UK National Screening Committee

Antenatal screening for Toxoplasmosis

External review against criteria set by the UK National Screening Committee (UK NSC)

Version: Final

Dr Jean Chapple,

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

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Abbreviations and glossary

T.gondii - Toxoplasma gondii - intra cellular organism that causes toxoplasmosis

CDC Centers for Disease Control and Prevention - one of the major operating components of the US Department of Health and Human Services

CSF Cerebro spinal fluid

DEFRA Department for Environment, Food & Rural Affairs

IgA Immunoglobulin A - an antibody plays a critical role in mucosal immunity

IgM Immunoglobulin M - a basic antibody is produced by white blood cells. It is the first antibody to appear in response to initial exposure to an antigen

KQ Key questions

NPV Negative predictive value

NSC National Screening Committee

PCR Polymerase chain reaction - a technique in molecular biology used to amplify a single copy or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.

PHE Public Health England

PPV Positive predicted value

SNSD Serious neurological sequelae

SOG Canada Society of Obstetricians and Gynaecologists of Canada

SYRCOTT Systematic Review on Congenital Toxoplasmosis study group, a European group of experts

Plain English Summary

Toxoplasmosis is a parasite that can infect most warm blooded animals, including humans. In most people the infection will be harmless and they won't have any symptoms. In the small amount of people that do have symptoms they will normally only experience a mild flu-like illness. Once a person has been infected with toxoplasmosis and has recovered they are usually protected from future infections. This is also true for pregnant women; an unborn baby is typically protected from toxoplasmosis if the mother had an infection in the past.

A pregnant woman with no history of infection can pass on toxoplasmosis to their unborn baby if they are exposed. Babies born with toxoplasmosis infections could have serious complications with their nervous system, eyes, heart and brain. However, the exact symptoms a baby might experience and how serious those symptoms might be is unclear.

Toxoplasmosis infections are common; infections are thought to be spread through the handling of uncooked meats, contaminated soil and cat litter. Because of the protection that a previous infection provides, infections in newborns are much rarer. It is not known how many women in the UK have no history of infection. In the UK, pregnant women are given advice to prevent infection. The most common advice aims to improve awareness of toxoplasmosis and to improve basic hygiene. The UKNSC review found that the advice does educate pregnant women about the risks but it was unclear if it changes their behaviour.

Some European countries currently screen for toxoplasmosis in pregnancy. When a woman is found to have no history of infection she will receive further tests throughout her pregnancy. If the screening test finds an infection further tests may be given to find out if the infection was recent. Pregnant woman with a recent infection may be given a test to see if the infection has been transmitted to the fetus. There are concerns about the accuracy of the screening tests, particularly in newborns. Some countries appear to have problems with adherence to the screening programme. There is also a reasonable risk that women are incorrectly told that they have a low risk of infection.

Toxoplasmosis infections are usually treated with antibiotics. It is unclear if treating the mother reduces the chance of passing the infection on to the baby or if it reduces the severity of symptoms in babies born with an infection. It is also uncertain what the best treatment for a baby with toxoplasmosis should be.

Many countries that currently screen for toxoplasmosis are considering removing the programme. It is increasingly believed that the effectiveness of a screening programme is limited. The adherence and management of screening programmes is not well understood. Furthermore, there are few effective options of for women and children who are at risk after the screening test.

Executive summary

Background

Toxoplasmosis is a common infection caused by the intracellular parasite *Toxoplasma gondii* (often shortened to *T.gondii*). It is found in a wide range of warm blooded animals across the world. Eighty to ninety per cent of acute infections in humans are asymptomatic, in the minority that are symptomatic patients are likely to just experience mild flu like symptoms. Once the immune system has responded to primary infection, the individual will remain sero-positive and protected from a repeat infection; this extends to fetal protection in previously infected mothers. In adults, toxoplasmosis can infect the eyes and lead to partial or complete loss of vision.

Primary infections in pregnant women are normally asymptomatic in the mother; however there is a low risk of transmission to the fetus. Although rare, congenital toxoplasmosis (infections in the infant) can cause severe permanent neurological or ocular disease (retinochoroiditis) leading to blindness, as well as cardiac and brain anomalies. In the 2011 UK NSC review, congenital toxoplasmosis was estimated to affect 1/10,000 live births, of which less than 5% would have severe neurological impairment and 20-30% would have intracranial or ocular lesions by three years old.

The current UKNSC recommendation is based on narrative reviews done in 2011 and 2006. The review's main conclusion was to highlight significant uncertainty about the burden of disease in infants, the effectiveness of treatment (neonatal and maternal) and accuracy of the screening tests.

Since 2011, there have been a number of reviews on toxoplasmosis infection and screening that bring current knowledge up to date. All emphasise the need for improved surveillance of the infection in the general population and in pregnant women. There is now more information on toxoplasmosis in immuno-compromised individuals such as people with HIV or who have had organ transplants who are at particular risk of reactivated infections.

Major publications giving the evidence for policies on toxoplasmosis or new information on toxoplasmosis in the UK since 2011 are:-

- UK Advisory Committee on the microbiological safety of food. Risk profile in relation to toxoplasmosis in the food chain. September 2012 http://www.food.gov.uk/sites/default/files/multimedia/pdfs/committee/acmsfrtaxopasm.pdf
- DEFRA and PHE Zoonoses Report 2012 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/236983/pb13987-zoonoses-report-2012.pdf
- Halsby K, Guy E , Said B, Francis J, O'Connor C, Kirkbride H, Morgan D Enhanced surveillance for toxoplasmosis in England and Wales,2008–2012 Epidemiol. Infect. (2014), 142, 1653–1660 – a response to a request for better surveillance of toxoplasmosis from the UK Advisory Committee on the microbiological safety of food
- Society of Obstetrician and Gynaecologists of Canada: prevention, screening and treatment guidance [published 2013]
- Di Mario e al., 2013 - Prenatal education for congenital toxoplasmosis A Cochrane review
- Corticosteroids as adjuvant therapy for ocular toxoplasmosis. Jasper S, Vedula SS, John SS, Horo S, Sepah YJ, Nguyen QD. Cochrane review 2013. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007417.pub2/pdf

2015 UKNSC review

The 2015 UKNSC update is a rapid review of the 5 clinical questions highlighted in the 2011 review. The findings for each of those key questions are as follows:

What is the spread and burden of toxoplasmosis?

- No studies were identified that addressed the uncertainty around the burden of disease in either congenital or maternal toxoplasmosis infections, within a UK population.

What is the prevalence of sero-negative women in the UK?

- The prevalence of seronegative women in the UK remains unclear. Demographic changes in recent years may challenge the historical data we currently have – specifically increasing maternal age at pregnancy and migration patterns of women entering the UK from countries with toxoplasmosis prevalence significantly different from the UK

How effective are the primary prevention interventions for toxoplasmosis?

- The UK has, like other countries, comprehensive literature offering pre-natal advice on prevention of toxoplasmosis. However a recent Cochrane review suggested that this information increases awareness but, crucially, not preventive behaviour. This review and poor understanding of the source of infection (uncooked meats, the environment and cats) questions the assumption that information giving is effective in primary prevention.

What is the diagnostic accuracy of the screening tests?

- There remain concerns about the poor performance of IgM and IgA tests in newborns.
- There are concerns about the adherence to screening polices with multiple antenatal appointments and tests. Recent papers have concentrated on adherence to screening protocols rather than on whether sero-positive women are missed because of deficient screening tests and how many sero-negative women are incorrectly put in a low risk group.

What is the effectiveness of antenatal and postnatal treatment of toxoplasmosis?

- Despite recent published research, there is still uncertainty about whether maternal treatment can reduce the severity of congenital cases in the newborn. There is some evidence that trying to prevent maternal-fetal transmission is of benefit but there are still significant limitations with the studies that report these outcomes.
- The correct neonatal treatment regimen is still unclear. A recent Cochrane review could not demonstrate whether corticosteroids as adjunct therapy (that is, additional) to anti-parasitic agents improve effectiveness of treatment of ocular toxoplasmosis.

