We present a case of disseminated congenital toxoplasmosis in a newborn born to a mother who had been immunized against toxoplasmosis before conception. The mother was reinfected, likely by ingestion of imported raw horse meat during pregnancy. This clinical presentation is exceptional in France and raised the possibility of infection by a highly virulent *Toxoplasma* strain. The strain responsible was isolated from the peripheral blood of the newborn, and when genotyped with microsatellite markers, it exhibited an atypical genotype, one which is very uncommon in Europe but had been described in South America. We tested the hypothesis of a reinfection with a different genotype by using an experimental mouse model, which confirmed that acquired immunity against European *Toxoplasma* strains may not protect against reinfection by atypical strains acquired during travel outside Europe or by eating imported meat.

After primary maternal infection by *Toxoplasma gondii* during gestation, the parasite may enter the fetal circulation by infection of the placenta. Placental transmission is less frequent when infection is acquired before the tenth week of pregnancy and is very rare when infection is acquired before conception. Without treatment, the incidence of fetal infection is 10%–15% for acquisition during the first trimester, 30% for the second trimester, and 60% for the third trimester [1]. Early maternal infection (during the first and second trimester) may result in severe congenital toxoplasmosis, including fetal death and spontaneous abortion. By contrast, late maternal infection (during the third trimester) usually results in subclinical toxoplasmosis in newborns. In these cases, infection initially goes unnoticed, but these babies can develop chorioretinitis during later life [2]. Acute infection is followed by the formation of cysts in chronic infection and is associated with an immune response that usually confers protection against reinfection. This chronic infection is characterized by stable titers of specific IgG. In immunocompetent mothers who have been immunized against toxoplasmosis before conception, immune mechanisms prevent transmission of the infection to their fetuses. We report a case of life-threatening, disseminated congenital toxoplasmosis in an infant born to an immunocompetent mother who had been immunized against toxoplasmosis before conception. We also isolated and characterized the strain that caused the infection.

**SUBJECTS, MATERIALS, AND METHODS**

A 31-year-old woman, native to France, gave birth at term to a 3050 g baby by cesarean delivery (this method of delivery was decided on as a result of dystocia). It was her second child, and the results of serological testing during her previous pregnancy were consistent with a past *Toxoplasma* infection. Several hours after birth, the
The diagnosis of congenital toxoplasmosis was suggested by the ophthalmologist, who found multiple foci of chorioretinitis on both eyes. The inflammation was moderate but involved the macula in the right eye. The diagnosis was confirmed by analysis of the newborn’s blood 8 days after birth: a polymerase chain reaction (PCR) assay with a direct amplification of the Toxoplasma B1 gene was positive, and T. gondii was isolated by inoculation into mice. PCR of cerebrospinal fluid samples was negative. Specific IgM antibody synthesis in serum from the newborn was demonstrated with an immunosorbent agglutination assay (ISAGA) (table 1). The results of an electroencephalogram, cranial radiograph, and ultrasound were normal, and the child was performing satisfactorily in school. Ophthalmologic examination shows a large scar in the right macula. The visual acuity is 2/10 in the right eye and 10/10 in the left eye; she wears corrective glasses and needs an orthoptic aid.

**Maternal clinical and laboratory data.** The results of tests for Toxoplasma antibodies performed in May 2001, before the beginning of the pregnancy (October 2001), were consistent with past infection (i.e., the results showed the presence of specific IgG antibodies in the dye test without detectable IgM). Serological results remained unchanged until 4 June 2002, at 32 weeks of pregnancy, when an increase in IgG titer was observed and confirmed 3 weeks later by further testing (table 1).

The mother recalled severe asthenia, general dizziness, headache, and abdominal pain occurring on June 11. She had eaten raw horse meat several times in May and June. Tests for underlying immunosuppression in the mother had negative results, including complete phenotypes of circulating T lymphocytes, functional testing of T lymphocytes, and serological testing for HIV. The mother had had autoimmune thyroiditis (Hashimoto disease) for years, and the level of antithyroglobulin antibodies was high at the time of birth, signaling active thyroiditis.

**Strain characterization.** T. gondii was isolated from the newborn’s peripheral blood 8 days after birth by mouse inoculation. The strain, called IPP-2002-URB, was virulent for mice at the time of isolation: all inoculated mice died 9 days after inoculation. The strain, called IPP-2002-URB, was virulent for mice at the first year of life. After 1 week of treatment, hypotonia and thrombocytopenia disappeared. Pulmonary signs lasted for 12 days, and chorioretinitis stabilized without the use of steroids. The last cranial ultrasound showed no ventriculare enlargement and only 1 calcification.

