ORIGINAL ARTICLE

Screening for congenital toxoplasmosis: accuracy of immunoglobulin M and immunoglobulin A tests after birth

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Objectives To determine the accuracy of postnatal screening for toxoplasma-specific immunoglobulin (Ig) M and IgA.

Setting Ten centres in three European countries.

Methods We compared results of the first postnatal IgM or IgA test in infants with infected mothers identified by prenatal screening with the reference standard for congenital infection status of specific IgG status at one year of age.

Results In all, 170 infected and 822 uninfected infants were analysed. Overall, IgM or IgA testing detected only 52–55% of infected infants. Sensitivity was highest between one and two weeks after birth and declined thereafter. Specificity was highest from four weeks after birth. For IgM, but not IgA, sensitivity was statistically significantly lower if the mother seroconverted in the first and second trimesters of pregnancy (29% and 34%, respectively) than the third (71%). Prenatal treatment with pyrimethamine–sulphonamide did not significantly reduce IgM or IgA sensitivity. Sensitivity was lowest for the immunofluorescence (IF) IgM test (10%) and the enzyme-linked immunosorbent assay (ELISA) IgM test (29%), but similar for the immunosorbent agglutination assay (ISAGA) IgM (54%), ISAGA IgA (58%) and ELISA IgA (52%) tests. Specificity was significantly lower for the ISAGA IgA test (91%) than for the ISAGA IgM (96%), IF IgM (100%), and ELISA IgA tests (98%).

Conclusions Poor performance of IgM and IgA tests in the newborn, particularly if the mother seroconverted in early pregnancy, casts doubt on the value of neonatal screening in industrialized countries where the risk of clinical manifestations during childhood is low. More accurate diagnostic tests are needed for newborns identified by prenatal screening.

INTRODUCTION

Toxoplasma gondii is a ubiquitous protozoan parasite that causes latent infection in 10–50% of adults in western industrialized countries.[1] When infection is acquired for the first time during pregnancy, transplacental transmission of the parasite occurs in 25–30% of women, causing congenital toxoplasmosis. Studies of infected children whose mothers were mostly treated during pregnancy have shown that one in 20 congenitally infected infants have symptoms of disseminated infection at birth and 15–20% have healed inflammatory lesions in the brain and/or in the retinochoroidal region of the eye, which can only be detected by imaging or ophthalmoscopy.[2] In the eye, new lesions can develop after birth, and by 5 years of age, about 30% of infected children have retinochoroidal lesions.[3] Less than 5% of children with eye lesions develop severe bilateral visual impairment.[3]

Screening for toxoplasma-specific immunoglobulin (Ig) M and IgA antibodies to detect congenital toxoplasmosis in early infancy occurs in two settings. Firstly, IgM testing of neonatal Guthrie card blood spots has been used in neonatal screening programmes in Denmark, Sweden, Ireland, Massachusetts and Brazil.[4–9] Secondly, IgM and IgA testing is used to test blood samples in newborns of infected mothers identified by the prenatal screening programmes that operate in most western European countries.[2] In both settings, the purpose of screening is to detect asymptomatic infected infants in whom anti-toxoplasma treatment can be started as soon as possible after birth in order to prevent formation of new toxoplasmic retinochoroidal lesions during childhood.[4,5] Without early testing, treatment may be delayed until infection status can be diagnosed at 12 months of age, or uninfected infants may be treated unnecessarily. Whether delay of treatment has clinical consequences is not known, as no studies have compared outcomes in treated and untreated infected infants.[10] However, evidence from a meta-analysis of all relevant cohort studies has recently reported no evidence that treatment during fetal life reduces the risk of retinochoroidal lesions.[2] In this report, we examine the performance of IgM and IgA as screening tests and do not directly address the critical question of treatment effectiveness.

Since the mid-1990s, the number of neonatal screening programmes has grown in response to evidence that neonatal Guthrie card screening for IgM detected 78% of infants with congenital toxoplasmosis diagnosed by serological follow-up during infancy.[5,9] These results were based on neonatal screening studies that included retrospective testing of stored maternal sera. As the studies comprised a total of 12 infected infants, of whom two had false-negative screening tests, they are quite uncertain. Further information on the performance of IgM and IgA testing can be obtained from studies of newborns whose mothers were identified by prenatal screening. However, to be comparable with the neonatal screening context, analyses need to be based on the first test performed and take into account any potential effects of prenatal treatment on antibody response. Our aim was to determine the accuracy of the first screening test for IgM and IgA as used in routine practice in 10 prenatal screening centres and to examine the implications for neonatal and prenatal screening programmes.

