Prediction of congenital toxoplasmosis by polymerase chain reaction analysis of amniotic fluid

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**Objective** To determine the accuracy of polymerase chain reaction (PCR) analysis of amniotic fluid for fetal toxoplasmosis according to clinical predictors of outcome and study centre.

**Design** Prospective cohort study.

**Setting** Nine European centres.

**Population** Women with suspected toxoplasma infection identified by prenatal screening.

**Methods** Logistic regression was used to examine the effects of gestational age at maternal seroconversion, treatment and timing of amniocentesis, on PCR accuracy, and to calculate the post-test probability of congenital toxoplasmosis.

**Main outcome measures** Infants had congenital toxoplasmosis if specific IgG persisted beyond 11.5 months. Uninfected infants had undetectable IgG in the absence of anti-toxoplasma treatment.

**Results** Of 593 PCR results, 64 were positive (57 confirmed infected), and 529 were negative (23 confirmed infected). The likelihood ratio for a positive PCR result decreased significantly with trimester at seroconversion, but did not change significantly for a negative result. Weak associations were detected between sensitivity and, inversely, with specificity, and gestational age at maternal seroconversion. There was no significant association between sensitivity and centre, type or duration of treatment, or timing of amniocentesis. Specificity differed significantly between centres (\(P < 0.001\)). The change in pre- to post-test probability of infection was maximal for a positive PCR after first trimester seroconversion, affecting 1% of women tested, and a negative PCR after third trimester seroconversion, affecting half the women tested.

**Conclusions** Prediction of the risk of congenital toxoplasmosis should combine estimates of test accuracy and maternal–fetal transmission, which take account of the gestational age at which the mother seroconverted. Local laboratory standards will affect the generalisability of these results.

**INTRODUCTION**

Prenatal diagnosis of congenital toxoplasmosis is based on detection of toxoplasma DNA in the amniotic fluid by polymerase chain reaction (PCR). Women with a positive PCR result are offered combination therapy with pyrimethamine–sulphonamide for the remainder of pregnancy, or, if the fetal ultrasound examination is abnormal, termination.\(^1\)–\(^3\) If the PCR result is negative, women are usually prescribed spiramycin treatment for the remainder of pregnancy due to the risk of false negative results and case reports of delayed mother to child transmission.\(^2,4\)

Prenatal PCR analysis of amniotic fluid has been used since the early 1990s\(^2,4\)–\(^9\) and has replaced cordocentesis followed by culture and serological analysis of fetal blood as amniocentesis has a lower risk of procedure-related fetal loss and PCR has improved sensitivity.\(^2,10\)–\(^13\)

The value of PCR diagnosis depends on how much knowledge of the test result changes the woman's risk of an infected fetus. For example, the probability of fetal infection in a woman who seroconverts at 12 weeks of gestation is 9\%.\(^1\) A negative test result can at most lower the
probability of fetal infection to zero, whereas a positive test result could theoretically increase the risk by 91%. Conversely, the risk of fetal infection for a woman who seroconverts at 36 weeks of gestation is 73%. Many clinicians would recommend treatment with pyrimethamine–sulphonamide at this level of risk, hence, only a negative result would lead to a change in management. Interpretation of PCR diagnosis is further complicated by reports that the sensitivity of PCR varies with gestational age at maternal seroconversion and the theoretical possibility that prenatal treatment reduces sensitivity.

We aimed to determine the accuracy of PCR analysis of amniotic fluid as performed in routine practice in nine centres in a prospective cohort study of toxoplasma-infected women. We examined how the accuracy of PCR varies according to gestational age at maternal seroconversion, maternal anti-toxoplasma treatment, timing of amniocentesis, and study centre.

