

National Screening Committee (NSC)  
Antenatal and Newborn Screening for  
Toxoplasmosis

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# Antenatal and Newborn Screening for Toxoplasmosis

## Report of the Working Group -- October 2001

Professor Catherine Peckham (Chair)  
Professor Martin Whittle (apologies)  
Dr Ruth Gilbert  
Dr Rick Holliman  
Professor Allan MacLean  
Dr Susan Cliffe (for Dr Angus Nicoll)  
Dr David Elliman  
Professor Elizabeth Anionwu  
Ms Pat ward (apologies)

### 1) INTRODUCTION

*Toxoplasma gondii* occurs world-wide and is one of the most common parasitic infections in humans. Infection is acquired by ingestion of viable tissue cysts in undercooked meat, or of oocysts excreted by cats and contaminating soil or water<sup>1,2</sup>. In this paper the feasibility, effectiveness and appropriateness of introducing prenatal or neonatal screening for congenital toxoplasmosis is evaluated, based on the criteria set out for the assessment of a screening programme by the UK National Screening Committee.

### 2) BACKGROUND

When primary infection occurs during pregnancy, *T.gondii* can be transmitted from the mother to her fetus. Fetal infection can result in inflammatory lesions in the brain, retina and choroid that may lead to permanent neurological damage or visual impairment. Rarely, disseminated fetal infection causes fetal or postnatal death.

#### ***2.1 Seroprevalence and incidence of infection in pregnancy***

Past exposure to infection is marked by specific IgG serum antibodies. Seroprevalence decreases with latitude, is higher in women born outside Britain, particularly in Africa or the West Indies, and is similar in black (13%) and white (12%) women born in Britain<sup>3</sup>.

Seroprevalence has fallen over the last 2 to 3 decades: in France (from 80-90% to 50-60%<sup>4,5</sup>), Switzerland (87% to 47%<sup>6</sup>), Sweden (34% to 18%<sup>7</sup>) and in the UK (22% to 8%)<sup>8</sup>. The decline appears to be due to a fall in the incidence of infection, particularly during childhood<sup>9</sup> leaving more women susceptible to infection during pregnancy.

Table 1 shows the estimated incidence rates for infection in pregnancy and the birth prevalence of congenital toxoplasmosis from studies done in the last 15 years. In Europe

the incidence of maternal infection ranges from less than 1 per 1000 susceptible pregnancies in Sweden and Norway, to 8/1000 in France. Reports of the birth prevalence of congenital toxoplasmosis range from less than 1 per 10,000 live births in Sweden and Massachusetts to an estimated 10 per 10,000 live births in France. In the absence of recent data for the UK it is reasonable to extrapolate from populations with a similar seroprevalence, lifestyle and latitude, such as Norway, Sweden and Massachusetts.

## ***2.2 Risks of mother to child transmission of infection, clinical manifestations and impairment***

The risk of mother to child transmission of infection rises steeply with gestational age at maternal infection from approximately 5% for women who seroconvert in the first trimester to 80% for those who seroconvert just before delivery<sup>1</sup>. In contrast, the risk of clinical signs (lesions in the brain or eye) in an infected child decreases from 60% to 80% for women who seroconvert in the first trimester to approximately 5% for those who seroconvert just before delivery<sup>1</sup>. Given the relationship between the risks of infection and clinical signs, the risk of giving birth to a child with clinical signs is greatest (10%) for women who seroconvert between 24 and 30 weeks of pregnancy and lowest before 12 weeks or at term<sup>10</sup>.

The most common clinical signs of congenital infection are intracranial calcifications and retinochoroiditis. Intracranial calcifications are usually detectable at birth and affect approximately 9% of infected children. Hydrocephalus occurs in less than 2% of infected children<sup>10,1</sup>. Eye lesions, caused by reactivation of latent (bradyzoite) cysts in the retina and choroid and the associated inflammatory reaction, can appear at any time during childhood, or even adult life. A recent cohort study, in which most of 181 infected children were treated pre- and postnatally, found eye lesions in approximately 10% of children by 1 year of age, 16% by 3 years and 23% by 7 years<sup>11</sup>.