METHODS

Population

The study design, methods, and testing and treatment schedules for the European multicentre study on congenital toxoplasmosis (EMSCOT) have been described in detail elsewhere.[11–13] In this report, we confined analyses to infants born in the 10 centres (in 3 countries) that operated prenatal screening. Neonatal screening centres could not be included as they did not follow up infants with negative results.

Data collection

We defined the reference standard for congenital toxoplasmosis status as persistence of specific IgG antibodies beyond 11.5 months of age (infected), and undetectable IgG between two and 11 months of age in the absence of anti-toxoplasma treatment (uninfected).[11,12] Persistence of specific IgG beyond 12 months is a widely accepted criterion for congenital toxoplasmosis, as maternally transmitted antibodies rarely persist beyond this age.[14] The criterion for absence of treatment in the case of negative IgG is because postnatal pyrimethamine–sulphonamide treatment can depress the IgG response.[15]

The type of test used for routine screening varied across the 10 centres as there was no uniform screening policy within or between countries. Our results, therefore, reflect the average screen test performance in routine practice in 10 regional screening centres. We grouped tests according to IgM or IgA antibodies, the test method (immunosorbent agglutination assay (ISAGA), enzyme-linked immunosorbent assay (ELISA) or immunofluorescence), and result (positive or equivocal versus negative). Cut-offs recorded before the start of the study were based on manufacturers' recommendations or published reports.[16] The test manufacturer used by various centres were as follows: IgM ISAGA (Biomerieux[17] 7 centres, in-house test 2 centres;[18] IgM ELISA (Biomerieux[17] 4 centres, Abbott[19] 1 centre, Sanofi-Pasteur[20] one centre, SFRI[21] 1 centre); IgM immunofluorescence (in-house assay 3 centres; IgA ISAGA (Biomerieux[17] 3 centres, in-house assay 3 centres;[18] IgA ELISA (SFRI 2 centres,[21] Sanofi Pasteur[20] 2 centres, Abbott[19] 1 centre).

Factors associated with detection rate and specificity

We determined whether the detection rate and specificity for neonatal IgM and IgA tests were associated with the trimester at maternal seroconversion, type of prenatal treatment (any pyrimethamine–sulphonamide combination versus spiramycin or no treatment), sample type (peripheral versus cord blood), or presence of intracranial or ocular lesions during infancy. We confined these analyses to the first test before 15 days after birth and preferentially used the ISAGA result, and if not available, the ELISA result, which had similar performance. We ignored the results of the immunofluorescence. The trimester at maternal seroconversion was imputed as the midpoint between the last negative and first positive maternal IgM test during pregnancy, or 14 days before a positive IgM test if the IgG result on that date was negative (IgG responds more slowly than IgM).[12,22] We used logistic regression to calculate the odds ratio for detection rate and specificity, and included any variables that had a P value of 0.2 or less in multivariable analyses. Confidence intervals for proportions were computed using the binomial exact method.[23] Analyses were carried out using SAS Version 9.1 (SAS Institute Inc., Cary, NC 27513, USA) except the binomial exact confidence intervals, which were computed using STATA (release 7, STATA press, Texas, USA). We determined the added value of a combination of IgM and IgA testing using results for newborns who had a first IgM and IgA test on the same date before 15 days old.

Type and timing of tests

The timing of testing is earlier for prenatal than that for neonatal screening, which is delayed until the hypothyroid and phenylketonuria tests at one week of age. The interval before confirmatory tests will depend on the efficiency of the programme. Timing of testing can be expected to affect the detection rate as IgM and IgA antibodies are produced as a transient response to acute infection.[1] To analyse the effect of timing on test performance, we included all tests during infancy and plotted sensitivity and specificity for each test type based on the first sample taken during each of the following age intervals: age zero (cord blood), and peripheral blood samples at weekly intervals from week 1 through to week 13, then for the first test between weeks 14 and week 68 after birth.

RESULTS

Population

A total of 1191 women were identified by prenatal screening. After exclusion of infants lost to follow-up before 12 months and women referred for fetal complications, 992 newborns were included in the analyses (Figure 1). One hundred and seventy (17%) infants had congenital toxoplasmosis. Two-thirds of the cohort (641/992; 65%) had cord blood tested and another 25% (244/992) had their first blood test done within two weeks (in total 90% tested before 15 days of age). The ISAGA test was the first IgM test before the infants were 15 days old in 88% (772/881) of children and the first IgA test in 42% (186/440) of those tested for IgA.