Table 1. Results of serological testing for mother and child infected with Toxoplasma.

<table>
<thead>
<tr>
<th>Patient, date</th>
<th>Dye test, IU/mL</th>
<th>ELISA, IU/mL</th>
<th>HS or AC/HS agglutination, IU/mL</th>
<th>IgG avidity</th>
<th>IgM ISAGA</th>
<th>IgA ISAGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 May 2001</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 February 2002</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>0.48</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25 March 2002</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4 June 2002</td>
<td>1600</td>
<td>524</td>
<td>100/800</td>
<td>0.48</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>27 June 2002</td>
<td>3200</td>
<td></td>
<td>400/1600</td>
<td>0</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>10 September 2002</td>
<td>400</td>
<td></td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Child, born on 27 June 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 July 2002</td>
<td></td>
<td></td>
<td>100</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 April 2003</td>
<td>10</td>
<td></td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 September 2003</td>
<td>400</td>
<td></td>
<td>200</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**NOTE.** Thresholds of positivity were 2 IU/mL for the dye test and agglutination test with formalin-fixed tachyzoites (HS antigen) and 3 IU/mL for ELISA (AxSym; Abbott); an AC/HS ratio (differential agglutination of acetone [AC]–fixed vs. HS–fixed tachyzoites) <4 indicated a nonacute pattern. An IgG avidity result > 0.3 (Vidas; BioMérieux) was interpreted as high avidity. An IgM immunosorbent agglutination assay (ISAGA) index from 3 to 12 was interpreted as positive for infants, and an IgA ISAGA index from 9 to 12 was interpreted as positive for adults.


date. In all these immunocompetent patients, the delayed transplant transmission of Toxoplasma was explained by a persistent or recurrent parasitemia over a prolonged period.

**DISCUSSION**

In relatively few cases, congenital toxoplasmosis results from reactivation of a latent infection in pregnant women with altered immune status, such as that resulting from systemic lupus erythematosus or hematological malignancies [6] and HIV infection [7–9]. Some case reports involved congenital toxoplasmosis transmitted from immunocompetent mothers infected before conception, but clinical and serological data permitted researchers to date the occurrence of the primary infection to a few months before the onset of pregnancy. Lymphadenopathy was the most frequent clinical presentation, and it occurred 1 [10], 2 [6, 11, 12], or 3 months [13] before conception. In one case [14], a flu-like syndrome was reported by the mother 2 months before conception, whereas in another case [15], the recent infection was asymptomatic and could be identified only by serological data. In all these immunocompetent patients, the delayed transplant transmission of Toxoplasma was explained by a persistent or recurrent parasitemia over a prolonged period.

**Experimental model of reinfection.** To test the hypothesis of reinfection, we created an experimental model of reinfection by IPP-2002-URB in mice chronically infected by a type II strain of T. gondii designated as types I, II, and III. To our knowledge, the case described in the present article is the sixth case of congenital toxoplasmosis as a consequence of maternal parasitemia following reinfection in an immunocompetent woman who had previous test results consistent with past toxoplasmic infection (table 3) that has been reported in the literature during the past 3 decades [16–20]. Our case is the first in which the Toxoplasma strain likely to be the origin of reinfection was isolated. In all 6 cases, the serological data collected before or at the beginning of the pregnancy ruled out a recent infection before conception (i.e., the presence of IgG and absence of IgM). Reinfection with another strain during pregnancy was a plausible explanation, with serological reactivation observed in the mother during gestation or at birth: increased titers of IgG were observed in all cases, the appearance of IgA was documented for all cases except patient 5, and the absence of IgM was documented for all cases except patient 2 (for whom data showed the appearance of IgM at week 28 of amenorrhea). For 2 cases (patients 2 and 6 [the present case]), a flu-like syndrome consistent with an acute toxoplasmic infection (table 3) that has been reported in the literature during the past 3 decades [16–20]. Our case is the first in which the Toxoplasma strain likely to be the origin of reinfection was isolated. In all 6 cases, the serological data collected before or at the beginning of the pregnancy ruled out a recent infection before conception (i.e., the presence of IgG and absence of IgM). Reinfection with another strain during pregnancy was a plausible explanation, with serological reactivation observed in the mother during gestation or at birth: increased titers of IgG were observed in all cases, the appearance of IgA was documented for 5 cases (IgA data was not reported for patient 5), and the absence of IgM was documented for all cases except patient 2 (for whom data showed the appearance of IgM at week 28 of amenorrhea). For 2 cases (patients 2 and 6 [the present case]), a flu-like syndrome consistent with an acute toxoplasmic infection had been reported by the mother before the observed serological reactivation during pregnancy. To support the hypothesis of maternal reinfection during pregnancy, the authors of all 6 case reports documented the absence of any underlying immunodeficiency in the mothers. In the case we describe, the mother had active Hashimoto thyroiditis. In this autoimmune disease, a defect in a subpopulation of NK immune cells has been described [21]. As NK cells are critical for the initiation of an im-