The long-term risk of neurological or visual impairment in infected children is poorly reported. Recent cohort studies report some degree of unilateral impairment in 25% to 50% of infected children with eye lesions<sup>10;12-16</sup>. Severe neurological impairment that is apparent in early childhood is rare: 2 of 91 infected children followed in 4 cohort studies<sup>12;13;15;16</sup> had mental retardation or hemiplegia. The extent of less severe developmental impairment is uncertain. One small study found no difference in school performance<sup>14</sup>. Few countries have information on the prevalence of symptomatic infected children. In England and Wales, a nationwide active surveillance study among paediatricians and an analysis of laboratory reports of congenital infection identified 14 cases of congenital toxoplasmosis born in 1989 (of approximately 700,000 live births); not all were severely affected and some were abortions or still births<sup>17</sup>.

### **Summary**

**Assuming a birth prevalence of congenital toxoplasmosis in the UK of 1 in 10,000, approximately 75 infected children would be born each year, less than 5% of whom would have severe neurological impairment**

### **2.3 Treatment**

Spiramycin or a combination of pyrimethamine-sulphonamide (sulphadiazine or sulphadoxine plus folinic acid) are widely used to treat toxoplasma infection in pregnancy and during infancy. Prenatal spiramycin treatment is usually given to reduce the risks of mother to child transmission and pyrimethamine-sulphonamide is used to reduce the risk of clinical manifestations in the infected child. Treatment is nearly always continued until delivery except in The Netherlands where treatment has been limited to six weeks<sup>12</sup>. After birth, infected infants are treated with alternating regimens of pyrimethamine-sulphonamide and spiramycin for 12 months to reduce the risk of retinochoroidal lesions appearing after birth.<sup>18</sup>

#### *2.3.1 Prenatal treatment to reduce the risk of mother to child transmission of infection*

Two systematic reviews have found no controlled trials<sup>19:20</sup>. Subsequently, two cohort studies (involving 141<sup>21</sup> and 554<sup>22</sup> seroconverting women) and one ecological comparison of cohorts (857 seroconverting women)<sup>23</sup> have been published. All three studies took into account the steep rise in risk of transmission with gestation at maternal infection and none of them found a significant reduction in transmission risk associated with either the type or timing of prenatal treatment. However, all involved retrospective studies, and lacked the power to exclude clinically important beneficial effects.

#### *2.3.2 Prenatal treatment to reduce the risk of clinical manifestations in infected children.*

The use of pyrimethamine-sulphonamide is largely based on experimental studies in animals which found that, compared with spiramycin, pyrimethamine-sulphonamide reaches higher concentrations in the fetus and penetrates the brain and cerebrospinal fluid<sup>24;25</sup>.

Studies examining the effect of prenatal treatment on intracranial and ocular lesions have produced inconsistent results. One cohort study (64 infected children<sup>21</sup>) found a significant reduction in the risk of lesions at one year, while the other cohort study (181 infected children<sup>11</sup>) and an ecological study<sup>23</sup> (253 infected children) found no evidence for an effect of type or timing of treatment. One explanation for these discrepancies is bias due to failure to exclude women referred with fetal abnormalities. Such bias would overestimate the treatment effect.

#### *2.3.3 Adverse effects of treatment*

Spiramycin has not been associated with serious adverse effects but must be prescribed on a named patient basis in the UK. Pyrimethamine has been reported to be teratogenic in animals but the effect on human fetuses has not been studied. In humans, the most common serious adverse effect is bone marrow depression which may be ameliorated by concurrent administration of folinic acid or reversed by cessation of therapy<sup>26</sup>. Severe adverse effects (rash, gastrointestinal upset, leucopenia) are common in HIV infected patients (40%)<sup>27</sup> but similar data are not available for pregnant women. Sulphonamide therapy, especially sulphadiazine, can cause haematuria and acute renal failure.

**There is no clear evidence that prenatal treatment reduces the risk of mother to child transmission of toxoplasmosis or the clinical manifestations in infected children. Pyrimethamine-sulphonamide is associated with serious adverse effects.**

#### ***2.4 Timing and mechanisms of fetal infection***

Information on the biology of *T.gondii* provides insight into the potential effects of treatment. The tachyzoite form of the parasite causes maternal and fetal infection and tissue damage and is highly sensitive to antibiotic treatment<sup>1</sup>. However, transformation to the bradyzoite cyst form, which is not susceptible to antibiotics<sup>28</sup>, occurs rapidly in immunocompetent individuals. Consequently, treatment may only be effective during certain windows of time: between maternal infection and transmission of the parasite to the fetus, and between fetal infection with the tachyzoite and transformation to the bradyzoite phase.

