Clinical signs of toxoplasmosis are very diverse and can be serious (foetal death). Prognosis of infection is principally dependent on the time of maternal infection and genotype of the *Toxoplasma* strain (greater virulence being associated with atypical genotypes) [6]. Congenital infection can lead to severe sequelae for the foetus and newborn, with neurological lesions or visual impairments often documented [7,8].

A national programme to prevent congenital toxoplasmosis has existed in France since 1978. In addition, since 1992, pregnant women who are not immune to toxoplasmosis have been tested monthly until delivery. Despite this, there have been no reliable data on the annual number of cases of congenital toxoplasmosis or the severity of infection. In 2006, a working group on congenital toxoplasmosis recommended that a laboratory-based system would be most appropriate for surveillance of this disease. The French National Institute of Public Health Surveillance (Institut de Veille Sanitaire, InVS) and the National Reference Centre for

Toxoplasmosis are responsible for this system, which has been active since June 2007 [9]. The system aims to collect information on cases of congenital toxoplasmosis diagnosed during pregnancy by amniocentesis, or diagnosed in newborns and infants under one year whose mother had seroconverted during pregnancy. The objectives of the surveillance are to estimate overall prevalence of the disease in France, monitor prevalence trends and estimate the proportion of cases with severe forms of infection (hydrocephalus, microcephalus and macular chorioretinitis).

Several preliminary surveys were undertaken to identify laboratories able to diagnose the infection in newborns or infants, in order to optimise surveillance of the disease [9]. A surveillance system was set up, ToxoSurv, based on a network of 35 specialised laboratories that are certified in prenatal and neonatal diagnosis of toxoplasmosis and 74 additional medical biology laboratories that occasionally carry out diagnosis. In this report, we present the results of the surveillance from 1 June to 31 December 2007, with retrospective data collection for the first six months of that year.

Methods

Case definitions

A case of congenital toxoplasmosis was defined as a foetus, newborn or infant aged under one year with at least one of the following [10]:

- *T. gondii* in body tissues or fluids by polymerase chain reaction (PCR), inoculation of mice, cell culture or immunocytochemistry
- specific IgM or IgA antibodies
- specific IgG antibodies within the first 12 months of life
- persistent IgG positivity until one year of age.

Case diagnosis and notification

Cases of congenital toxoplasmosis are reported to the National Reference Centre for Toxoplasmosis in two ways: firstly, via internet data entry for the 35 specialised laboratories (through http://www.chu-reims.fr/professionnels), using specifically developed software, Voozanoo (EpiConcept). Secondly, the 74 additional laboratories send paper forms to the National Reference Centre for Toxoplasmosis, where the notifications are entered through the internet data entry system. Two notification forms were created: one for cases diagnosed antenatally, the other for postnatal diagnoses.

As described in 2008 [9], patient data are reported, such as estimated gestational age at the time of maternal infection and age of mother), pregnancy outcome (abortion, foetal death or living newborn) and clinical status of the newborn or child (particularly neurological lesions and visual impairments, e.g. chorioretinitis, with localisation).

Demographic data on the distribution of births by region were obtained from the National Institute for Statistics and Economic Studies (INSEE).

Cases diagnosed between 1 January and 31 December 2007 in France and French overseas departments were included in our analysis.

Definitions of prevalence and incidence regions

Overall prevalence of congenital toxoplasmosis is defined as follows: (LB + FD + IA) divided by the total number of live births in France in 2007, where LB is the number of live-born infants with congenital toxoplasmosis, FD is the number of deaths of foetuses with congenital toxoplasmosis (from 20 weeks' gestation) and IA is the number of induced abortions or terminations of pregnancy after prenatal diagnosis of congenital toxoplasmosis (at any gestational age).

The incidence of congenital toxoplasmosis is defined as the number of live-born infants with congenital toxoplasmosis divided by the total number of live births in France in 2007.

Results

Epidemiology

During 2007, 31 laboratories reported at least one congenital toxoplasmosis case through the surveillance system (29 specialised diagnostic laboratories and two laboratories occasionally carrying out diagnosis). A total of 272 cases were notified for 2007: 38 (14%) were notified in antenatally, 74 (27%) in ante- and postnatal periods and 160 (59%) in the neonatal and postnatal periods.