Since the last policy review, no new evidence has come to light on any above that would change the recommendation that screening for toxoplasmosis in pregnancy or in the newborn period should not be offered.

Conclusions

- There have been no major changes in the state of knowledge of toxoplasmosis screening and treatment since the 2011 review.
- Countries that have been running screening programmes for many years are questioning their national policy. Denmark has stopped its newborn blood spot screening programme and France is awaiting the results of a large multi centre randomised controlled trial of prevention of mother to child transmission.
- All countries running screening programmes report a rise in the proportion of pregnant women who are sero-negative and who subsequently need further screening for acute infection during their pregnancy.

Introduction

Toxoplasmosis is a common infection caused by the intracellular parasite *Toxoplasma gondii* (often shortened to *T.gondii*); it is found in a wide range of warm blooded animals across the world. Eighty to ninety per cent of acute infections in humans are asymptomatic. In the minority that are symptomatic patients are likely to experience only mild flu like symptoms[1]. Once the immune system has responded to primary infection, the individual will remain sero-positive and protected from a repeat infection; this extends to fetal protection in previously infected mothers.

The most common routes of human infection are thought to be through toxoplasmosis oocyst contamination of the environment (such as water, soil with cat faeces) and the handling and consumption of undercooked meat. However, the relative contribution of each to the total number of infections in England and Wales is unknown[2]. Most countries rely on public health messages about hand washing and food handling to prevent primary infection. Sero-prevalence in adults varies considerably with high sero-prevalence (> 50%) occurring in countries where raw meat is commonly eaten (such as France, 54%[3]) and in tropical regions of Latin America or Sub-Saharan Africa where cats are numerous and the climate is favourable to oocyst survival[4].

The monitoring of human infections in the UK is variable across the 4 countries, toxoplasmosis is not a notifiable disease in England & Wales but it is notifiable in Scotland. There are two surveillance systems that provide minimum figures of new infections. The Department for Environment, Food & Rural Affairs (DEFRA) collects figures on laboratory confirmed infections in humans in the UK. Since 2011, in Scotland, efforts also have been made to differentiate as clearly as possible between recently acquired infections and identifications of infections that may have been acquired longer ago, reporting only those which are believed to have been acquired during the reporting period.

Primary infections in pregnant women are normally asymptomatic in the mother but there is a low risk of transmission to the fetus. Although rare, congenital toxoplasmosis (infections in the infant) can cause severe permanent neurological or ocular disease (retinochoroiditis) leading to blindness, as well as cardiac and brain anomalies. In the 2011 UK NSC review, congenital toxoplasmosis was estimated to affect 1/10,000 live births, of which less than 5% would have severe neurological impairment and 20-30% would have intracranial or ocular lesions by three years old.

The gestational age at which seroconversion occurs is an important risk factor for serious outcomes in the infant. The placenta remains infected for the duration of the pregnancy and may act as a reservoir supplying viable organisms to the fetus throughout pregnancy. Infection early in pregnancy appears to increase the risk of a higher burden of congenital disease, but the risk of transmission to the fetus is lower. In contrast, the risk of transmission is higher when the maternal infection is later in the pregnancy but the severity of the outcome in a neonatal transmission is considerably lower. The maternal-fetal transmission rate increases with gestational age at maternal seroconversion, from less than 15% at 13 weeks of gestation to over 70% at 36 weeks[5]. Transmission to the fetus may occur in women who acquire their primary infection during pregnancy. Rarely, congenital transmission has been detected in chronically infected pregnant women whose infection was reactivated because they were immune-compromised by drugs or infection such as HIV.

The diagnosis of toxoplasmosis in pregnancy based on symptoms alone is not a viable measure to detect infection, as symptoms (if present) are often nonspecific. Only serological testing can determine immuno-competency and the diagnosis of subsequent infection in women who were originally sero-negative. In the mother, IgG and IgM assays are thought to be the most appropriate test but these tests are complicated by the requirement of set cut-offs and the interpretation of possible outcomes. There is an estimated 6% false positive rate for a single test.

If both IgM and IgG are positive, further diagnosis is required to determine when the infection occurred and its duration. Generally, a positive IgG assay demonstrates a previous infection and a positive IgM assay suggests a recent infection. The diagnostic pathway is further complicated by tests to determine fetal transmission and possible infection in the neonate – some of which require invasive amniotic fluid and fetal blood samples.

Toxoplasmosis in pregnancy is normally treated with antibiotics (most commonly spiramycin), with further antibiotic treatment (sulfadiazine plus pyrimethamine) when transmission to the fetus is

confirmed or suspected. These treatments are thought to be limited and will not prevent all transmissions nor lessen the severity of symptomatic congenital toxoplasmosis in all foetuses that are infected in utero. Once born, neonates with congenital toxoplasmosis are treated with antibiotics (pyrimethamine and sulfadiazine), again with limited success. Research on more efficient treatments continues, primarily in countries that do screen, notably France.

Current policy

The UKNSC currently recommends screening for toxoplasmosis is not offered in pregnancy. The last evidence review that underpinned this recommendation was published in 2011 and concluded that there was no justification for screening for toxoplasmosis in pregnant women, noting the key findings listed below:

- The aim of a prospective screening policy is to determine if the women is sero-negative (had no previous infection) and is therefore susceptible to a primary infection (and if infected, carries a risk of transmission to the fetus). This approach is recommended in some European countries. The screening pathway would require repeat tests throughout pregnancy on women initially found to be sero-negative.
- The false detection rate is high in maternal diagnostic tests (approximately 6% if one screening test is used).
- Women who test positive (and were previously seronegative) are not at significant risk of fetal infection.
- 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. Furthermore, it is suspected that pyrimethamine-sulphonamide is associated with serious adverse effects.
- The effect of congenital toxoplasmosis on developmental and visual impairment in later childhood is unknown.
- A systematic review carried out by the Systematic Review on Congenital toxoplasmosis study group (SYRCOTT), a European group of experts, concluded in 2007 that despite three decades of prenatal screening for congenital toxoplasmosis in some European countries there was still uncertainty about the effectiveness of prenatal treatment.

There is limited guidance on the management of toxoplasmosis in the UK. NICE guidance recommends that:

- Routine antenatal serological screening for toxoplasmosis should not be offered because the risks of screening may outweigh the potential benefits.
- Pregnant women should be informed of primary prevention measures to avoid toxoplasmosis infection.

The NICE Antenatal Care Guidance up date March 2013 found no new key evidence for screening. There are also UK Standards for Microbiology Investigations, published in 2012 by the HPA (now part of the PHE). International guidelines may provide more informative prevention strategies. Notable examples include the American CDC guidance and the Canadian SOG guideline.

Current update review

The current review considers whether the volume and direction of the evidence produced since the 2011 external review indicates that the previous recommendation should be reconsidered. Five criteria are considered in this update, with particular focus given to areas the 2011 review identified as uncertain, or supported by insufficient evidence. The main criteria and key questions reviewed are:
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Criterion	Key Questions (KQ)	# KQ Studies Included
1 - The condition should be an important health problem	What is the scale of toxoplasmosis infection? What is the severity of the condition and what are the implications of congenital toxoplasmosis on neonatal development?	78 Pregnancy outcome 14 Prognosis and long-term outcomes of congenital toxoplasmosis 13

2 - The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage	What is the prevalence of sero-negative women in the UK?	78
3 - All the cost-effective primary prevention interventions should have been implemented as far as practicable		24
5 - There should be a simple, safe, precise and validated screening test	This review addresses updates on the following questions on screening test accuracy: What is the accuracy of the detection of acute toxoplasmosis infection in the mother? In infected women can the test determine a recent infection from a chronic infection? What is the accuracy of the tests that determine mother to child transmission? What is the accuracy of the detection of congenital toxoplasmosis in the neonate? What is the accuracy of the detection of sero-negative women?	71 Antenatal (8) Antenatal/neonatal (2) Neonatal (18) General population (38) Reviews (5)
Criteria 8. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment	What is the effectiveness of antenatal and postnatal treatment of toxoplasmosis?	14 Antenatal (5) Antenatal and neonatal (2) Neonatal (7)

Method

A literature review was carried out by Paula Coles using Medline, Embase, and the Cochrane Library for publications between January 2010 and 22 September 2014. 287 relevant publications were identified

Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

Criterion 1 - The condition should be an important health problem

Background

The 2011 review reported that no evidence had been published that would alter the conclusion of an earlier UKNSC review (Gilbert and Peckham., 2002) that "congenital toxoplasmosis is estimated to affect 1/10,000 live births, of which less than 5% would have severe neurological impairment and 20 – 30% would have intracranial or ocular lesions by three years old".