METHODS

Toxoplasma-infected women were prospectively identified by prenatal screening in nine European centres between January 1996 and March 2000. The seven French centres offered monthly re-testing of susceptible women. The remainder offered three monthly re-testing: Vienna, and one laboratory centre (Italy) serving two clinical centres (Naples and Milan). Criteria for enrolment and details of prenatal treatment and follow up have been reported elsewhere. The reference standard for congenital toxoplasmosis was persistence of specific IgG antibodies beyond 11.5 months postnatal age, and for absence of congenital toxoplasmosis, undetectable specific IgG in the absence of anti-toxoplasma treatment of the child at the time of testing. We separately report PCR results for non-live births, which could not fulfil these reference criteria, and describe the pathology and parasitological findings. In addition, there may have been under-reporting of fetal losses, and terminations, with selective reporting of those with abnormalities who were more likely to be thoroughly investigated by pathologists.

Twins were excluded to avoid the possibility of results being attributed to the wrong twin. Amniocentesis and PCR analysis were performed according to the local clinical protocol. Results were reported as positive, equivocal or negative, but the latter two categories were analysed as ‘negative’. The date of maternal seroconversion was analysed as the midpoint between the last negative IgG test during pregnancy and the first date both IgM and IgG were positive, or 14 days before an IgM positive and IgG negative result. The midpoint imputation produces similar results to the more complex approach reported elsewhere, given that most women with infected babies were re-tested monthly (unpublished data available from the authors). We excluded women without a negative IgG test date during pregnancy unless they gave birth to an infected child in which case the last negative test was assumed to have occurred at conception. In infected fetuses, anti-toxoplasma treatment may depress the amount of toxoplasma DNA in amniotic fluid to give false negative results. We therefore determined the effect of prenatal treatment on sensitivity by analysing the duration of any type of treatment before amniocentesis, and by comparing women treated before amniocentesis with spiramycin with those treated with pyrimethamine–sulphonamide, and untreated women. We also determined whether sensitivity increased with the interval between seroconversion and amniocentesis, as would be expected given the hypothesis that parasite transmission from the placenta to fetus is delayed.

We estimated sensitivity, specificity, likelihood ratios (LRs) and post-test probabilities for positive and negative PCR results for each trimester of pregnancy at maternal seroconversion. Using logistic regression, we separately determined the effect of gestational age at maternal seroconversion (measured in weeks), and centre, on sensitivity and specificity. We included duration and type of prenatal treatment before amniocentesis, and the interval between gestation at seroconversion and amniocentesis, in the model to determine their effect on sensitivity. Finally, using Bayes’ theorem, we combined the results of the regression analysis of sensitivity and specificity with the pre-test probability of congenital toxoplasmosis for the entire cohort, to derive the post-test probability of congenital toxoplasmosis.

Confidence intervals for sensitivity and specificity were computed using the binomial exact method and for the LRs, using the log method. Confidence intervals for positive and negative predictive values were computed using Wilson’s method. Analyses were carried out using SAS Version 8.02 (SAS Institute, Cary, North Carolina) except the binomial exact confidence intervals, which were computed using STATA (release 7, STATA press, Texas, USA). Differences in the LRs according to gestational age at trimester of seroconversion were tested using the Mantel–Haenszel \( \chi^2 \) test of homogeneity.

RESULTS

A total of 1215 births were enrolled in nine centres (Fig. 1). Ten pairs of twins (n = 20) were excluded. Of the remaining 1195 women, 417 (35%) did not undergo amniocentesis: 27% (113/417) of these were diagnosed with congenital toxoplasmosis as previously reported. In the 778/1195 (65%) that had PCR diagnosis performed, 86 live born babies were lost to follow up before congenital infection status was confirmed using the reference criteria (12.7% or 11/86 had a positive PCR result) and there were 14 fetal losses (Table 1). PCR was positive in eight fetuses that underwent therapeutic abortion at 20 weeks of gestation or more. Five of these fetuses had intracranial pathology, positive culture of fetal tissues or both at autopsy.
Table 1. PCR, autopsy and laboratory results in fetal losses occurring in women identified by prenatal screening.