Factors associated with the detection rate and specificity

The detection rate and specificity are shown according to a range of clinical characteristics in Table 1. The detection rate for IgM was lower in newborns whose mothers seroconverted in the first and second trimesters compared with those seroconverted in the third trimester. Among infected infants, the odds ratio for detection was 0.16 (95% confidence interval [CI]: 0.05, 0.58) in the first trimester, and 0.22 (0.11, 0.43) in the second trimester, compared with the third trimester. The detection rate was also reduced in newborns whose mothers received pyrimethamine–sulphonamide compared with those treated with spiramycin or those who had no treatment (odds ratio [OR] 0.36; 0.19, 0.68). A test for interaction between trimester and treatment type was not significant (likelihood ratio test, $P = 0.47$). We found no evidence for a significant association between detection rate and sample type or presence of lesions ($P>0.05$). In the multivariate analyses, there was little change in the effect of trimester at seroconversion on detection rate (OR for detection in the first trimester 0.18; CI 0.05, 0.63; and second trimester 0.27; CI 0.13, 0.56), but the association with pyrimethamine–sulphonamide was no longer statistically significant (OR 0.53; CI 0.26, 1.07). None

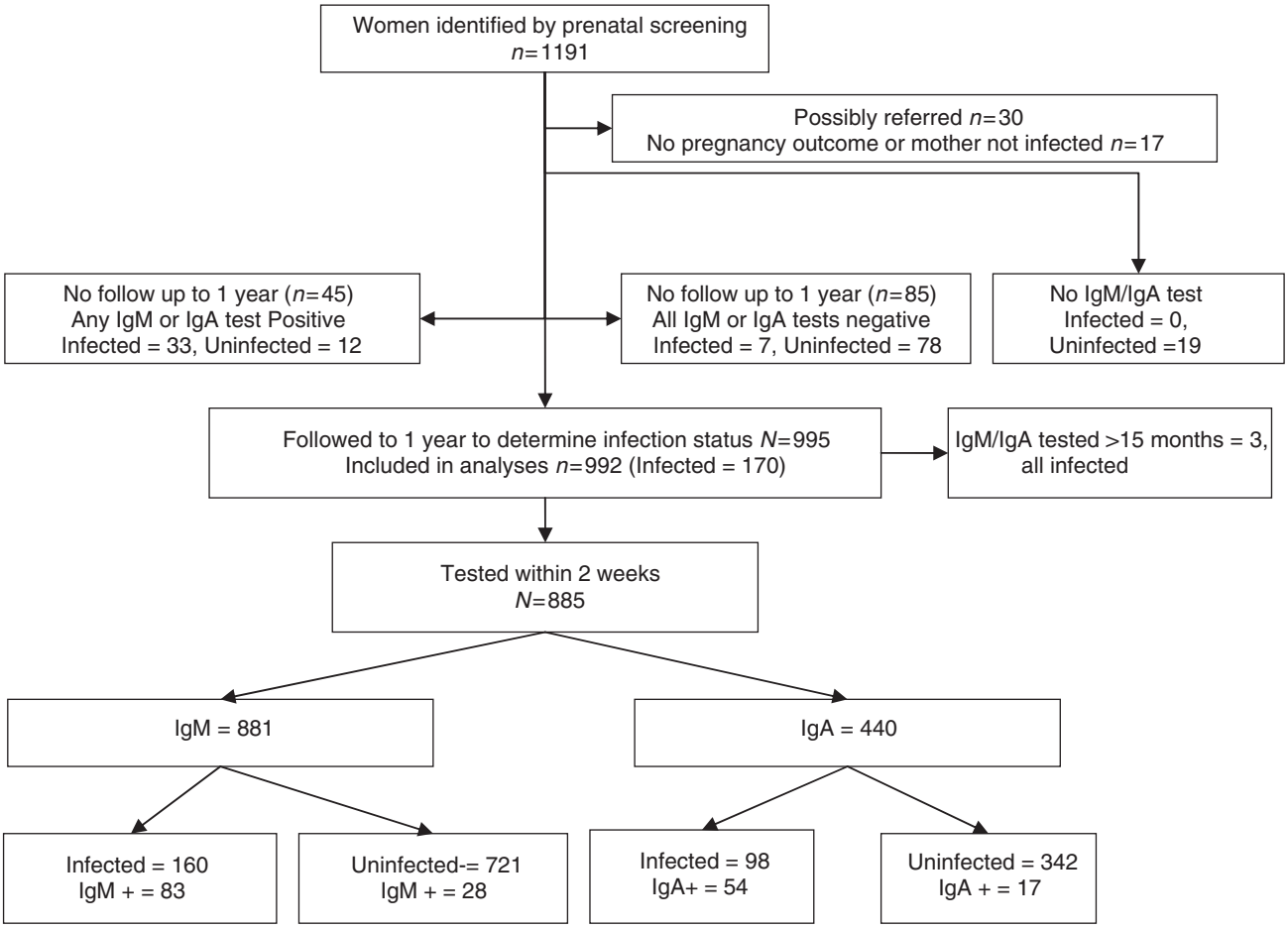

Figure 1 Flow diagram to show women identified by prenatal screening and included in the analyses

Table 1 Sensitivity and specificity of IgM and IgA tests according to clinical characteristics (95% CI)

	Total infected		Total uninfected		Total infected*		Total Uninfected	
Characteristic	IgM+	Detection rate %	IgM−	Specificity %	IgA+	Detection rate %	IgA+	Specificity %
Trimester 1†								
ALL	4/14	29 (8,58)	443/459	97 (94,98)	2/5	40 (5,85)	214/223	96 (92,98)
P&S treated	1/7	14 (0,28)	97/102	95 (89,98)				
Spiramycin/untreated	3/7	43 (10,82)	346/357	97 (95,98)				
Trimester 2†								
ALL	23/67	34 (23,47)	175/181	97 (95,98)	20/43	47 (31,62)	81/88	92 (86,97)