Transmission to the fetus may occur in women who acquire their primary infection during pregnancy. Rarely, congenital transmission has been detected in chronically infected pregnant women whose infection was reactivated because they were immune-compromised by drugs or infection such as HIV. The placenta remains infected for the duration of the pregnancy and may act as a reservoir supplying viable organisms to the fetus throughout pregnancy. The maternal-fetal transmission rate increases with gestational age at maternal seroconversion, from less than 15% at 13 weeks of gestation to over 70% at 36 weeks[5].

In contrast, disease severity decreases with gestational age, with first trimester infection resulting in fetal loss or major sequelae. The overall risk of congenital infection from acute *T. gondii* infection during pregnancy ranges from 20% to 50% without treatment[6].

Over 90% of neonates with congenital infection show no clinical signs of infection at birth[7]. Neonates, when no treatment is given, are at substantial risk of developing long-term sequelae, including chorioretinal disease (up to 85% of infected children) and major neurological abnormalities, as well as psychomotor and mental impairments[8]. Acute maternal infection has also been implicated as a cause of intrauterine fetal death[9].

A cohort of 430 children infected with T. gondii alive in 2005 in Lyon found an overall transmission rate during primary infection was 30%. Retinochoroiditis incidence was 24% in the prospective cohort. During follow-up, recurrences appeared in 29% of cases[10].

Current UKNSC review question

As the burden of disease and incidence of toxoplasmosis is uncertain in the UK, the 2015 update review sought any large multicentre surveillance studies published since 2011 and undertaken within the UK, which would be able to describe the scale of toxoplasmosis infections and the burden of disease caused by congenital toxoplasmosis infection adequately.
The review focussed specifically on the uncertainties highlighted in the 2011 review:

- The risk of maternal infection on the pregnancy outcome
- The prognosis of congenital infection on the neonate
- The likelihood of severe outcomes in relation to when sero-conversion occurs and the suspected route of transmission to the neonate of congenital toxoplasmosis on neonatal development

Description of evidence

78 papers on the epidemiology of toxoplasmosis were identified in the update search. Of those, three were surveillance studies; one study reported on the global burden of disease, one study reported findings from the French screening programme with only one UK human surveillance study. Estimates of congenital infection vary by more than a hundred fold.

<u>Global burden</u>
A 2013 WHO review of the global burden of toxoplasmosis from nine data bases concluded that the global incidence of congenital toxoplasmosis was 1.5 per 1000 livebirths with high burdens seen in South America, Middle Eastern and low-income countries[11]. The WHO report included country specific outcomes that were made using different methods of surveillance, definitions of disease and modelling of data. Furthermore, no details are given on the source of the denominator data. Finally, it

is noted that waterborne toxoplasmosis is increasingly recognized in outbreaks and in endemic areas and can result in posterior uveitis at any age – therefore estimates of ocular toxoplasmosis in young children cannot be assumed to be the result of congenital infection.

England & Wales

Although toxoplasmosis is not a notifiable disease in England and Wales, the UK Advisory Committee on the Microbiological Safety of Food has recommended that more accurate figures on the burden of disease in the UK are needed[12]. In 2012, the first five years of data (2008-12) from an enhanced surveillance scheme were published. The authors state there may be under ascertainment of cases, with only more severe cases being reported. They do not comment on whether infected pregnant women were more likely to be seen as 'serious' and reported. There were 190 pregnant cases (including 12 who were both pregnant and immuno-suppressed with HIV) and 33 congenital cases. 179 of the mothers had acute infection and 11 had indeterminate infection. Thirty of the congenital cases had acute infection, and three had reactivated infection. From these cases, 29 mother–child pairs could be identified. Of the 33 congenital cases, seven were defined as in utero infections, 24 occurred in infants aged <1 year, and two were in children aged 1–9 years. One of these two children had been a congenital case at birth and first entered the dataset when they developed eye problems in later childhood. The second was a reactivated infection that was diagnosed when the child was one year old).

Over three quarters of pregnant cases were asymptomatic while 28 (14.7%) suffered a fetal loss or stillbirth. The congenital cases were all classified as having congenital toxoplasmosis, but 16 reported additional symptoms, over and above the symptoms used to classify toxoplasmosis (Sabin's tetrad – hydrocephalus, chorioretinitis, convulsions, intracranial calcifications). There was one report of a death due to toxoplasmosis, in a 1-month-old male infant suffering from congenital infection[13]. There are no data on how many pregnancies are legally terminated because of fetal malformation from congenital infection.

There were 3,591,708 live births in England and Wales between 2008-12 recorded by ONS[14]. This gives a birth prevalence of congenital toxoplasmosis of 0.9 reported cases per 100,000 live births. However, this should only be used as a calculated minimum birth prevalence because of possible under reporting and the limitations of the source data described above.

France

France implemented a national programme to prevent congenital toxoplasmosis in 1978 because of a reported high prevalence of sero-positive women at that time. The sero-prevalence has fallen from 84% of French women aged 15 to 45 in the 1960s to 44% in 2003[15]. In 2007, the national laboratory-based system for the surveillance of the disease reported a total of 272 congenital 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 per 10,000 live births and the incidence rate of the disease at birth was 2.9 per 10,000 live births; the estimated incidence rate of symptomatic congenital toxoplasmosis was 0.34 cases per 10,000 live births[16].

What are the implications of congenital toxoplasmosis on neonatal development?

The 2011 review concluded that "the effect of congenital toxoplasmosis on developmental and visual impairment in later childhood is unknown". There were 27 papers on the outcome of infection found in the update search; however none of these studies were included in the review as they did not report outcomes on the natural history of a maternal or congenital infection, within a UK (or analogous) population.

Criterion 1. Not met. There have been no new papers published that give reliable estimates of Toxoplasma infections in general populations, pregnant women or neonates. Estimates of congenital infections vary by more than a hundred fold. No evidence was identified that provides any more information on the burden or progression of toxoplasmosis infections in either the mother or the neonate.

Criterion 2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

Background

Congenital toxoplasmosis is caused by a maternal primary infection. Appraisal of the screening test for susceptibility, interventions and prospective screening pathway needs reliable information on the sero-prevalence of toxoplasmosis and the proportion of sero-negative women in the UK.

Toxoplasma sero-prevalence is known to vary geographically and with age. In general, tropical regions of Latin America or Sub-Saharan Africa where cats are numerous and the climate is favourable to oocyst survival and countries where consumption of uncooked meat is common have higher population rates of infection. Whilst antibodies are found in 20 - 40% of adults in the UK and USA, sero-prevalence is higher in Central Europe, South and Central America, and in West Africa (50-80%) and similar or lower in South East Asia, China and Korea (4-39%) and Scandinavia (11-28%). From studies undertaken since the early 1990s, sero-prevalence in Europe varied from 8.1% in the UK to 77.4% in the former Yugoslavia[17].

Current UKNSC review

The 2015 update review aimed to assess the volume and direction of evidence, published since 2011, on the prevalence of toxoplasmosis in the UK, with particular reference to the proportion of women who are sero-negative. As the incidence rate of toxoplasmosis is associated with lifetime exposure and location, sub-group analysis of these risk groups will be considered separately.