##### ***2.4.1 Mother to child transmission of infection***

There are two possible mechanisms for transmission of infection from mother to fetus<sup>1:29:30</sup>. Infection could be transmitted to the fetus via the placenta shortly after maternal infection. This mechanism underpins the rationale for frequent re-testing of susceptible women in France so that treatment can be started as soon as possible after maternal infection. An alternative or co-existing mechanism is that the parasite forms inflammatory foci in the placenta with tachyzoites released into the fetal circulation at a later point in pregnancy. Wide acceptance of this hypothesis has resulted in the standard policy of continuing to treat infected women throughout pregnancy despite a negative diagnosis of fetal infection.

Experimental studies in animals show that mother to fetus transmission of infection occurs during maternal parasitaemia<sup>1:31</sup>. In humans, parasitaemia subsides as the maternal serological response develops, but information about the timing of transmission is indirect. Early transmission is suggested by the strong association between gestation at maternal infection and transmission risk: fetuses exposed to maternal infection for longest have the lowest risk of infection, whereas the reverse would be seen if transmission was delayed. If transmission does occur during parasitaemia, prenatal treatment would be given too late to prevent mother to child transmission of infection.

##### ***2.4.2 Evidence for a latent phase between fetal infection and organ damage***

Animal studies show that transformation to the encysted bradyzoite form starts to occur within days of infection<sup>32:33</sup>, probably due to stresses caused by the humoral and cell mediated immune responses<sup>1:32:34</sup>. However, direct evidence of the time to encystment in the human fetus is not available.

##### ***2.4.3 Evidence for a latent phase between fetal infection and organ damage later in infancy or childhood***

Systemic signs of toxoplasma infection such as hepatosplenomegaly, rash and jaundice are likely to reflect continuing tachyzoite replication in immune-competent and immune-deficient infants. Unless treated, further organ damage is likely. However, bradyzoite cysts are found in infected children with or without signs of intracranial calcifications or

retinochoroiditis<sup>1</sup>. A key unanswered question is whether there is persistence or re-emergence of the free tachyzoite in immune competent infants and fetuses, which would benefit from prolonged antibiotic treatment.

**Summary: There is a lack of evidence for a latent phase, when treatment might have an effect, between maternal infection and transmission of the parasite to the fetus and between fetal infection and organ damage in fetal or postnatal life.**

### **3) IMPLEMENTATION OF PRENATAL SCREENING**

As primary toxoplasma infection is usually asymptomatic, infection can be detected only by serological testing. Women are tested at their first antenatal visit and those with no detectable antibodies to *T.gondii* are re-tested at intervals throughout pregnancy and, in some centres, once after delivery. Seroconversion (a change from undetectable to detectable toxoplasma-specific IgG and/or IgM) indicates acquisition of infection during pregnancy. The costs of re-testing clearly depend on the prevalence of toxoplasma infection. For example in France 54% of pregnant women have evidence of past infection and less than half require repeated testing during pregnancy<sup>4</sup>. In contrast, in the UK and Norway, 90% of women would require repeated testing during pregnancy.

#### ***3.1 Identification of infected women***

##### *3.1.1. Women whose initial screening test is seronegative*

Susceptible pregnant women are re-tested monthly in France<sup>35</sup> and Switzerland<sup>36</sup>, and three monthly in Austria, Germany<sup>36</sup>, and Italy<sup>37</sup>. Monthly testing has the advantage of earlier treatment. However, with increasing numbers of prenatal visits more women have false positive test results. For example, based on an incidence per susceptible pregnancy of 0.9%, as in France, the incidence of toxoplasmosis per month is 0.1%. Using a single screening test with 99% specificity, for every 1000 women tested at each monthly test (usually 6 during pregnancy) there will be one true positive and 10 false positive test results. In the UK, where the incidence of maternal infection is about 1 tenth that in France, there would be 100 false positive results for each true positive at each monthly test. In both settings, approximately 6% of pregnant women would have false positive results (1% per month). False positive test results can be reduced by performing several tests on the same sample and on repeat samples, but at additional cost. French law stipulates that infection during pregnancy must be diagnosed by at least 2 positive tests.