The distribution of congenital toxoplasmosis according to gestational age at the time of maternal infection was variable. Estimates of the age were available for 235 of the 272 cases: 17 (7%) occurred after maternal infection in first trimester (0–12 amenorrhea weeks) of pregnancy, 83 (35%) after maternal infection in the second trimester (13–26 amenorrhea weeks) and 135 (58%) after maternal infection in the third trimester (27–40 amenorrhea weeks) (Figure 1). For 37 cases, the date of the infection was not determined, due to lack of information about previous serological examinations.

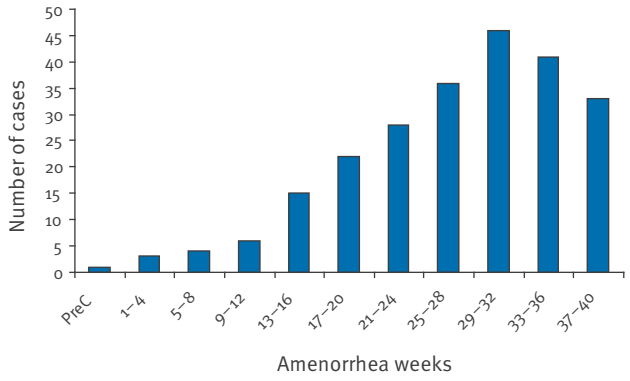
The prevalence of the disease varied according to the mothers' age at delivery: it was highest in young women aged under 20 years (Figure 2).

Geographical distribution of cases was variable, with a higher prevalence observed in the north-east and south-west of France (Figure 3). Additionally, nine cases were reported from Cayenne (French Guiana), one from Martinique and one from Réunion, but none from Guadeloupe.

As there were 818,700 live births in France and French overseas departments in 2007, the overall prevalence of congenital toxoplasmosis observed was 3.3 (95% CI:

Figure 1

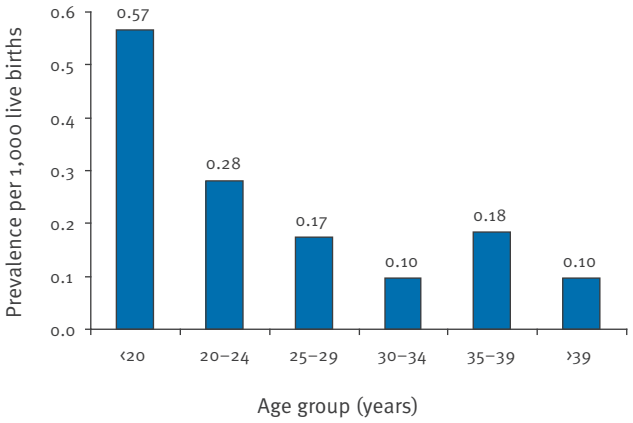
Congenital toxoplasmosis cases by gestational age at maternal infection expressed in amenorrhea weeks, France, 2007 (n=235)



PreC: preconception.

Figure 2

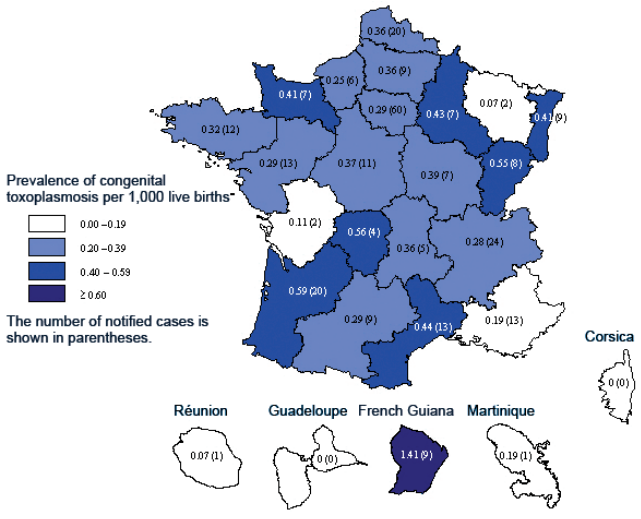
Prevalence of congenital toxoplasmosis per 1,000 live births by maternal age at delivery, France, 2007



Source: National Institute for Statistics and Economic Studies (INSEE), 2007.

Figure 3

Regional distribution of congenital toxoplasmosis prevalence per 1,000 live births, France, 2007 (N= 272)



2.9 to 3.7) per 10,000 live births and the incidence at birth was 2.9 (95% CI: 2.5 to 3.2) per 10,000 live births.

The distribution of the disease according to the month of the children's birth showed no seasonality in disease transmission (data not shown).