Description of evidence

78 papers published on the epidemiology of toxoplasmosis since 2011, from which there are 4 new papers on the epidemiology of toxoplasmosis in the UK.

<u>Prevalence of toxoplasmosis in England & Wales</u>

The majority of papers published since 2011 reported international general prevalence rates – 39.3% in Iran[18], 27.97% in Mexico[19] and up to 54 % in southern European countries such as France and Italy[20]. All countries monitoring both general and pregnant populations report a decline in prevalence over the last two decades[21]. Since Austria and France established prenatal screening, the prevalence of toxoplasmosis has declined from 50% to 35% and 84% to 44% respectively[22]. This decrease is in part attributable to a decrease in infection in childhood, probably associated with increased standards of living, and has also been linked to changes in meat husbandry and consumption. All countries report increasing prevalence of toxoplasmosis antibodies with age, presumably as older people have a greater life time exposure to infection.

As the prevalence of toxoplasmosis infection falls in the general population, there is an increased proportion of women susceptible to infection in pregnancy and a potential increase in the incidence of congenital toxoplasmosis. However, resources needed for screening increase as the population prevalence falls, because antenatal screening programmes identify a greater proportion of susceptible women who then need monitoring for acute infection throughout pregnancy. Programmes vary in their protocols, but most specify initial testing by the end of the first trimester and at least one test in each of the following trimesters, In France, monthly testing is advised.

Historical antibody prevalence studies suggest that levels of toxoplasmosis are lower in the UK than in many other European countries, with between 7% and 34% of the UK population infected prior to 2001[23]. Data from three studies carried out around 1989-1992 in Sheffield, the East of England and Wales provide some limited data on sero-prevalence in women of child-bearing age ranging from 8-10% in England to 22% in Wales, whereas a prevalence of 50% has been found in the over 50s. Similar sero-prevalence results have been found in Scotland. These apparent variations in sero-prevalence within England and Wales have been confirmed in a systematic study of blood donor sera

collected from throughout the British Isles during 1990-1991[24]. There have been no more recent UK studies to look at antibody status in the general or pregnant populations.

Sub-group analysis of demographic changes in the UK
There have been considerable changes in the demographics of pregnant women in the UK over the last two decades that may have an effect on the proportion of women are seronegative for toxoplasmosis in pregnancy and therefore susceptible to a primary toxoplasmosis infection in pregnancy - maternal age and the proportion of mothers who were born outside the UK.

Maternal age
As lifetime exposure to toxoplasmosis increases with age, an increase in the age at which women have children may decrease the numbers of sero-negative women. The average age of mothers in England & Wales has been increasing since 1975 with increasing numbers of women delaying childbearing to later ages. This may be due to a number of factors such as increased participation in higher education, increased female participation in the labour force, the increasing importance of a career, the rising opportunity costs of childbearing, labour market uncertainty, housing factors and instability of partnerships[25].

Table 1 Comparison of first births in 1970, 2011 and 2012 (Source ONS)

	1970	**2011**	**2012**
% of births to women aged over 35 that are first births	10.0%	27.7%	25.0%
% of first births that are to women aged over 35	2.1%	13.0%	12.9%
% of all births that are to women aged over 35	7.9%	20.0%	19.8%

Table 2 Comparison of maternal age and place of birth 2010-2013 (Source ONS)

Year	Mothers aged 30 and over as % of all births	Mean age of first time mothers	Mean age of all mothers	Mothers born outside the UK	Most common countries of birth for mothers born outside the UK
2010	48%	27.8 years	29.5 years	25.1%	Poland
2011	49%	27.9 years	29.7 years	25.5%	Poland
2012	49%	28.1 years	29.8 years	25.9%	Poland
2013			30.0 years	26.5%	Poland, Pakistan and India

Mothers born outside the UK
Travel exposes people to diseases which may be relatively rare in their country of birth. Theoretically, migration means that women who have been born and lived for part of their lives in another country with a high prevalence of toxoplasmosis may be more likely to be protected against toxoplasmosis infection in pregnancy as they have already been infected, but there have been no epidemiological studies in the UK that adequately assesses this hypothesis. A small study in Italy showed a higher proportion of sero-positivity in pregnant immigrant women in a very specific and local population[26]. This contrasts to another small area of Italy where all congenital toxoplasmosis cases occurred in women from Africa, Asia, Eastern Europe and South America and none in women who had always lived in Italy[27].

The proportion of births to mothers born outside the UK has increased every year since 1990 when it was 11.6 per cent. By 2001, it was 16.5% and by 2005 20.8%[28] . In recent years, the highest proportion of mothers born abroad was from Poland. Sero-prevalence during a 6-year study of pregnant women in Poland decreased from 45.4% in 1998 to 39.4% in 2003, with a yearly decline in prevalence of 1.0%[29].

Surveillance
Public Health England and the Public Health Wales Toxoplasma Reference Unit in Swansea established an enhanced surveillance system for toxoplasmosis in 2008. The system is designed to

collect incidence data, primarily in vulnerable clinical groups in the UK where the infection represents the greatest risk to health. The first 5 years of data from an enhanced surveillance scheme for toxoplasmosis in England and Wales was published in 2013[30]. Between 2008 and 2012, 1824 cases were reported, with an average of 365 each year. There were 1109 immuno-competent cases, the majority presenting with lymphadenopathy, and 364 immuno-suppressed cases, with central nervous system and systemic symptoms most frequently reported. There were also 190 pregnant and 33 congenital cases. The authors are open about the limitations of their study. It is likely that only severe cases of toxoplasmosis are reported (and the effect of this on the reporting of infected pregnant women and babies with congenital toxoplasmosis is unknown) as samples are referred to the Toxoplasma Reference Unit only where primary testing is equivocal or where confirmation will help to exclude other diagnoses that might require significant clinical intervention. Surveillance does not include any estimate of the proportion of women who are sero-negative.

Table 3 UK confirmed human cases of toxoplasmosis, confirmed by laboratory 2010-2012[31]

Year	England & Wales	Scotland	Northern Ireland	UK total
2010	345	67	2	414
2011	341	62	0	364
2012	311	16	0	327

Criterion 2. Not met. An enhanced surveillance system for toxoplasmosis in England and Wales was established in 2008 and its first report published in 2014. However, the authors acknowledge that under reporting is likely. No data on the proportion of women who are sero-negative are available. Health Protection Scotland established a notification system in 1990, but no reviews of congenital toxoplasmosis or prevalence in pregnant women or the general population have been published since its introduction.

There have been considerable changes in the demography of pregnant women in England and Wales over the last two decades which may theoretically have a small effect on the prevalence of sero-negative women. It is likely that sero-negativity in the UK has risen in line with countries where prevalence has been monitored but no evidence for this was identified.

Criterion 3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

Background

In the UK, toxoplasmosis primary prevention is recommended by NICE guidance[32]. In common with many other countries, UK recommendations advise women on the measures they can take to avoid contact with the common sources of toxoplasmosis infection. There is a summary of advice given in different countries in an appendix of the 2012 Advisory Committee on the Safety of Food risk profile in relation to toxoplasmosis in the food chain 2012[33].

Hygiene measures such as hand washing and careful food handling and storage can offer protection against many infectious diseases that can cause problems in pregnancy including influenza, listeriosis, cytomegalovirus and salmonella as well as toxoplasmosis, but guidance on toxoplasmosis does not stress the universal importance of hand washing and food hygiene to prevent a range of infections which can complicate pregnancy.

Current UKNSC review

The 2011 review concluded *"Primary prevention of congenital toxoplasmosis is a desirable intervention and its benefits have been shown to be effective in observational studies. Further RCT's have been recommended to confirm the benefits of this approach and to quantify the impact of different educational interventions"*

The 2015 review aimed to assess the volume and direction of evidence, published since 2011, on the effectiveness of pre-natal advice on the prevention of toxoplasmosis.

Description of evidence

There were 24 papers identified in the update search that looked at knowledge of pregnant women and professionals and what advice is given on primary prevention of toxoplasmosis, both domestically and internationally. All involved small numbers of women and professionals and all conclude that more information on primary prevention of infections, including toxoplasmosis is required.