P&S treated	13/47	28 (16,43)	46/46	100 (93,99)				
Spiramycin/untreated	10/20	50 (27,73)	129/135	96 (91,98)				
Trimester 3†								
ALL	56/79	71 (60,81)	50/56	89 (78,96)	32/50	64 (49,77)	30/31	97 (83,99)
P&S treated	17/25	68 (47,85)	14/15	93 (68,99)				
Spiramycin/untreated	39/54	72 (58,84)	36/41	88 (74,96)				
Treatment								
P&S treated	31/79	39 (28,51)	157/163	96 (92,99)	22/44	50 (35,65)	30/33	91 (76,98)
Spiramycin/untreated‡	52/81	64 (53,75)	511/533	96 (94,97)	32/54	59 (45,72)	295/309	95 (93,98)
Sample type								
Peripheral	18/43	42 (27,58)	209/213	98 (95,99)	13/23	57 (34,77)	121/127	95 (90,98)
Cord	65/117	56 (39,57)	459/483	95 (93,97)	41/75	55 (43,66)	204/215	95 (91,97)
Lesions during infancy								
Eye and/or Brain	13/26	50 (30,70)	2/3§	67 (9,99)	9/16	56 (30,80)	3/3§	100 (37,100)
No lesion	70/134	52 (43,61)	666/693	96 (94,97)	45/82	55 (43,66)	322/339	95 (92,97)
Overall	*83/160*	*52* (*44,60*)	*668/696*	*96* (*94,97*)	*54/98*	*55* (*45,65*)	*325/342*	**95** (**92,97**)

*Results not shown for treatment by trimester due to small cell size
†Trimester 1 = 0–14 completed weeks, 2 = 15–27 completed weeks, 3 = 28 weeks or more
‡Proportion untreated = 45/614 (7%) if IgM tested, 23/363 (6%) if IgA tested
§Lesions are intracranial calcification, presumed to be due to reasons other than congenital toxoplasmosis or to be false positive cranial ultrasound scan results
P&S, pyrimethamine-sulphonamide; ALL, acute lymphocytic leukaemia

of the factors examined was significantly associated with the detection rate for IgA.

Immunoglobulin M specificity was significantly increased if seroconversion occurred in the first or second trimesters than if it occured in the third (OR for the first trimester 3.32; 95% CI: 1.24, 8.88; and second trimester 3.5; 95% CI: 1.08, 11.33). Peripheral blood samples were not significantly associated with improved specificity (OR 2.73; 0.94, 7.80). These results did not change in the multivariable model. In contrast, there was no evidence of any association between trimester at seroconversion or sample type with IgA specificity.