<table>
<thead>
<tr>
<th>PCR AF</th>
<th>Gestational age at seroconversion</th>
<th>Type of fetal loss</th>
<th>Weeks of gestation at delivery</th>
<th>Additional information on CT status from laboratory investigations or autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>10</td>
<td>TOPtox</td>
<td>22</td>
<td>Positive mouse culture of placenta. Negative mouse culture of fetal tissues</td>
</tr>
<tr>
<td>+</td>
<td>13</td>
<td>TOPtox</td>
<td>20</td>
<td>Cysts in placenta (histology)</td>
</tr>
<tr>
<td>+</td>
<td>17</td>
<td>TOPtox</td>
<td>28</td>
<td>Negative mouse culture of AF, intracranial calcification</td>
</tr>
<tr>
<td>+</td>
<td>9</td>
<td>TOPtox</td>
<td>33</td>
<td>Negative mouse culture of AF, disseminated signs, positive mouse culture of brain tissue</td>
</tr>
<tr>
<td>+</td>
<td>17</td>
<td>TOPtox</td>
<td>27</td>
<td>Doubtful intracranial lesions on US scan, no evidence of CT at autopsy</td>
</tr>
<tr>
<td>+</td>
<td>13</td>
<td>TOPtox</td>
<td>24</td>
<td>Positive mouse culture of AF, pos IgM, IgA, WB (IgM and IgG) of cord blood</td>
</tr>
<tr>
<td>+</td>
<td>9</td>
<td>TOPtox</td>
<td>21</td>
<td>Positive mouse culture of AF, absence of cysts (fetal histology), diffuse inflammatory lesions, myocarditis, and pneumonitis</td>
</tr>
<tr>
<td>+</td>
<td>11</td>
<td>TOPtox</td>
<td>27</td>
<td>Positive mouse culture AF, cerebral lesions on US scan, necrotic lesions at autopsy</td>
</tr>
<tr>
<td>–</td>
<td>23</td>
<td>SB</td>
<td>41</td>
<td>Nil</td>
</tr>
<tr>
<td>–</td>
<td>10</td>
<td>SB</td>
<td>31</td>
<td>Nil</td>
</tr>
<tr>
<td>–</td>
<td>20</td>
<td>SB</td>
<td>34</td>
<td>Positive mouse culture AF, neg mouse culture and PCR placenta</td>
</tr>
<tr>
<td>–</td>
<td>PC</td>
<td>SB</td>
<td>37</td>
<td>Nil</td>
</tr>
<tr>
<td>–</td>
<td>7</td>
<td>misc</td>
<td>19</td>
<td>Negative mouse culture of AF</td>
</tr>
<tr>
<td>–</td>
<td>PC</td>
<td>misc</td>
<td>21</td>
<td>Nil</td>
</tr>
</tbody>
</table>

misc = miscarriage (gestation < 24 weeks); SB = stillbirth (gestation > 23 weeks); TOPtox = termination for toxoplasmosis; AF = amniotic fluid; CT = congenital toxoplasmosis; PC = no negative IgM/IgG results after conception. If fetal toxoplasmosis was present, last negative test assumed to have occurred at conception. Seroconversion is likely to have occurred preconception.

1 PCR result in amniotic fluid: + = positive PCR result; – = negative or equivocal PCR result.
2 Seroconversion calculated as midpoint between last negative and first positive IgM test or 14 days before IgM positive test date, if IgG negative result on same date.
A total of 678 live births were included in the descriptive analyses of results for each centre (85 infected and 593 uninfected; Table 2). Overall, 12.1% (82/678) had a positive PCR result. As test accuracy differed in Italy compared with other centres and was significantly lower for specificity ($P < 0.001$), this centre was excluded from further analyses. Most women (464/593; 78%) seroconverted before 20 weeks of gestation. Amniocentesis was performed between 11 and 39 weeks of gestation but three-quarters of the women (433/593; 73%) underwent amniocentesis in the second trimester (15 to 27 completed weeks). Most women (570/593; 96%) underwent amniocentesis four or more weeks after seroconversion and the median interval between seroconversion and amniocentesis was 9.1 weeks (interquartile range: 6.3–12.0 weeks).