Practices in antenatal and postnatal diagnosis

Antenatal diagnosis: amniocentesis was performed in 112 cases: 108 were positive. The median delay between estimated date of maternal infection and amniocentesis was six weeks (range: 1–17). Half of the tests were carried out between weeks 5 and 8 of pregnancy.

Ultrasound examinations were carried out for 82 pregnant women with antenatal diagnosis (73%), among these a majority were performed during the second trimester of pregnancy. The examinations were abnormal in 13 of the women, with severe lesions observed for four cases. Magnetic resonance imaging was performed in 28 of the women.

Postnatal diagnosis: infection was diagnosed postnatally in 160 children (59%). Of these, 130 (81%) were diagnosed before the age of two months; 22 (14%) were diagnosed between the age of two months and one year.

Clinical outcomes

A total of 11 (4%) terminations of pregnancy were reported: six abortions were performed for medical reasons (cerebral lesions were detected by ultrasound examination in four cases) and there were five foetal deaths (due to cerebral lesions in four cases). In six cases, maternal infection was acquired in first trimester and in five cases, in the second trimester. No pregnancies were terminated following late maternal infection.

For 27 foetuses diagnosed in the antenatal period, the clinical outcome was unknown (Figure 4). Among the 234 live-born infants, the male–female sex ratio was 0.92. Among live-born infants, 206 (87%) were asymptomatic and 28 (13%) symptomatic: the incidence of symptomatic congenital toxoplasmosis was estimated to be 0.34 cases (95% CI: 0.2 to 0.5) per 10,000 live births. Among symptomatic children, 21 had moderate lesions (intracranial calcifications and/or peripherical chorioretinitis) and seven (3%) had a severe form of the disease (three with hydrocephalus and four with macular chorioretinitis) (Figure 4).

Discussion

The observed prevalence of toxoplasmosis has decreased by nearly 20% from 1995 to 2003 in France [2]. Previously, only retrospective or small-scale studies on prevalence were attempted in very few hospital centres in the country. We concluded that a laboratory-based surveillance system was the most adapted for surveillance of congenital toxoplasmosis, because

laboratories carry out the diagnosis of infection in mothers and then in foetuses or newborns [9].

The number of congenital toxoplasmosis cases observed in France in 2007 is considerably lower than that estimated in the 2007 report of the French Food Safety Agency (272 versus 600). This is probably because the French Food Safety Agency used the estimated number of seroconversions during pregnancy from the 1995 national perinatal survey [4]. The calculated incidence rates of congenital toxoplasmosis in 2007 are also lower than the reported rates of congenital infection during the 1980s and 1990s. The incidence rates for these decades were certainly overestimated because they were derived from mathematical models considering using and estimated incidence rates. The number of cases directly observed in 2007 is probably more robust and reliable than that of 1995 due to the exhaustive process adopted for notification (all laboratories carrying out the diagnosis in France were invited to participate in the surveillance).