**Table 2. Detection of experimentally induced mixed infections in mouse brains by microscopic cyst examination and microsatellite analysis.**

<table>
<thead>
<tr>
<th>Reinflection delay, mouse number</th>
<th>Number of cysts in brain, PRU-β-Gal/IPP-2002-URB</th>
<th>Microsatellite B17 alleles, 334 bp (PRU-β-Gal)/352 bp (IPP-2002-URB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month after initial infection</td>
<td>1</td>
<td>614/0</td>
</tr>
<tr>
<td>2</td>
<td>343/4</td>
<td>+/-</td>
</tr>
<tr>
<td>3</td>
<td>290/6</td>
<td>+/-</td>
</tr>
<tr>
<td>4</td>
<td>372/6</td>
<td>+/-</td>
</tr>
<tr>
<td>5</td>
<td>180/3</td>
<td>+/-</td>
</tr>
<tr>
<td>6</td>
<td>Not donea</td>
<td>Not donea</td>
</tr>
<tr>
<td>4 months after initial infection</td>
<td>1</td>
<td>229/1</td>
</tr>
<tr>
<td>2</td>
<td>203/2</td>
<td>+/-</td>
</tr>
<tr>
<td>3</td>
<td>419/4</td>
<td>+/-</td>
</tr>
<tr>
<td>4</td>
<td>93/4</td>
<td>+/-</td>
</tr>
<tr>
<td>5</td>
<td>100/2</td>
<td>+/-</td>
</tr>
<tr>
<td>6</td>
<td>142/23</td>
<td>+/-</td>
</tr>
</tbody>
</table>

**NOTE.** Mice were initially infected with a transfected type II strain (PRU-β-Gal) and reinfected either 1 or 4 months later with IPP-2002-URB. a Because of death 12 days after reinfection.
munological intestinal response against *T. gondii* [22], it cannot
be ruled out that this underlying disease could have favored oral
reinfection.

The immune response of the mother might be over-
whelmed when reinfection occurs as the result of a massive
inoculum [16], a different infectious stage (oocyst vs. cysts)
[17], or a strain with a different genetic background [20]. In
the 6 cases of reinfection during pregnancy presented in table
3, epidemiological risk factors were present, such as contact
with kittens (patients 1, 2, and 4), consumption of imported
raw meat (horse meat was consumed by patient 6, described
here), birthplace and residence, or travel abroad (patient 4
could have been exposed in Brazil and patients 3 and 5 in
France after primary infection in Haiti and/or French Guiana
and Angola, respectively).

All 6 cases of congenital toxoplasmosis after maternal reinfec-
tion were diagnosed because the newborns were symptomatic.
In 3 cases (patients 2, 3, and 4), the clinical diagnosis was re-
vealed by typical toxoplasmic chorioretinitis. In the 3 other cases
(patients 1, 5 and 6), the clinical presentation was more severe,
with a disseminated toxoplasmosis leading to spontaneous abort-
ton in patient 1, cardiac abnormalities in the offspring of patient
5, and a bacterial sepsis-like infection in the infant described in
this article, which is very uncommon in congenital toxoplasmo-
sis [23]. These severe and unusual clinical presentations might
be explained by an infection during pregnancy due to a highly
virulent strain. In our case, the *Toxoplasma* strain (IPP-2002-
URB) was isolated from the peripheral blood of the newborn,
which traduces the high capacity for dissemination of this strain.
Furthermore, the genetic analysis of the strain showed an atyp-
ical genotype that is very uncommon in France, where 96% of
gonital toxoplasmosis is due to a single genotype, type II [24].
Conversely, type II strains seem rare outside Europe and North
America. In South America, *Toxoplasma* strains are genetically
more diverse, with many different genotypes described mainly
in Brazil and the Guianas [3, 25–27]. These atypical South Amer-
ica strains, initially called “exotic” strains, belong to several
haplogroups that are endemic to South America [28, 29]. Be-
cause a large amount of the horse meat eaten in France is im-
ported from South America (Argentina, Uruguay, and Brazil), it
is likely that the infecting strain in the case presented here orig-
nated from these countries, where similar atypical genotypes
had already been described [3]. Even if there is still no evidence
for a correlation between atypical strains and severe toxoplas-
mosis, disseminated cases in immunocompetent patients in
French Guiana or Suriname [25, 30] and congenital toxoplas-
mosis [24] are more often associated with atypical genotypes of
*T. gondii*.