A 2013 Cochrane review assessed the effects of prenatal education for preventing congenital toxoplasmosis and included data from two cluster-randomised controlled trials involving a total of 5455 women. Data could not be combined because of the high heterogeneity between the two trials. One study was from Canada and involved 432 women randomly assigned to a 10-minute presentation during prenatal class about toxoplasmosis prevention or to a usual prenatal class. Losses to follow-up were high and 285 completed the post-test questionnaire in the third trimester. Only 5% of the intervention women recalled having obtained information on toxoplasmosis prevention during prenatal classes.

The other trial, conducted in France, involved 5023 pregnant women with no evidence of toxoplasmosis infection (sero-negative) who were randomly assigned to receive a brochure and an audiotape containing information for toxoplasmosis prevention, or to usual prenatal class. Losses to follow-up were high and 2790 completed both pre-test and post-test questionnaire on behaviour (44.5% loss to follow-up), whereas 3949 women were tested for blood antibodies (22.4% loss to follow-up). Women's behaviour did not change after the intervention. Similarly, the sero-conversion rate was not statistically different between the two groups (13 out of 2591 women seroconverted in the intervention and four out of 1358 in the control group).The authors concluded that prenatal education for congenital toxoplasmosis has a significant effect on improving women's knowledge but has no effect on changing women's behaviour[34].

Are there other primary prevention interventions?
Public health interventions aimed at preventing all toxoplamosis infections such as reducing *Toxoplasma* in the food chain could have a beneficial effect for pregnant women[35] as well as the general population.

Toxoplasmosis is a potential cause of morbidity in all infected people and can be particularly serious in immune-compromised individuals, such as those with HIV or organ transplants. Several papers [36] [37] [38] [39] report an increase of pregnant women infected with HIV and also comment on the rising prevalence of HIV and transplants in the general population. The US Centers for Disease Control and Prevention CDC have targeted toxoplasmosis as one of five Neglected Parasitic Infections for public health action because of the number of people infected, severity of the illnesses and ability to prevent and treat them. These infections are considered neglected because relatively little attention has been devoted to their surveillance, prevention, and/or treatment. They include Chagas disease, cysticercosis, toxocariasis, toxoplasmosis, and trichomoniasis [40].

A vaccine based on the live attenuated S48 strain of toxoplasmosis has been developed for veterinary use but is not suitable for humans as it may revert to a pathogenic strain[41] [42]. The vaccine is expensive and does not store well, so is unlikely to be used to prevent the disease in animals.

An added complexity for primary prevention is that there are few studies on the primary source of infection. Most guidance for pregnant women emphases the role of cats in *Toxoplasma i*nfection, however it is unknown if it is more important for women to follow food hygiene advice. The 2012 food standards agency report on toxoplasmosis noted that four large case control studies (none from the UK) identified consumption of undercooked meat as the most important risk factor for pregnant women. Of those four studies, the largest and most geographically comprehensive study estimating this risk factor to account for 30-60% of cases. Whilst only a small number of outbreaks have been reported, the majority of these were linked to consumption of raw or undercooked meat or raw goat milk. However, risk factors reflecting environmental contamination were also identified in the case control studies. This study, added to the fact that strict vegetarians can become infected with *Toxoplasma*, shows that oocyst contamination of the environment can play an important part in infection[43].

The occurrence of waterborne outbreaks support a continuing role for oocysts in human infection but a recent study has shown that oocyst contamination of the environment is largely restricted to cat

defaecation sites. Less than 0.9% of cats have been found to actively shed *Toxoplasma*-like oocysts[44]. The Advisory Committee on the Safety of Food recommends surveillance of toxoplasmosis infections in humans, animals and the distribution of oocysts in the environment.

Criterion 3. Partially met. The 24 published papers look at knowledge of pregnant women and professionals and what advice is given on primary prevention of toxoplasmosis in different countries in different continents. All involved small numbers of women and professionals and all conclude that more information on primary prevention of infections, including toxoplasmosis is needed.

Hygiene measures such as hand washing and careful food handling and storage can offer primary protection against many infectious diseases that can cause problems in pregnancy, from influenza to listeriosis, cytomegalovirus and salmonella as well as toxoplasmosis. The published papers focused on prevention of toxoplasmosis, with very specific advice on handling cats and cat faeces because of the role played by felines as the only animals in which *Toxoplasma* can fully live out its life cycle and in which the sexually mature forms of the parasite occur. However, it is estimated that 30 to 60% of *Toxoplasma* infections are from undercooked meat and there are no figures on the proportion of infections from direct contact with cats (with less than 1% of cats actively shedding oocysts) or from oocysts in the local environment.

A 2013 Cochrane review assessed the effects of prenatal education for preventing congenital toxoplasmosis from two cluster-randomised controlled trials involving a total of 5455 women The authors concluded that prenatal education for congenital toxoplasmosis has a significant effect on improving women's knowledge but has no effect on changing women's behaviour[45].

Toxoplasmosis is a potential cause of morbidity in all infected people and can be particularly serious in immune-compromised individuals, such as those with HIV or organ transplants. Several papers report an increase of pregnant women infected with HIV and also comment on the rising prevalence of HIV and transplants in the general population. Public health interventions aimed at preventing toxoplamosis infections in both humans (and animals to reduce *Toxoplasma* in the food chain) could have a beneficial effect for pregnant women and the general population.

Criterion 5. There should be a simple, safe, precise and validated screening test

Background

International screening programmes usually offer screening for toxoplasmosis in early pregnancy using IgG, with further tests on women who are sero-positive to confirm diagnosis and see whether the infection occurred before or during the pregnancy using IgM levels. Women who screen sero-negative are offered further screening throughout pregnancy (at intervals ranging from monthly to once in each trimester) to see if they develop a primary infection during the pregnancy.

The 2014 Society of Obstetricians and Gynaecologists of Canada guideline provides the most recent outline of an international screening and diagnostic pathway:-
"The diagnosis of toxoplasmosis is typically made by serum testing. A test that measures immunoglobulin G (IgG) is used to determine if a person has been infected. It is particularly important in pregnant women to try to estimate the time of infection as this affects the risk of prenatal damage to the baby so a test which measures immunoglobulin M (IgM) is also used along with other tests such as an avidity test. The IgG avidity test measures the strength of IgG binding to the organism. Avidity, in most cases but not all, shifts from low to high after about 5 months. If the avidity is high, this suggests infection at least 5 months before testing"

The prevalence of chronic toxoplasmosis infections reported in the literature varies enormously. While this may be true variance due to different environmental and cultural factors, different methods used to diagnose acute and chronic infections can also contribute. Newer methods of diagnosis include the serum IgG avidity test, polymerase chain reaction (PCR) and Western blots of serum from mother-

baby pairs[46]. There is a wide range of commercial screening kits available, reference laboratories may use the Sabin-Feldman dye test and IgM ELISA test as more standardised but specialist diagnostic tests.

Diagnosis can be made by direct observation of the parasite in stained tissue sections, cerebrospinal fluid (CSF), or other biopsy material. These techniques are used less frequently because of the difficulty of obtaining these specimens. Molecular techniques that can detect the parasite's DNA in the amniotic fluid can be useful in cases of possible mother-to-child (congenital) transmission.

Ocular disease in infants is diagnosed based on the appearance of the lesions in the eye, symptoms, course of disease, and often serologic testing."

Current UKNSC review

The previous report noted that there were significant uncertainties around the screening and diagnosis of toxoplasmosis infection and susceptibility.

The 2015 review considered the volume and direction of evidence, published since 2011, on the diagnostic accuracy of tests to identify recent infection in mother and baby as well as the accuracy of tests in identified sero-negative women (and therefore, those susceptible to primary infections during pregnancy). The following sub-questions were undertaken:

- What is the accuracy of the detection of acute toxoplasmosis infection in the mother?
- In infected women can the test determine a recent infection from a chronic infection?
- What is the accuracy of the tests that determine mother to child transmission?
- What is the accuracy of the detection of congenital toxoplasmosis in the neonate?
- What is the accuracy of the detection of sero-negative women?