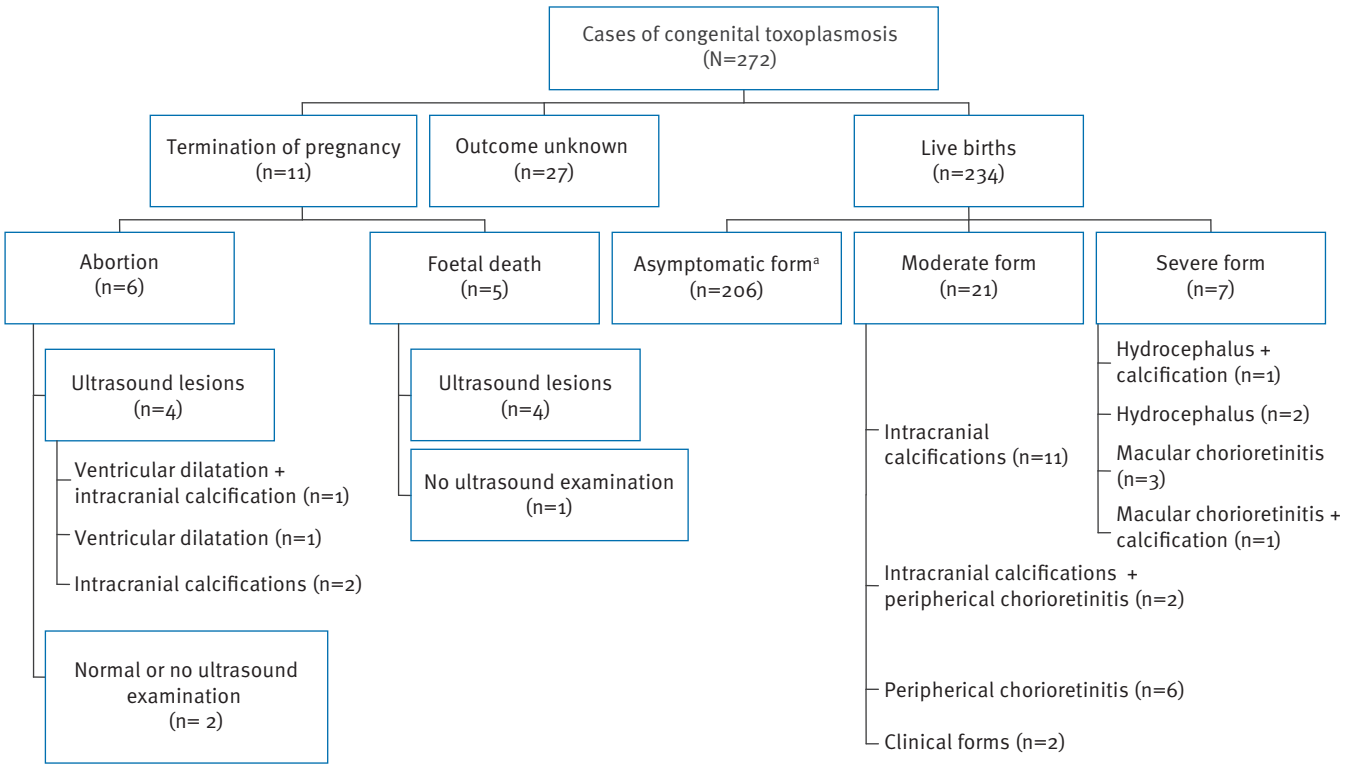
The incidence of congenital toxoplasmosis observed in France in 2007 was 2.9 (95% CI: 2.5 to 3.2) per 10,000 live births. Incidence data from other countries are very scarce and often calculated on regional data collected before 2000. The prevalence of congenital toxoplasmosis observed in France in 2007 is in the same range as incidences per 10,000 births reported in other European countries, e.g. in Poland (5.5, 95% CI: 0.2 to 29, per 10,000 live births) [11], Denmark (2.1 per 10,000 live births) [12] and Switzerland (4.3 per 10,000 live births) [13], but is much higher than that reported in Sweden (0.73, 95% CI: 0.2 to 2.1, per 10,000 live births) [14].

The incidence rate of symptomatic congenital toxoplasmosis was estimated to be 0.34 (95% CI: 0.2 to 0.5) cases per 10,000 live births in France in 2007. Although the overall seroprevalence of toxoplasmosis is much lower in England, the incidence rate of symptomatic congenital toxoplasmosis observed in a study in England and Ireland between 2002 and 2004 (0.16, 95% CI: 0.08 to 0.28 per 10,000 live births) [15] is comparable to that of France.

We observed large variations in the prevalence of the disease between geographical regions. A similar geographical distribution was observed for the seroprevalence reported in pregnant women in 2003 [2]. Only 11 (4%) of the cases were notified from French overseas departments. These regional disparities could reflect the transmission of *Toxoplasma* in the population and could be linked to climatic factors and the eating habits of women (e.g. eating raw meat). Similar climatic or eating habit disparities at regional level are observed in different European countries. However, most do not have a congenital toxoplasmosis screening programme because of lack of evidence of its cost-effectiveness. Data published from these countries concern only symptomatic forms of the disease and are thus not exhaustive.

Figure 4

Outcomes of congenital toxoplasmosis, France, 2007 (N= 272)



[a] One infected child dead at birth without clinical signs of congenital toxoplasmosis.

The distribution of congenital toxoplasmosis according to gestational age at the time of maternal infection was variable, with the majority of disease occurring when maternal infection occurred during the last trimester of pregnancy. This is in accordance with foetal transmission rates previously reported in large cohorts [5]. Congenital toxoplasmosis appears to be more frequent in children from younger mothers, especially those under 20 years. This is probably associated with the fact that young women are generally less informed about the risks of congenital toxoplasmosis in pregnancy and thus adhere less well to the antenatal screening programme and to the recommendations for avoiding contamination [16]. As cases occurred regularly during the year, there was no seasonality in transmission of congenital infection.

Some 60% of congenital cases diagnosed in 2007 were diagnosed at birth, with the majority diagnosed before the age of two months, as a result of serological examinations of newborns and babies. Sometimes diagnosis occurred late (up to the age of one year). Immunological tests must be performed regularly until definitive disappearance of maternal antibodies enables confirmation of the absence of infection.