Post-test probability of congenital toxoplasmosis

Using the figures from Table 1, the prevalence (or pre-test probability) of congenital toxoplasmosis can be calculated as 3, 27 and 59% in the first, second and third trimesters, respectively. Given a positive IgM result, these probabilities would increase to 20% (95% CI: 6, 44%) in the first trimester, 79% (60, 92%) in the second trimester and 90% (80, 96%) in the third trimester. A negative IgM result would reduce these probabilities to 2% (1, 4%), 20% (15, 26%) and 32% (21, 43%) in the first, second and third trimesters, respectively. The largest changes, and hence most informative results, would be a positive test after seroconversion in the second trimester (change from 27% to 79%) and a negative test after seroconversion in the third trimester (change from 59% to 32%). Immunoglobulin M testing is not informative for newborns of mothers who seroconverted in the first trimester as few tests are positive (20/473; 4%) and, with a post-test probability (or positive predictive value) of only 20%, four out of five infants with a positive result would be uninfected.

Combined IgM and IgA test results

Table 2 shows the post-test probability of congenital toxoplasmosis for infants who underwent IgM and IgA tests before two weeks of age. Overall results are given, without subdivision by trimester, because of the reduced sample size. Post-test probability was 100% if both the first IgM and IgA tests were positive, although this occurred in only 10% of newborns (17/182). The post-test probability was 26% if only one test was positive and 10% if both were negative. Consequently, for the 20% (36/182) of infants in whom the first test was positive, a second test was useful as, if it was positive, the probability of congenital toxoplasmosis increased substantially. However, if the first test was negative (whether IgM or IgA), having a second positive test did not substantially increase the probability of congenital infection.

Type of test

The detection rate did not differ significantly between the ISAGA IgM, ISAGA IgA and ELISA IgA tests, but was statistically significantly lower for the ELISA IgM and immunofluorescence tests than for any other IgM tests (*P* values for between-test comparisons 0.009–0.034) (Table 3). Specificity was significantly lower for the ISAGA IgA test compared with the ISAGA IgM and ELISA IgA tests.

Timing of test

Figure 2 shows detection rate and 95% CIs of the ISAGA IgM test according to the infant's age after birth. The detection rate was unchanged till week 2 but declined thereafter. The pattern was similar for the ELISA IgM test, and for the ISAGA and ELISA IgA tests (results not shown). Specificity increased to 100% by four weeks for all tests (results not shown).

DISCUSSION

The first IgM or IgA test detected just over half the infants with congenital toxoplasmosis. Detection by IgM was lowest for newborns whose mothers seroconverted in the first or second trimesters. More than two-thirds of infants detected by IgM or IgA were born to mothers who seroconverted in the third trimester and, therefore, have a very low risk of neurological or visual impairment.[3,13] The ISAGA IgM and IgA and ELISA IgA tests performed best, but positive results need to be quickly confirmed by testing a second sample as the detection rate was optimal up to two weeks of age and declined thereafter.

Table 2 Post test probability of congenital toxoplasmosis with combined IgM and IgA test results

Test result	Congenital toxoplasmosis status			Post test probability of infection %
	Infected	Uninfected	Total	
IgM+AND IgA+	17	0	17	100 (83, 100)
IgM+IgA−	1	2	3	26 (9, 51)
IgM−IgA+	4	12	16	
IgM−AND IgA−	14	132	146	10 (5, 16)
Total	36	146	182	

Table 3 Accuracy of first blood test performed by two weeks of age according to test type*

Test type	Test result in CT+		Test result in CT−		Sensitivity % (95% CI)	Specificity % (95% CI)
	Positive	Negative	Positive	Negative		
ISAGA IgM	82	71	22	597	54 (45, 62)	96 (95, 98)
ELISA IgM	12	29	8	212	29 (17, 46)	96 (93, 98)
IF IgM	1	9	0	56	10 (1, 46)	100 (92, 100)
ISAGA IgA	22	16	14	134	58 (41, 73)	91 (84, 95)
ELISA IgA	33	30	4	211	52 (40, 65)	98 (95, 99)

CT+/− = infected with congenital toxoplasmosis (+) or uninfected (−)
*Median number of tests performed on the first sample = 1 (range 1–4)

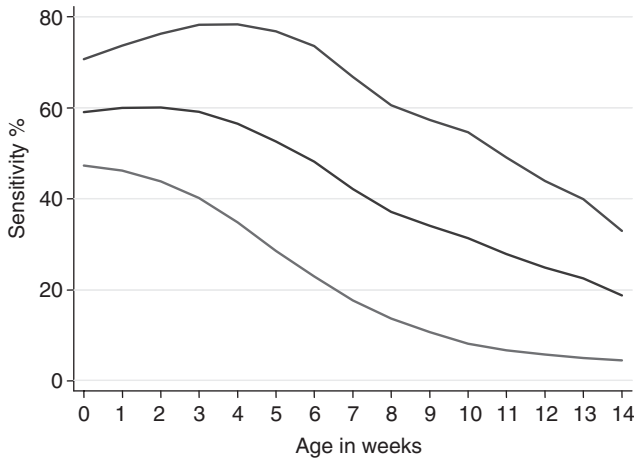

Figure 2 Detection rate (upper and lower lines represent 95% confidence limits) for the first ISAGA IgM test according to postnatal age