### Table 3. Reported cases of congenital toxoplasmosis transmitted from immunized mothers who experienced reinfection during pregnancy, from literature of the past 3 decades.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Child’s clinical data</th>
<th>Maternal data</th>
<th>Year, source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Spontaneous abortion at 12 weeks of gestation, growth retardation</td>
<td>None</td>
<td>Resident of France; contact with a kitten early in pregnancy</td>
</tr>
<tr>
<td>2</td>
<td>Strabismus and chorioretinitis at 9 months, no other complications at 3 years</td>
<td>Flu-like syndrome at 19 weeks</td>
<td>Resident of France; contact with kittens in eighteenth week of pregnancy</td>
</tr>
<tr>
<td>3</td>
<td>Cataract and chorioretinitis at one month</td>
<td>None</td>
<td>Resident of France, born in Haiti; lived in French Guiana for 7 years</td>
</tr>
<tr>
<td>4</td>
<td>Chorioretinitis at 3 weeks, no other abnormalities at 13 months</td>
<td>None</td>
<td>Born in Brazil, resident of Switzerland for 6 years; travel to and contact with kittens in Brazil in fifth month of pregnancy</td>
</tr>
<tr>
<td>5</td>
<td>Disseminated toxoplasmosis at birth, favorable outcome</td>
<td>None</td>
<td>Born in Angola, resident of France for 2 years</td>
</tr>
<tr>
<td>6</td>
<td>Disseminated toxoplasmosis at birth; decreased visual acuity in right eye and normal psychomotor development at 5 years</td>
<td>Flu-like syndrome at 33 weeks</td>
<td>Native resident of France; raw horse meat consumption between weeks 27 and 32 of pregnancy</td>
</tr>
</tbody>
</table>

**NOTE.** NR, not reported.
The results of our experimental model confirmed reinfection by the atypical strain IPP-2002-URB in mice chronically infected by a type II strain of \textit{T. gondii}. This experimental model had already been used to demonstrate the possibility of reinfection in mice by different \textit{T. gondii} strains (type II challenged by type I or III) \cite{4,31,32}. The definitive proof of reinfection in our patient would require the isolation and identification of the initial infecting strain, which would be nearly impossible to obtain. The only alternative would be serotyping \cite{33,34}, with results showing different serotypes in the mother before and after serological reactivation, and in the newborn. Serotyping was attempted in this case, but was unsuccessful for the mother before reactivation because titers of anti-\textit{Toxoplasma} antibodies were too low.

In France and probably elsewhere in Europe, congenital toxoplasmosis following maternal reinfection during pregnancy is exceptional. In these countries, past immunity usually protects against reinfection because generally only 1 genotype (type II) circulates in humans and in the environment \cite{35,36}, and as a consequence, there is a very low probability of reinfection with different genotypes. However, in other areas, such as South America, where the genetic diversity of \textit{Toxoplasma} is higher, reinfecction with different genotypes is likely to occur more frequently. For instance, in Brazil, where cases of reinfection have been described for acquired toxoplasmosis \cite{37}, congenital toxoplasmosis due to reinfection during pregnancy might not be so exceptional. Thus, we assume that pregnant women from Europe who have been immunized against type II strains but are traveling in tropical areas or eat imported meat during pregnancy are at risk of reinfection by atypical strains. Conversely, as reported in this review (see patients 3 and 5 in table 3), women born in Africa or South America, and likely immunized against atypical \textit{Toxoplasma} strains before conception, could also be at risk of reinfection by a type II strain when they migrate to European countries.

In conclusion, cases of reinfection with \textit{T. gondii} involving an immunocompetent pregnant woman are exceptional but show that the presence of residual IgG-specific antibodies is not always synonymous with protection against a new \textit{Toxoplasma} infection. To our knowledge, the case described here is the first in which the \textit{T. gondii} strain involved in reinfection was isolated, characterized, and studied in an experimental mouse model that suggested immunity against a type II strain may not be protective against a reinfection with a different genotype, especially if it is atypical. Because there is increasing evidence that \textit{Toxoplasma} strains are genetically more diverse outside Europe, health-care providers in Europe should be aware of this possibility when pregnant women travel abroad or eat imported meat.

**Acknowledgments**

We would like to thank our colleagues M. Robin and H. Vrillon from the maternity ward of Saint Maurice Hospital for providing serological results for the mother and Anne Dao and Jean-François Dubremetz for providing us the transfected strain PRU β-Gal.

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