Description of the evidence

There have been 71 papers on diagnostic tests published since the last review.

<u>What is the accuracy of the detection of acute toxoplasmosis infection in the mother (IgM, IgG and IgA serological testing)? In infected women can the test determine a recent infection from a chronic infection?</u>

There were ten new papers on antenatal diagnosis of toxoplasmosis identified in the update search, the populations included in these studies ranged from 19 to 2000 women. All emphasised findings of false negative results, where women were initially found to be sero-negative but found to be sero-positive when another test was used.

Diagnosis of infection is based on tests on blood serum aimed at detecting IgM and IgG antibodies against *Toxoplasma gondii*. Seroconversion is defined by the appearance of IgG. However, IgM antibodies are not an accurate marker for discriminating between acute and latent infection. Detection of residual or persistent IgM may occur months or even years after primary infection, while the IgG avidity test is a rapid means of identifying latent infections in pregnant women who exhibit both IgG and IgM anti-*Toxoplasma* antibodies on initial testing during pregnancy. Commercial reagents continue to vary considerably in detecting low concentrations of antibodies during early seroconversion[47 48]. Positive results obtained in new highly sensitive *Toxoplasma* IgG assays have been observed in serum that gave negative results in reference assays. Four papers propose ways of refining diagnostic tests by neutralization assay[49], use of dense granule antigen gra6 in an IgG avidity test[50] and immunoblotting[51]. Avidity tests based on lysed whole-cell *Toxoplasma gondii* antigen are currently used to exclude recently acquired infections; however, the use of recombinant antigen(s) might improve the diagnostic performance of avidity tests and facilitate the development of more standardized assays[52].

A 2013 French study, assessed and compared the performances of four commercially available *Toxoplasma* IgG avidity tests in 206 immuno-competent and immuno-compromised patients with acute and latent toxoplasmosis[53].The positive predictive value of high avidity to confirm latent toxoplasmosis was 100% for all the assays, indicating that high avidity is a hallmark of latent infection.

However, the negative predictive value of high avidity ranged from 99.2% to 95.3% between commercial kits, indicating that acute toxoplasmosis could not be reliably diagnosed based on low IgG avidity alone. The authors conclude that the avidity test provides a rapid means for identifying latent *Toxoplasma* infection in immuno-competent pregnant women with both IgG and IgM anti-*Toxoplasma* antibodies on initial testing.

There were no new papers identified on the accuracy of IgA testing. IgA antibodies may be detected in sera of acutely infected adults and congenitally infected infants using ELISA or ISAGA methods. As is true for IgM antibodies to the parasite, IgA antibodies may persist for many months to more than one year. For this reason they are of little additional assistance for diagnosis of the acute infection in the adult[54].

What is the accuracy of the PCR tests that determine mother to child transmission?

If the mother has had an acute infection in pregnancy, diagnostic tests may be undertaken to see if fetal infection has occurred. Diagnostic tests include amniocentesis (with a small risk of causing miscarriage through the procedure) with polymerase chain reaction (PCR) testing of the amniotic fluid and ultrasound scanning to look for evidence of structural anomalies such as hydrocephalus caused by toxoplasmosis rather than detecting an infective agent.

There are considerable limitations to both tests. A 2002 prospective cohort study in nine European centres found in 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. 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[55]. There is no new information on the accuracy of PCR tests to confirm fetal infection. No new studies were identified that reported outcomes on the accuracy of ultrasound scans. Furthermore it should be noted that, without additional diagnostic testing of the fetus, it is difficult to attribute abnormalities found in the scan to Toxoplasma.

What is the accuracy of the detection of congenital toxoplasmosis in the neonate?
There were eighteen papers included from the update search, with a range of babies studied from 18 to 785. The papers studied a variety of sites that might show infection– blood, including dried blood spots, cerebro-spinal fluid and placentas.

Similar problems arise in confirming the diagnosis of congenital toxoplasmosis infection in babies as in mothers. Detection in the newborn is of limited use because of lack of knowledge about benefits from early treatment.

One paper looked at polymerase chain reaction in neonatal cerebrospinal fluid[56]. IgM and IgA antibodies and CSF PCR, when combined, yielded a higher sensitivity for diagnosis of congenital toxoplasmosis when compared with the performance of each test alone.

Researchers have looked at the possibility of using dried blood spots to look detect congenital toxoplasmosis using IgM Western blotting (WB), IgA enzyme immunoassay (EIA), and DNA amplification by real-time PCR. These give a low sensitivity but high specificity and are affected by card storage[57]. Newborn screening for toxoplasmosis using dried blood spots was terminated in Denmark August 2007, after it became apparent that no benefit of treatment could be shown.[58]

Even with using high sensitivity methods on fresh blood, newborns with congenital toxoplasmosis can have negative toxoplasmosis IgM at birth. In those who have these antibodies, the positive period may be quite short[59].

The increased sensitivity of IgA assays over IgM assays for diagnosis of congenital toxoplasmosis may represent an advance in diagnosis of the infection in the fetus and newborn. In a number of newborns with congenital toxoplasmosis and negative IgM antibodies, the serological diagnosis has been established by the presence of IgA and IgG antibodies. However, only one paper included the use of IgA in neonates as part of newborn blood spot screening for toxoplasmosis in Denmark[60]. No

data on any differences between sensitivity and specificity were given.

Screening of 785 placentas showed poor sensitivity (25%) but good specificity (99%), positive predictive value (93%), and negative predictive value (95%)[61].

What is the accuracy of the detection of sero-negative women?
There were seven papers included from that update search that looked at the efficacy of screening programmes. None of these papers gave sensitivity or specificity of tests.

The only recent paper study to report accuracy outcomes for a rapid diagnostic test studied 266 women in Cotonou, in Benin. However, this study was not carried out in the context of a universal screening programme. Performances for IgG were: sensitivity 97%, specificity 100%, PPV 100%, NPV 97.10%. For IgM, sensitivity was 33.3%, specificity 100%, PPV 100%, NPV 99.2%.[62].

Antenatal screening programmes rely on early identification of sero-negative women who are then rescreened at regular intervals in pregnancy to ascertain if they subsequently become acutely infected with toxoplasmosis. Recent studies from Italy, Austria and France and have shown that there is a poor adherence to the screening scheme for maternal *Toxoplasma* infections in pregnancy as many recommended examinations are missed[63]. Recent papers have concentrated on adherence to screening protocols rather than on whether sero-positive women are missed because of deficient screening tests and how many sero-negative women are incorrectly put in a low risk group. Lack of surveillance of cases has been identified as a factor in missing congenital infection.

Italian law has required serological screening for toxoplasmosis by the thirteenth week of pregnancy with sero-negative women undergoing further checks every 30 - 40 days until delivery (a total of 5 - 7 screenings) since 1998. Of the 4,694 women who initiated and completed a pregnancy in the period 2006 – 2008, a total of 84.1% of the women underwent their first screening during the first trimester. Sero-negative women underwent an average of 3.7 screenings during pregnancy, with 34.9% undergoing five or more. Sixty percent of the women underwent at least one screening per trimester[64].

A study in Northern Italy looked at adherence to screening among Italian and migrant women. Late screening after 12 weeks gestation was recorded in 13.6% - 9.35% Italian women and 31.9%in immigrant women. 82.1% of eligible migrants were not correctly monitored for toxoplasmosis during pregnancy[65].