Table 3 summarises the PCR results according to trimester at maternal seroconversion. LRs for a positive PCR result. As test accuracy differed in Italy compared with other centres and was significantly lower for specificity ($P < 0.001$), this centre was excluded from further analyses. Most women (464/593; 78%) seroconverted before 20 weeks of gestation. Amniocentesis was performed between 11 and 39 weeks of gestation but three-quarters of the women (433/593; 73%) underwent amniocentesis in the second trimester (15 to 27 completed weeks). Most women (570/593; 96%) underwent amniocentesis four or more weeks after seroconversion and the median interval between seroconversion and amniocentesis was 9.1 weeks (interquartile range: 6.3–12.0 weeks).

Table 3. Accuracy of PCR analysis of amniotic fluid in live-born infants according to trimester at maternal seroconversion.

<table>
<thead>
<tr>
<th>Trimester at seroconversion (weeks)</th>
<th>Total</th>
<th>CT+</th>
<th>CT−</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR2 positive</th>
<th>LR negative</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st (0–14)</td>
<td>357</td>
<td>3</td>
<td>6</td>
<td>0.33</td>
<td>0.99</td>
<td>0.67</td>
<td>0.75</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.07–0.70)</td>
<td>(0.98–1.00)</td>
<td>(13.32–1010)</td>
<td>(0.42–1.06)</td>
<td>(0.22–0.98)</td>
<td>(0.96–0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd (15–27)</td>
<td>200</td>
<td>37</td>
<td>9</td>
<td>0.80</td>
<td>0.97</td>
<td>0.20</td>
<td>0.88</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.47–0.85)</td>
<td>(0.92–0.99)</td>
<td>(10.34–59.36)</td>
<td>(0.11–0.36)</td>
<td>(0.74–0.96)</td>
<td>(0.89–0.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd (≥28)</td>
<td>36</td>
<td>17</td>
<td>8</td>
<td>0.68</td>
<td>0.91</td>
<td>0.35</td>
<td>0.94</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.66–0.81)</td>
<td>(0.57–0.99)</td>
<td>(1.13–49.42)</td>
<td>(0.19–0.64)</td>
<td>(0.71–0.99)</td>
<td>(0.31–0.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>593</td>
<td>57</td>
<td>23</td>
<td>0.71</td>
<td>0.98</td>
<td>0.29</td>
<td>0.89</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.61–0.81)</td>
<td>(0.97–0.99)</td>
<td>(24.69–110.4)</td>
<td>(0.21–0.41)</td>
<td>(0.78–0.95)</td>
<td>(0.93–0.97)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PPV = positive predictive value; NPV = negative predictive value; CT = congenital infection status; + = positive result; − = negative or equivocal PCR result.

1 Completed weeks (e.g.: 14 + 6 days).

2 The likelihood ratio is the probability of the test result in infected infants divided by the probability of the test result in uninfected infants. It is used to calculate the post-test odds of disease (which can then be converted into a probability estimate), by multiplying the likelihood ratio by the pre-test odds of disease.52

interval between seroconversion and amniocentesis (odds ratio 0.98: 0.82–1.16). The odds ratio for a positive test result if amniocentesis occurred four or more weeks after seroconversion (66/80) compared with less than four weeks (14/80) was 0.63 (0.16–2.49).

The logistic regression analyses showed that in women who gave birth to uninfected infants, specificity decreased from 99.0% (98.1–99.8%) if seroconversion occurred at 12 weeks of gestation, to 91.5% (89.1–93.9%) if seroconversion occurred at 30 weeks: the odds ratio for a negative PCR result per week of gestation was 0.88 (0.80–0.97).