In terms of clinical outcome, pregnancies were terminated in 11 (4%) of cases, principally because of foetal cerebral lesions. Prenatal prevention programmes can detect severe forms of congenital infection, usually by ultrasound examination. Magnetic resonance imaging is used less frequently as a first-line diagnostic tool, being usually reserved for confirmatory diagnosis. When severe lesions are diagnosed, abortions for medical reasons are recommended. This prenatal prevention policy could explain why at birth, the majority of congenital infections were asymptomatic. Only seven severe forms were observed in 2007.

Another possible explanation for the low rate of severe forms is that most maternal infections occurred during the second and third trimester of pregnancy. Infection at these stages has been shown to result in a less severe clinical presentation [5,17] It is interesting to note that the severe form leading to foetal death was observed in cases of early maternal infection, as is often reported in literature [7,8,18]. The severe forms are hydrocephalus (three cases in newborns) and macular chorioretinitis (four cases in newborns): they represented only 0.1 per 10,000 live births in France in 2007. At birth, intracranial calcifications were observed in half of symptomatic cases but without clinical consequences, while chorioretinitis appeared to be less frequent. However, ocular lesions are the major complication of congenital toxoplasmosis leading to visual impairment in long-term follow-up [8]. Eye examinations at birth only partially estimate the burden of congenital toxoplasmosis, as new lesions may be observed during the first two years of life (when the children are at high risk of developing new lesions [8]) or at any time later in life [19,20].

We observed only 28 symptomatic forms of infection at birth (12% of cases) in 2007 in France. Studies have shown that in the absence of prenatal screening and antenatal treatment, the frequency of chorioretinitis and cerebral lesions was higher [21]. In the European Multicentre Study on Congenital Toxoplasmosis (EMSCOT) study [18], 20% of infants had one or more clinical manifestations. In some European countries, however, there are few data on clinical manifestations of congenital toxoplasmosis as there are no screening programmes in place. In Denmark, where neonatal screening was performed, 12 of 47 infected children (25.5%) had clinical signs at birth [7].

In our study, 88% of infected infants were asymptomatic at birth – a figure higher than other published studies, with 81% asymptomatic in the SYROCOT study (a systematic review of congenital toxoplasmosis) [21]. These figures could suggest a positive impact of prenatal screening. Treatment may also have an impact on these figures. In France, spiramycin is prescribed when seroconversion occurs in pregnant women. All such women were treated with this antibiotic, although its impact on vertical transmission is still controversial. When amniocentesis is positive, spiramycin treatment is stopped and a pyrimethamine–sulfonamide combination is generally prescribed until delivery. This antibiotic combination is considered to be effective in reducing the risk of severe congenital sequelae.

The surveillance system in France only detects lesions evident at birth. The true burden of congenital toxoplasmosis should be evaluated by long-term follow-up of cases, as congenitally infected newborns that are asymptomatic at birth are at risk of developing ocular lesions during childhood and adolescence, leading to visual impairment [18]. However, long-term case follow-up is not the objective of this surveillance programme.

Systems for the surveillance of congenital toxoplasmosis in European countries are very variable and are principally dependent on prevalence rate. A recent investigation aimed to describe these different systems in Europe [22]. The results showed that, of the 28 countries investigated, only four had a specific surveillance system for congenital toxoplasmosis: in addition to France, the others were Denmark, with a programme based on neonatal Guthrie card adapted for testing for *Toxoplasma*-specific IgM (which was discontinued in July 2007), Germany, where cases have been notifiable since 2001, and Italy, with surveillance of live newborns (but confined to a regional programme in the Campania region since 1997).

Conclusions and public health perspectives

The surveillance system for congenital toxoplasmosis in France appears to be effective and, for the first time, provides reliable data. Surveillance needs to continue for several years in order to assess the overall prevalence of the disease and to follow its trend. Toxoplasmosis seroprevalence among women

of childbearing age is regularly estimated in France through national perinatal surveys based on cross-sectional surveys of births at a national level during a given week. With these two indicators, it will be possible to perform economic analyses – as carried out by Ancelle *et al*. in a recent study [23] – for the development of different screening strategies. Surveillance of congenital toxoplasmosis is an indispensable tool to assess the efficiency of new screening strategies that could be implemented in France in the future.

Members of the National Reference Centre for Toxoplasmosis and Toxosurv network in alphabetical order:
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