In Austria, a nationally mandated prenatal serological congenital toxoplasmosis screening program was introduced in 1974 in response to a high incidence of 7.8 infected infants per 1,000 births. In a prospective observational study, 5,545 consecutive women were included over a 19-month period. Routine prenatal maternal toxoplasmosis serology screening was performed along with additional cord blood serology screening at delivery. Fetal cord blood serology included Sabin-Feldman dye and IgM immunosorbent agglutination assay testing. There was evidence of a prior chronic infection in 1,830 (33.0%) women and 3,708 (66.9%) were not infected. Seven (0.13%) were diagnosed with acute *Toxoplasma* infection based on seroconversion. Of these, four manifested transmission, and three did not. Of the seven infected women, routine prenatal maternal screening identified acute infection in only two of the women, one of whom had an infected fetus with an abnormal prenatal ultrasound. Fetal cord blood serology screening identified an additional five women, three with infected foetuses[66]. This suggests that antenatal screening tests were not picking up all infected women and that identification of *Toxoplasma* gondii infection by prenatal maternal serological testing is improved by the addition of maternal and/or fetal serological testing at birth.

The French Health Authority (Haute Autorite de Sante) has debated the national screening policy but maintained it for five years pending randomised clinical trials. Recent data is available to answer some of the questions, but not the place of prenatal therapy. The sensitivity of prenatal diagnosis has progressed, while the place of termination of pregnancy in treatment has decreased. The incidence of toxoplasmosis in the French population has fallen. Some studies have shown evidence supporting prenatal therapy for infected fetuses. Studies of prophylactic therapy are purely observational and mostly study spiramycin. A multicentre randomised clinical trial of prevention of mother-to-child transmission of *Toxoplasma* gondii is underway (the TOXOGEST study). This paper does not comment on the screening tests used. [67].

In contrast, a health economics paper based on the French (Paris) screening protocols and applied to the United States population concluded from its model that screening is cost-saving for rates of congenital infection above 1 per 10,000 live births. If universal screening drives the cost of testing and diagnosis down, then costs would be saved at lower prevalence of infected babies. This study constructed a decision-analytic and cost-minimization model to compare monthly maternal serological screening, prenatal treatment, and post-natal follow-up and treatment versus no systematic screening or perinatal treatment. Costs were based on published estimates of lifetime societal costs of developmental disabilities and current diagnostic and treatment costs. Probabilities were based on published results and clinical practice in the United States and France. Universal monthly maternal screening for congenital toxoplasmosis with follow-up and treatment is found to be cost-saving, with savings of $620 per child screened. Results are robust to changes in test costs, value of statistical life, sero-prevalence in women of childbearing age, fetal loss due to amniocentesis, and to bivariate analysis of test costs and incidence of primary *T. gondii* infection in pregnancy[68]. The model used and these cost benefit analysis assumptions may not be applicable to other countries, including the UK, and should not be used to make the case for screening in the absence of reliable data on how any screening programme meets the NSC criteria.

Criterion 5. Not met. The prevalence of chronic toxoplasmosis infections reported in the literature varies considerably. While this may be true variance due to different environmental and cultural factors, different methods used to diagnose acute and chronic infections may also play a part. Newer methods of diagnosis include the serum IgG avidity test, polymerase chain reaction (PCR) with body fluids and tissues, and Western blots of serum from mother-baby pairs. No new screening or diagnostic tests have been identified in this review.

There are no new data on the accuracy of the laboratory screening tests traditionally used in screening programmes. There is a wide range of commercial kits available for diagnosis of toxoplasmosis infection but commercial reagents continue to vary considerably in detecting low concentrations of antibodies during early seroconversion.

Recent papers have concentrated on adherence to screening protocols rather than on whether sero-positive women are missed because of deficient screening tests and how many sero-negative women are incorrectly put in a low risk group.

Two recent reviews of screening tests have led to consideration of stopping screening for Toxoplasmosis . Denmark no longer tests dried blood spots and the French Health Authority has debated the national screening policy but maintained it for five years pending the results of on-going randomised clinical trials of prevention of mother-to-child transmission.

Lack of surveillance of cases of congenital toxoplasmosis has been identified as a factor in missing congenital infection, and in differentiating between infections passed on by the mother and those acquired in the early years of life, where the mother screened as a true negative.

Criterion 8. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

Background

The 2014 Society of Obstetricians and Gynaecologists of Canada clinical guideline summarises the two goals of antenatal drug therapy for toxoplasmosis, depending on whether or not fetal infection has occurred. These recommendations are shared internationally and represent the most up-to-date evidence based advice.

1. If maternal infection has occurred but the fetus is not infected, spiramycin is used for fetal prophylaxis (to prevent spread of organisms across the placenta from mother to fetus).[1]Spiramycin is a macrolide antibiotic that is concentrated in but does not readily cross the placenta, and therefore is not reliable for treatment of fetal infection. Use is aimed at preventing vertical transmission of the parasite to the fetus, and it is indicated only before fetal infection. Its use during pregnancy has been recommended by many investigators in Europe

and North America. It should be prescribed for the duration of the pregnancy if the amniotic fluid polymerase chain reaction is reported negative for *T. gondii.*

2. If fetal infection has been confirmed (usually by a positive amniotic fluid polymerase chain reaction) or is highly suspected, pyrimethamine and sulfadiazine are used for treatment. Pyrimethamine is a folic acid antagonist that acts synergistically with sulfonamides. This drug should not be used in the first trimester because it is potentially teratogenic. It produces a reversible, doserelated depression of the bone marrow and therefore must be combined with folinic acid.The combination of pyrimethamine and sulfadiazine results in a significant decrease in disease severity.

Current UKNSC review

A 1999 (updated in 2006) Cochrane Review of 3332 studies (none of them randomised controlled trials of treatment) published in the past 30 years concluded that prenatal treatment in the presence of seroconversion during pregnancy does not lower transmission risk but could reduce congenital toxoplasmosis severity[6970]. Current evidence is insufficient to confirm that treating mothers who seroconvert during pregnancy prevents fetal infection[71]. No randomised controlled trials have been identified and no further studies have been published to change guidance since 2010.

The 2011 review concluded that the efficacy of the available treatments of toxoplasmosis in pregnancy and for an infant (<12months) with a congenital infection is uncertain. This review explored maternal treatment and its effect on transmission rates and severity of symptoms in the neonate and the continued treatment in neonates.

The 2015 review considered the volume and direction of evidence, published since 2011, on the effectiveness of antenatal and neonatal treatment. Comparative, prospective, studies were prioritised.

Description of the evidence

There were five papers included from the update search on toxoplasmosis anternatal treatment, two on antenatal and neonatal treatment and seven on neonatal treatment.

<u>Antenatal treatment</u>

A 2013 systematic review of randomised clinical trials for treatment of human toxoplasmosis found no trials evaluating drugs for toxoplasmosis in pregnancy, or for congenital toxoplasmosis[72]. A particular drawback of the available treatments is the lack of efficacy against the tissue cyst of the parasite, but there are some possible molecular targets[73].

Four antenatal treatment papers from Brazil reported on community-based, cross-sectional prospective studies. They conclude that treatment with spiramycin may not prevent vertical transmission completely, but suggest that it can delay infection, resulting in less damage to the baby if clinical symptoms are used as an outcome[74].

A much larger observational prospective cohort European study across fourteen countries used serious neurological sequelae (SNSD) as an outcome measure Two-thirds of the cohort received prenatal treatment (189/293; 65%). 23/293 (8%) fetuses developed SNSD of which nine were pregnancy terminations. Prenatal treatment reduced the risk of SNSD but the authors counsel caution on this interpretation because of the low number of SNSD cases and uncertainty about the timing of maternal seroconversion. The odds ratio for prenatal treatment, adjusted for gestational age at maternal seroconversion, was 0.24 (95% Bayesian credible intervals 0.07-0.71). This effect was robust to most sensitivity analyses. The number of infected fetuses needed to be treated to prevent one case of SNSD was three after maternal seroconversion at 10 weeks, and 18 at 30 weeks of gestation. Pyrimethamine-sulphonamide treatment did not reduce SNSD compared with spiramycin alone[75].

<u>Post natal treatment</u>
Again, there are no randomised controlled trials of treatment. The literature highlights the very different drug regimes in different countries – the protocols vary in drugs given, timing and dose of drug and length of total treatment.