##### *3.1.2 Women whose initial screening test is seropositive*

A range of serological tests are performed in women who are IgG positive at their first antenatal test in order to determine the likelihood of postconceptional infection. As specific IgM lasts months or years (depending on the assay used)<sup>1</sup>, further tests for high or rising IgG titre, low IgG avidity<sup>38</sup>, IgA antibodies or a combination of these, are required. None of these tests reliably determine the timing of infection and most women identified will have acquired infection pre-conception and are not at risk of fetal infection. A further problem is the lack of a validated test, although the Sabin-Feldman dye test has been used as a reference standard. Screening and confirmatory tests and the

cut-offs used vary between laboratories. Even when the same test is used, variations in agreement have been reported between laboratories<sup>39</sup>.

### **Summary**

**In seronegative women undergoing repeated serological testing the screen false positive rate would be high (approximately 6% if one screening test is used). Most treated women whose first test is seropositive are not at significant risk of fetal infection.**

### ***3.2 Diagnosis of fetal infection***

Once maternal infection has been confirmed, spiramycin is usually offered immediately and the woman referred for fetal diagnosis involving amniocentesis and in some centres detailed ultrasound examination. Amniocentesis usually takes place after 14 weeks of gestation and is associated with a risk of fetal loss of 0.9% (95% CI 0.0 to 1.9)<sup>40</sup>. There is no consensus regarding the timing of amniocentesis, which is offered immediately in some centres and delayed for 4 weeks in others. Women with positive PCR detection of toxoplasma DNA in amniotic fluid usually have their treatment changed to pyrimethamine-sulphonamide. However, evidence is lacking that pyrimethamine-sulphadiazine is more effective than spiramycin in the treatment of clinical manifestations of congenital toxoplasmosis<sup>11:21</sup>. Also, as the sensitivity of PCR is 64% (95% CI: 53-75%)<sup>41</sup>, a negative PCR does not rule out fetal infection. Although the specificity of PCR is almost 100% in reference laboratories much lower rates have been reported for some laboratories<sup>42</sup>. Consequently, in the absence of good quality control, some women with false positive PCR results will be prescribed pyrimethamine-sulphonamide.

Infected women usually undergo regular fetal ultrasound to detect ventricular enlargement and intracranial calcifications. The latter has rarely been reported before 22-24 weeks gestation. Late termination of pregnancy may be offered if fetal infection and ultrasound abnormalities are confirmed. However, terminations have been reported in women solely on the basis of a positive IgM test<sup>37</sup>.

**Summary: There are known harms associated with fetal diagnosis and no evidence that diagnosis leads to a beneficial change in antibiotic treatment.**

### ***3.3 Postnatal diagnosis of congenital toxoplasmosis***

The reference standard for the diagnosis of congenital toxoplasmosis is the persistence of toxoplasma-IgG beyond 12 months of age. A positive diagnosis can be made earlier, given a positive PCR result or specific IgM or IgA antibodies detected in peripheral (not cord) infant blood samples. The early exclusion of congenital infection, to avoid unnecessary postnatal treatment, is more problematic. Exclusion of congenital infection is based on undetectable antibodies, usually between 6-12 months of age, in the absence of treatment<sup>43</sup>. The sensitivity of tests for IgM or IgA in early infancy is limited: estimates range from 73% (95% CI: 62-82%)<sup>44</sup> in infants of women treated prenatally, to 85% (95% CI: 71% to 99%) for children born to untreated women<sup>15</sup>. This means that a negative test in early infancy does not rule out congenital infection. In order to avoid

unnecessary treatment, some centres withhold treatment in children born to women infected in early pregnancy who are at low risk of congenital toxoplasmosis, provided IgG antibody levels decline during early infancy<sup>10</sup>. An alternative strategy offered by specialist laboratories involves tests for specific antibody bands using the ELISA technique or immunoblot. Combinations of these tests have been reported to have a sensitivity of 98%<sup>45;46</sup>.

### ***3.4 Potential adverse consequences of screening***

At all stages in the screening pathway, the risk of harm is high and the benefits are uncertain. The potential benefits and harms are summarised in Table 2.