Our results for sensitivity and specificity are lower than in previous studies[5,18,24] except for one multicentre study that reported a detection rate of 41–43% for IgM and specificity of 96–99%.[25] There are several possible explanations for these differences. First, by excluding referred cases and achieving a high rate of follow up, we minimized selection biases that tend to overestimate the detection rate by favouring inclusion of definitely infected IgM/IgA-positive babies and loss to follow-up infected babies that are IgM/IgA negative. Second, to reduce selection bias, we used the first test in each category. The detection rate is increased when any positive result is counted from multiple tests. Third, three[5,18,24] of the four previous studies were conducted in single laboratories actively engaged in research into serological tests. This may have improved test accuracy above the average. In contrast, our study reflects test performance as used in routine practice in 10 regional screening centres. Fourth, test types differ. Wallon *et al.*[24] evaluated the ISAGA IgM and ELISA IgA, Pinon *et al.*[18] used a test developed within the laboratory, Lebech *et al.*[5] used an ELISA test and Naessens *et al.*[25] did not specify the type of IgM or IgA tests included. Fifth, differences may be due to chance. We estimated the detection rate of IgM for newborns of mothers who did not receive pyrimethamine–sulphonamide and seroconverted after 10 weeks of gestation (the lower time point for inclusion in the study by Lebech *et al.*) to be 58% (trimester specific rate times, weeks at risk, assuming a constant incidence rate of infection). This is well within the CI for the detection rate reported by Lebech *et al.*[5] (78%; 95%CI: 51, 100%). Sixth, differences in the proportion of women receiving pyrimethamine–sulphonamide treatment may account for differences in the detection rate. However, this effect is likely to be small as we found a weak, non-significant effect of pyrimethamine–sulphonamide treatment, and no other studies have reported a statistically significant association.[24–26]

Clinical implications

For prenatal screening, the poor performance of IgM and IgA tests means that more accurate tests or additional tests and follow up are required to decide on postnatal treatment in the 80% of newborns who have a negative IgM or IgA test result.[27] Options include the Western blot or enzyme-linked immunofiltration assay. These require specialist laboratory expertise, and although they are becoming more widely available, they are expensive, and their accuracy in routine clinical practice needs to be evaluated.[28–31]

The implications for neonatal screening are that a positive test detects infected infants with a good prognosis and fails to detect nearly half of all infected infants, particularly those most at risk of adverse outcomes whose mothers were infected in early pregnancy. In practice, these results may overestimate test performance in neonatal screening. First, our results are based on serum samples, whereas test sensitivity can be lower for filter paper blood samples.[32] Second, our results included cord blood samples which were slightly more sensitive than peripheral blood samples. Third, confirmation of filter paper screening results within the first two weeks of life, before sensitivity declines, is rarely possible to achieve. In neonatal screening centres within the EMSCOT, cohort confirmatory tests were performed relatively late at a median age of 25 days (range 1–89 days) (unpublished data for 46 infected infants in the EMSCOT study).

Neonatal screening fails to fulfil two further criteria for screening programmes.[33] The prognosis for infected children is very good. On average, they have similar levels of developmental and behavioural problems as uninfected children,[34] and bilateral visual impairment is extremely rare, particularly, in children whose mothers seroconverted in the latter half of pregnancy.[13,35,36] Second, there is no evidence that postnatal treatment is effective, and it can have serious adverse effects.[10,37] In addition, diagnosis and follow up in infancy is associated with increased parental anxiety 3–4 years after birth.[34]

In conclusion, the benefits of detecting a low proportion of infected infants with a good prognosis in order to offer treatment of uncertain effectiveness[10,37] may not outweigh the potential harms. Neonatal screening should, therefore, only be conducted in the context of a randomized controlled trial to assess treatment efficacy. These conclusions may not apply to endemic tropical countries where the rate of complications is much higher than in Europe or North America.[38–40]

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Conflict of interest statement

All authors declare they have no conflicts of interest. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data.

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