The National Collaborative Chicago-based Congenital Toxoplasmosis Study calls for daily administration of pyrimethamine in combination with sulfadiazine for several months, then 3 times a week for a total of twelve months. This scheme needs frequent white blood cell counts that often result in the discontinuation of treatment because of severe neutropenia even with the concomitant administration of folinic acid. A referral centre in Toulouse, France administers pyrimethamine with sulfadoxine every 2 weeks for 2 years, and is associated with less toxicity. The efficacy may even be improved, as judged by the rate of new chorioretinal lesions[76] .

Recent multicentre studies show that postnatal treatment does not prevent ocular lesions: a prospective cohort study over 16 years in Marseilles 5% of treated children had choroiditis lesions at birth, 20% at 5 years, and 30% at 8 years of age. Furthermore, no consensus exists about the duration of postnatal treatment (3 months in Denmark versus 12 months in France)[77].

If a child does develop ocular manifestations of toxoplasmosis (whether infected before birth or acquired post-natally) a combination anti-parasitic therapy with pyrimethamine, sulfadiazine and clindamycin or azithromycin is considered standard practice. Anti-parasitic therapy can only stop the multiplication of the parasite and does not eliminate it from the human body. A 2002 Cochrane systematic review found inadequate evidence supporting routine use of anti-parasitic therapy for ocular toxoplasmosis. There have been some well-conducted randomised trials of the role of corticosteroids in the management of ocular toxoplasmosis but they have not provided evidence on whether use of corticosteroids is more effective than use of anti-parasitic therapy alone, when corticosteroid should be initiated in the treatment regimen (early versus late course of treatment), and which dosage and duration of steroid use is best. A 2012 Cochrane review again found no answer to the question of whether corticosteroids as adjunct therapy (that is, additional) to anti-parasitic agents improve effectiveness[78]. It concluded that several questions remain unanswered by well-conducted randomised trials in this context, including whether use of corticosteroids is more effective than use of anti-parasitic therapy alone, when corticosteroids should be initiated in the treatment regimen (early versus late course of treatment), and which dosage and duration of steroid use is best.

Future treatments

Photodynamic therapy seems to be a safe and effective approach to the long-term control of subfoveal choroidal neovascularization associated with toxoplasmic retinochoroiditis. Further trials are needed to validate these findings[79].

Criterion 8. Not met.
No further reliable evidence from randomised controlled trials or published studies has added to the conclusion of the updated 2006 Cochrane Review that prenatal treatment in the presence of seroconversion during pregnancy does not lower transmission risk but could reduce congenital toxoplasmosis severity. This appears to be because treatment does not affect oocysts in the placenta. Current evidence is insufficient to confirm that treating mothers who seroconvert during pregnancy prevents fetal infection[80].

A 2012 Cochrane review again found no answer to the question of whether corticosteroids as adjunct therapy (that is, additional) to anti-parasitic agents improve effectiveness of treatment of ocular toxoplasmosis. It concluded that several questions remain unanswered by well-conducted randomised trials in this context, including whether use of corticosteroids is more effective than use of anti-parasitic therapy alone, when corticosteroids should be initiated in the treatment regimen (early versus late course of treatment), and which dosage and duration of steroid use is best. Treatment protocols vary considerably world wide in drugs given, timing and dose of drug and length of total treatment and their effectiveness is uncertain.

Conclusion

Criterion 1 The condition should be an important health problem
What is the scale of toxoplasmosis infection?

- There have been no new papers published that give reliable estimates of *Toxoplasma* infections in general populations, pregnant women or neonates in the UK. Estimates of congenital

infections vary by more than a hundred fold worldwide and also vary between local populations in the same country.

What are the implications of congenital toxoplasmosis on neonatal development?

- There have been no new papers that address the risk of maternal infection on the pregnancy outcome, the prognosis of congenital infection on the neonate and the likelihood of severe outcomes in relation to when sero-conversion occurs and the suspected route of transmission to the neonate of congenital toxoplasmosis on neonatal development.

Criterion 2 The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

- An enhanced surveillance system for toxoplasmosis in England and Wales was established in 2008 and its first report published in 2014. However, the authors acknowledge that under reporting is likely. Health Protection Scotland established a notification system in 1990, but no reviews of congenital toxoplasmosis or prevalence in pregnant women or the general population have been published since its introduction.

- There have been considerable changes in the demography of pregnant women in England and Wales over the last two decades which may theoretically have a small effect on the prevalence of sero-negative women. It is likely that sero-negativity in the UK has risen in line with countries where prevalence has been monitored but no evidence for this.

Criterion 3 All the cost-effective primary prevention interventions should have been implemented as far as practicable

- The 24 papers published since 2010 look at knowledge of pregnant women and professionals and what advice is given on primary prevention of toxoplasmosis in different countries in different continents. All involved small numbers of women and professionals and all conclude that more information on primary prevention of infections, including toxoplasmosis is needed.

- Hygiene measures such as hand washing and careful food handling and storage can offer primary protection against many infectious diseases that can cause problems in pregnancy, from influenza to listeriosis, cytomegalovirus and salmonella as well as toxoplasmosis. The published papers focused on prevention of toxoplasmosis, with very specific advice on handling cats and cat faeces because of the role played by felines as the only animals in which *Toxoplasma* can fully live out its life cycle and in which the sexually mature forms of the parasite occur.

- It is estimated that 30 to 60% of *Toxoplasma* infections are from undercooked meat.

- A 2013 Cochrane review assessed the effects of prenatal education for preventing congenital toxoplasmosis from two cluster-randomised controlled trials involving a total of 5455 women The authors concluded that prenatal education for congenital toxoplasmosis has a significant effect on improving women's knowledge but has no effect on changing women's behaviour[81].

- Toxoplasmosis is a potential cause of morbidity in all infected people and can be particularly serious in immune-compromised individuals, such as those with HIV or organ transplants. Several papers report an increase of pregnant women infected with HIV and also comment on the rising prevalence of HIV and transplants in the general population. Public health interventions aimed at preventing all toxoplamosis infections, such as reducing *Toxoplasma* in the food chain could have a beneficial effect for pregnant women and the general population.

Criterion 5 There should be a simple, safe, precise and validated screening test

- The prevalence of chronic toxoplasmosis infections reported in the literature varies enormously. While this may be true variance due to different environmental and cultural factors, different methods used to diagnose acute and chronic infections may also play a part. Newer methods of diagnosis include the serum IgG avidity test, polymerase chain reaction (PCR) with body fluids and tissues, and

Western blots of serum from mother-baby pairs. No new screening or diagnostic tests have been identified in this review.

- There is a wide range of commercial kits available. Commercial reagents continue to vary considerably in detecting low concentrations of antibodies during early seroconversion

- Recent papers have concentrated on adherence to screening protocols rather than on whether sero-positive women are missed because of deficient screening tests and how many seronegative women are incorrectly put in a low risk group.

- Lack of surveillance of cases has been identified as a factor in missing congenital infection.

Criterion 8 There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

- No further reliable evidence from randomised controlled trials or published studies has added to the conclusion of the updated 2006 Cochrane Review that prenatal treatment in the presence of seroconversion during pregnancy does not lower transmission risk but could reduce congenital toxoplasmosis severity. This appears to be because treatment does not affect oocysts in the placenta. Current evidence is insufficient to confirm that treating mothers who seroconvert during pregnancy prevents fetal infection.

  A 2012 Cochrane review again found no answer to the question of whether corticosteroids as adjunct therapy (that is, additional) to anti-parasitic agents improve effectiveness of treatment of ocular toxoplasmosis. . It concluded that several questions remain unanswered by well-conducted randomised trials in this context, including whether use of corticosteroids is more effective than use of anti-parasitic therapy alone, when corticosteroids should be initiated in the treatment regimen (early versus late course of treatment), and which dosage and duration of steroid use is best. Treatment protocols vary considerably worldwide in drugs given, timing and dose of drug and length of total treatment and their effectiveness is uncertain.

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