Evidence from a study in the Netherlands found that prenatal screening was not entirely acceptable to clinicians or patients in that country. Only 50% of infected women received treatment during pregnancy (six weeks of spiramycin-sulfadiazine treatment were recommended)<sup>12</sup> and the investigators were unable to persuade paediatricians to treat any of the 12 infected but asymptomatic infants identified.

### ***3.5 Cost of the screening programme***

Economic evaluations of screening for congenital toxoplasmosis require answers to two key questions: a) what is the risk of impairment due to congenital toxoplasmosis; and b) how much is this risk reduced by treatment? Studies to date have failed to undertake sensitivity analyses which simultaneously test the effect of a range of risk estimates and treatment effects and have not taken account of the costs relating to the large number of women falsely identified as positive<sup>47-51</sup>.

The current cost of serological testing for the prenatal screening programme in France is estimated to be 0.5 billion francs per year (approximately £50 million for 780,000 births per year), based on government figures for the amount reimbursed per test and the number of tests performed<sup>52;53</sup>. Costs of treatment or clinical care were not included. In the UK, prenatal screening would involve monthly re-testing of 90% of pregnant women at an approximate cost of £10 per sample tested for IgG and IgM. Assuming 6 repeat tests during pregnancy, prenatal screening would exceed £40 million per year

### ***3.6 Research agenda***

#### ***3.6.1 Monitoring the screening programme and quality assurance standards.***

Where screening programmes operate, quality control of serological and PCR testing is essential. A particular problem is the widespread treatment of women identified by tests for recent infection (rising IgG titre or low IgG avidity), most of whom were infected preconception. Notification of infected pregnant women would provide information on the size of this problem and make it easier to implement uniform criteria for prenatal treatment. Finally, information on the birth prevalence of congenital toxoplasmosis is essential to inform policy makers of the size of the problem, to monitor trends over time in response to policy or environmental changes, and to monitor regional differences.

### *3.6.2 Evaluation of treatment*

There have been no randomised controlled trials of prenatal screening for congenital toxoplasmosis. Given the low incidence of maternal infection, trials comparing screened with unscreened women would need to be prohibitively large. Few would regard trials which identify infected women and then randomise them to treatment versus no treatment as ethical. Information on the effect of prenatal treatment must therefore be drawn from cohort studies. These need to address the effect of prenatal treatment on functional impairment in the infected child.

Randomised controlled trials are required to determine the effect of postnatal treatment in children without signs of active disease at birth.

### *3.6.3 Evaluation of testing and follow up strategies*

Information is required on the predictive value of combinations of tests for maternal and congenital infection, treatment effectiveness and prognosis of infected children in order to devise efficient management and monitoring strategies.

## **4). ALTERNATIVE PREVENTION STRATEGIES**

### ***4.1 Primary prevention for pregnant women***

There is consensus that women should be provided with information about how to avoid toxoplasma infection before or early in pregnancy. However a French study found that only 17% of women who knew they were susceptible and had received health information reported any action to avoid infection<sup>54</sup>. A case control study in 6 European centres identified undercooked meat and cured meat products as the principal factor contributing to between 30% and 63% of infections in pregnant women. Contact with soil contributed to a substantial minority of infections (6% to 17%)<sup>2</sup> and soil contamination of unwashed fruit and vegetables has been reported as a risk factor in other studies<sup>55</sup>. Studies are required to determine the effect of health messages focussed on these risk factors on the incidence of infection in pregnant women.

### ***4.2 Primary prevention for the whole population***

Primary prevention of toxoplasma infection in the general population may have a much greater impact on morbidity and mortality from toxoplasmosis than strategies confined to pregnant women. Primary prevention strategies could include veterinary public health interventions, such as labelling to indicate toxoplasma-free meat and improved farm hygiene to reduce animal infection. Research is required to determine the feasibility and effects of these approaches on toxoplasma infection and associated morbidity across the population as a whole. There is evidence that mortality and morbidity due to postnatally acquired toxoplasmosis, both in immune competent and deficient individuals far exceeds the burden of disease due to congenital toxoplasmosis<sup>56</sup>. If a societal perspective of the potential costs and benefits is taken, primary prevention may be the most rational option

## 5). NEONATAL SCREENING

Neonatal screening aims to identify neonates with congenital toxoplasmosis, most of whom would be asymptomatic, so that treatment can be offered and infants monitored so that problems are detected early.