Figure 2 shows the pre-test risk of congenital toxoplasmosis and the post-test risk after a positive or negative PCR diagnosis according to gestational age at maternal seroconversion. PCR diagnosis provides most information when the change from pre-test to post-test risk is greatest. For example, for a woman who seroconverts at 12 weeks of gestation, a positive PCR diagnosis would increase her risk of an infected fetus from 9% to 84%, whereas a negative result would reduce her risk to 3%. However, as only 4/357 (1%) women had a positive PCR result in the first trimester, predictions should be regarded with caution as they represent extrapolation of the model. In practice, the value of PCR in the first trimester is augmented by the additional positive PCR results in women who subsequently underwent therapeutic abortion. In contrast, in a woman who seroconverts at 36 weeks of gestation, a positive PCR diagnosis would increase her risk of an infected fetus from 73% to 99%, whereas a negative result would reduce the risk to 44%.

**Fig. 2.** The probability of giving birth to an infant with congenital toxoplasmosis is plotted against the weeks of gestation at maternal seroconversion. The bold line shows the probability before testing for the entire cohort. The long dashed line depicts the post-test probability given a positive PCR result (the positive predictive value), and the dotted line, the post-test probability given a negative PCR result (1 minus the negative predictive value). As shown in Table 2, there is a wide confidence interval around the post-test probability, particularly for women who seroconvert in early pregnancy when the number of infected babies is small.

**DISCUSSION**

For clinical decisions, test accuracy needs to be considered in combination with the steep increase in the probability of congenital toxoplasmosis with gestational age at maternal seroconversion. Test accuracy, measured by LRs for a positive and negative PCR result, changed significantly with trimester at maternal seroconversion. A positive PCR result in the first trimester was associated with the largest increase in the probability of congenital toxoplasmosis but only occurred in 1.1% of women tested who delivered a live birth (4/357). A negative PCR result was associated with the largest decrease in the probability of congenital toxoplasmosis when seroconversion occurred in the third trimester and was found in half the women tested at this time.

Additional clinical value of PCR for first trimester seroconversions is illustrated by the 10 women who seroconverted in the first trimester and suffered fetal losses, of whom 6 underwent therapeutic termination following fetal monitoring that was instituted after a positive PCR result. We did not include fetal losses in the overall analyses because there was less certainty about their congenital infection status as they did not achieve the reference standard. In addition, there was evidence of selective ascertainment of such pregnancies, which probably favours fetuses with complications as more likely to be investigated and those with a negative amniocentesis as less likely to be thoroughly investigated. The resultant bias would favour overestimation of sensitivity. For example, if the fetal losses born to women that seroconverted in the first trimester are added to Table 2, the sensitivity would be 57% (8/14) instead of 33% for live births.

Our findings for the overall performance of PCR diagnosis are consistent with previous reports identified in a systematic search and summarised in Table 4. One strength of the present study is that women were prospectively identified and a high proportion of their infants were followed up postnatally to exclude or confirm congenital toxoplasmosis by widely accepted criteria. We thereby minimised biases inherent in previous retrospective studies. One weakness of the study is that PCR diagnosis was performed according to the varying protocols and the technical quality of each laboratory. The results therefore represent an average measure of the performance of PCR in European reference centres. PCR protocols and quality control (including DNA extraction protocols) are known to vary between laboratories, as does test accuracy as shown by a controlled experimental study. Apart from Italy, we found no significant difference in test accuracy between centres. However, the power to detect a difference was limited due to small cell sizes.

We found that the sensitivity of PCR was lower given seroconversion in early pregnancy, but this finding was not significant. Similar results have been reported by Romand et al. However, in contrast to their analysis, which involved
241 of the same patients, we did not find that sensitivity was reduced in women who seroconverted in late pregnancy. This may be because of small numbers of women tested in late pregnancy, different inclusion criteria for the analyses and differences in the way gestational age was categorised. Possible explanations for the low sensitivity of PCR diagnosis in the first trimester include, chance, reduced number of fetal cells for analysis, and the possibility of delayed transmission.4,19 The latter explanation cannot be ruled out in some fetuses with false negative PCR results.2,20,21 However, the hypothesis that fetal and maternal immune responses reduce the amount of free parasite over time would be more consistent with the weak evidence for a decline in sensitivity with increasing interval between seroconversion and amniocentesis found by us and others.4,7,32