### *5.1 The screening test*

Neonatal screening programmes operating in Massachusetts<sup>13</sup>, Poznan (Poland)<sup>57</sup> and Denmark<sup>15</sup> are based on the detection of toxoplasma specific IgM on Guthrie card blood spots. The sensitivity of the test is 85%<sup>15</sup> and the predictive value has been reported to be 50% or more in all<sup>13;15;57</sup>. There is some evidence that screening misses a small number of severely affected children who are IgM negative<sup>13;57</sup>.

### *5.2 Treatment of congenitally infected infants*

Treatment regimens vary from 3 months of pyrimethamine-sulphonamide alternating with spiramycin in Denmark, to 12 months in Massachusetts. Children with clinical signs are usually prescribed continuous pyrimethamine-sulphonamide therapy for one year<sup>13</sup>. Pyrimethamine and sulphadiazine (or sulphadoxine) has been shown to be effective against the tachyzoite form of the parasite in children with AIDS<sup>27</sup>. However, no comparative studies have been published of the effect of postnatal treatment versus no treatment, or of treatment duration on the risk of clinical signs or impairment in the long term.

### *5.3 Adverse effects of treatment*

Permanent or temporary discontinuation of therapy due to adverse side effects has been reported in 10% to 35% of children<sup>13;58</sup>. Pyrimethamine and sulphadiazine, or sulphadoxine (fansidar) have a depressive effect on IgG production<sup>59;60</sup> but whether this has any effects on childhood response to infective agents is not known. Fatalities due to Steven's Johnson syndrome have been reported as a rare, potential adverse effect of fansidar<sup>61</sup>. Spiramycin, commonly prescribed in an alternating regimen with pyrimethamine-sulphonamide, has been associated with a prolonged Q-T interval on electrocardiograms in preterm infants and with cardiac arrest in two infants<sup>62</sup>.

### *5.4 Costs*

The cost of neonatal blood spot screening and confirmatory testing has been estimated to be approximately one-tenth of the cost reported for prenatal screening in France for the same size population (personal communication, Eskild Petersen, Denmark).

### **Summary**

**The detection of specific IgM on neonatal blood spots is feasible, moderately sensitive, highly specific and low cost. However, the benefits of early treatment with the regimens currently available have not been evaluated in a randomised controlled trial and the optimum duration of treatment is not known.**

## **CONCLUSIONS**

### **Prenatal screening**

- ◆ Congenital toxoplasmosis is estimated to affect approximately 1 in 10,000 live births in the UK. Less than 5% have severe neurological impairment detectable in infancy and approximately 20-30% of infected children are expected to have intracranial or ocular lesions by three years old. The effect of congenital toxoplasmosis on developmental and visual impairment in later childhood is unknown.
- ◆ There is a lack of evidence for latent phases when treatment might prevent transmission of the parasite to the fetus or fetal organ damage. Cohort studies provide no clear evidence for a beneficial effect of prenatal treatment on mother to fetus transmission or clinical signs in the infected child.
- ◆ The effect of prenatal treatment on functional impairment in later childhood is unknown.
- ◆ Serological screening would be very labour intensive, require substantial service investment, and additional antenatal clinic visits. A large proportion of women identified by screening would be falsely positive or have been infected before pregnancy.

### **Neonatal screening**

- ◆ Neonatal screening is technically feasible and would not result in an excessive burden of false positive results.
- ◆ No comparative studies have evaluated whether postnatal treatment has any effect on clinical manifestations in infected children. Adverse effects of treatment are common.
- ◆ Randomised controlled trials are required to determine the effectiveness of antibiotic treatment during infancy on clinical signs and developmental function.

### **Primary prevention**

- ◆ Information about how to avoid toxoplasmosis in pregnancy may be the most cost effective approach to preventing congenital toxoplasmosis. The feasibility and effects of veterinary public health strategies, such as meat labelling and improved farm hygiene should be explored.