The lack of evidence for an effect of prenatal treatment on PCR sensitivity has been reported by others,4,7 although in these studies treatment was with spiramycin only, or a combination of spiramycin and pyrimethamine-sulphonamide, and it was not possible to study the effect of each regimen alone. Our study lacked power to detect an effect of treatment vs no treatment due to small numbers of untreated women. In contrast, a study using a monkey model and a non-encysting strain of Toxoplasma gondii found that treatment with pyrimethamine-sulphonamide reduced the sensitivity of PCR analysis of amniotic fluid.33 Failure to detect an effect of treatment may be due to rapid encystment of the parasite, the small number of false negative results or the relatively crude classification of results as positive or negative. A recent study has demonstrated the accuracy of toxoplasma DNA quantification in amniotic fluid by quantitative PCR for predicting the risk of severe clinical outcomes, particularly if maternal infection was acquired before 20 weeks.34

The finding of reduced specificity in women seroconverting in late pregnancy has not been reported elsewhere and should be regarded with caution as this is based on one false positive result in the third trimester. False positive results are most likely to reflect error or contamination during processing rather than presence of toxoplasma DNA in the amniotic fluid of an uninfected fetus.31 Given this explanation, a trend in specificity with gestational age at maternal seroconversion lacks biological plausibility and is likely to be a chance finding.

The authors agreed that PCR testing is useful if termination of pregnancy for toxoplasmosis is being considered. We did not reach a consensus about the value of routine PCR testing due to differing interpretations of the evidence regarding the benefits of changing from spiramycin to pyrimethamine-sulphonamide treatment and differing perceptions of the adverse effects of amniocentesis.35

### CONCLUSIONS

Positive and negative LRs decreased with trimester at seroconversion. The sensitivity of PCR diagnosis increased with gestational age at maternal seroconversion, but there was no evidence that sensitivity was significantly influenced by treatment or the timing of amniocentesis. This finding needs to be confirmed with larger sample sizes. Clinicians can use Fig. 2 to predict the risk of congenital toxoplasmosis based on a positive or negative test result and the gestational age at which the mother seroconverted. Local laboratory standards will affect the generalisability of these results.

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### Table 4. Studies reporting the accuracy of PCR testing of amniotic fluid for congenital toxoplasmosis.

<table>
<thead>
<tr>
<th>Authors and years of publication</th>
<th>No. of women</th>
<th>Congenital toxoplasmosis</th>
<th>Uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PCR+</td>
<td>PCR–</td>
</tr>
<tr>
<td>Grover et al., 199036</td>
<td>43</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Dupouy-Camet et al., 199237</td>
<td>44</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Cazenave et al., 1992b</td>
<td>80</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Hohlfeld et al., 19942</td>
<td>339</td>
<td>37</td>
<td>1</td>
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<tr>
<td>Jenum et al., 1998f</td>
<td>102</td>
<td>10</td>
<td>7</td>
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<tr>
<td>Gratzl et al., 1998g</td>
<td>49</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Foulon et al., 19999</td>
<td>46</td>
<td>20</td>
<td>2</td>
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<tr>
<td>Robert-Gangneux et al., 1999k</td>
<td>94</td>
<td>16</td>
<td>5</td>
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<td>Romand et al., 200111</td>
<td>270</td>
<td>48</td>
<td>27</td>
</tr>
<tr>
<td>Bessieres et al., 200217</td>
<td>148</td>
<td>56</td>
<td>4</td>
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<tr>
<td>Antsaklis et al., 200239</td>
<td>79</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>EMSCOT, 2002</td>
<td>568</td>
<td>50</td>
<td>19</td>
</tr>
<tr>
<td>Total reported</td>
<td>1862</td>
<td>282</td>
<td>72</td>
</tr>
</tbody>
</table>

1 241/270 patients included in EMSCOT cohort.
Members of the European Multicentre Study on Congenital Toxoplasmosis (EMSCOT)


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References


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