This working paper was prepared by Dr Ruth Gilbert and Professor Catherine Peckham from the Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, London and amended after the working group meeting in December 2000. Submitted to the Antenatal Screening Subgroup in March 2002

**Figure1.**

**Congenital Toxoplasmosis and Associated Clinical Signs:**

**Estimated annual risk in UK population assuming 750,000 livebirths per year**

Susceptible pregnant women (estimated at 90%)	675,000
Maternal infections in pregnancy (assume 0.5/1000 susceptible pregnancies)	345
Fetal infections (assume an overall transmission rate of 20%)	69
Clinical signs in infected children (assume that 20% have signs by 3 years*)	14
Severe impairment (assume 5%)	3

\* the significance of these is not clear

**Table 1.**

**Results from population-based cohort studies to show the incidence of maternal infection (per susceptible 9 month pregnancy) and the birth prevalence of congenital toxoplasmosis.**

Study, Country and recruitment period	Number of pregnant women (% immune)	Number of seroconverting women	Incidence /1000 susceptible pregnancies	Number of live births with congenital toxoplasmosis	Birth prevalence of congenital toxoplasmosis/10,000 live births
Conyn van Spaendonck <sup>12</sup> Netherlands 1987-1988	28049 (45%)	55	5.4 (4.1-7.1)	12	4.3 (2.2, 7.5)
Lappalainen et al <sup>63</sup> Finland 1988-1989	16733 (20%)	28	3.4 (2.3-4.9)	4	2.4 (0.7, 6.1)
Lebech et al <sup>15</sup> Denmark 1992-1996	89873 (28%)	141	2.9 (2.4-3.4)	26	3.0 (1.98-4.37)
Ancell et al <sup>4</sup> France 1995*	12919 (54%)	32	8.1 (5.7-11.7)		10*
Evengard (2001 in press) Sweden 1997-9	40978 (14%)	12	0.5 (0.26-0.89)	3	0.73 (0.15-2.14)
Norway 1992-1993 <sup>64</sup>	33740 (11%)	17	0.82 (0.48-1.32)	11	3.3 (1.63-5.83)
Guerina Massachusetts <sup>13</sup> 1986-1994	635,000 (10%)			48	0.8 (0.6-1.1)
Paul Poznan, Poland 1999-1998 <sup>57</sup>	27516 (59%)			13	4.7 (2.5-8.1)

All figures take account of mean interval between last negative and first positive test and corrected for a 9 month pregnancy (seroconversion observed over an interval of 25 to 30 weeks according to centre).

\* estimated figure assuming transmission risk of 29%

**Table 2. Summary of potentially beneficial and harmful consequences of prenatal screening for toxoplasmosis**

<b>Intervention</b>	<b>Benefits</b>	<b>Harms</b>
<b>Prenatal drug treatment</b>	May reduce transmission risk and risk of clinical manifestations in infected children	<b>Pyrimethamine-sulphonamide:</b> bone marrow depression (dose dependent), respiratory distress, tachycardia, convulsions, haematuria, renal failure, gastrointestinal upset, rash. Teratogenic in rats. Fansidar (pyrimethamine-sulphadoxine) has been associated with fatalities due to Steven's Johnson syndrome.
<b>Postnatal drug treatment</b>	May reduce appearance of retinochoroidal lesions after birth and associated visual impairment.	Inconvenience of giving medication throughout infancy. Pyrimethamine-sulphonamide: (as above) Spiramycin: prolonged Q-T interval and cardiac arrests have been attributed to spiramycin treatment.
<b>Amniocentesis</b>	Informs change in treatment. Positive results lead to immediate postnatal assessment and treatment. Negative result may provide reassurance.	Fetal loss, maternal discomfort. Most women have a negative result and must wait till late infancy to exclude congenital infection.
<b>Fetal ultrasound</b>	Reassurance if no abnormalities. Informs decision to terminate if lesions found.	Findings are poorly correlated with subsequent impairment. Requires monthly visits.
<b>Termination</b>	Allows informed choice about pregnancy	A substantial proportion of normal fetuses are likely to be terminated.
<b>Blood sampling</b>	Allows confirmation of infection status Allows titration of dosage of pyrimethamine-sulphonamide against blood count.	Painful and distressing, particularly for children.
<b>Routine ophthalmic examinations</b>	Early detection of sight threatening lesions and assessment of vision. May detect active lesions, which may benefit from treatment. Exchange of information with parents.	Examination is difficult and distressing. Anxiety that a sight threatening lesion could appear at any age. Implications for employment in later life.
<b>Information from results in early infancy</b>	Positive IgM/IgA in early infancy rules in congenital toxoplasmosis.	Most parents have a child with negative results and must wait till IgG antibodies disappear in late infancy.

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