UK National Screening Committee

Antenatal screening for HTLV infection

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: Final

Solutions for Public Health

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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://legacy.screening.nhs.uk/screening-recommendations.php and the policy review process is described in detail at https://www.gov.uk/guidance/evidence-and-recommendations-nhs-population-screening#evidence-review-process

Abbreviations List

ATLL	Adult T–Cell Leukaemia/ Lymphoma
CI	Confidence Interval
CLEIA	Chemiluminescent Enzyme Immunoassay
CLIA	Chemiluminescent Immunoassay
CMIA	Chemiluminescent Microparticle Immunoassay
EIA	Enzyme Immunoassay
ELISA	Enzyme Linked Immunosorbent Assay
HAM	HTLV-Associated Myelopathy
HTLV	Human T-Cell Lymphotrophic Virus
IA	Immunofluorescence Assay
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value
PA	Particle Agglutination
PCR	Polymerase Chain Reaction
PPV	Positive Predictive Value
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RCT	Randomised Controlled Trial
TSP	Tropical Spastic Paraparesis
UK	United Kingdom
UK NSC	UK National Screening Committee
US	United States

Competing Interest

All SPH authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: grants from Public Health England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Plain English Summary

Human T-cell lymphotrophic virus (HTLV) types I and II are a viruses that can be passed from person to person in various ways; particularly via an infected blood transfusion or through having unprotected sex. HTLV can also be passed from mother to child in pregnancy or during a caesarean birth, but the most common way that HTLV is passed from mother to child is through breastfeeding. HTLV is common in some parts of the world but rarer in Western Europe.

Most people with HTLV do not experience any symptoms but a small number of people can develop serious illness after a long period without any symptoms. These illnesses include leukaemia or myelopathy (a nervous system condition). There is no cure for HTLV so the focus is on preventing infection, for example, by avoiding breastfeeding or limiting the length of time that an infected mother breastfeeds their child.

This document reviews new evidence about antenatal screening for HTLV infection. It looks at evidence published between January 2011 and January 2017. The aim of an antenatal screening programme for HTLV infection would be to prevent serious illnesses associated with HTLV by promoting the avoidance of breastfeeding by mothers who are HTLV positive.

The UK National Screening Committee (UK NSC) published its last review in 2012. This recommended against introducing a screening programme for HTLV infection in pregnancy in the UK. The current review looks at some key questions:

1. how many pregnant women have HTLV-I and II in the UK?
2. what is the accuracy of antenatal screening tests for HTLV?
3. how effective is avoiding breastfeeding at reducing HTLV transmission?

This update review of the evidence found that no new evidence has been published that would change the conclusions of the previous UK NSC review. Therefore the UK NSC still cannot recommend antenatal population screening for HTLV. The key concerns are:

- the number of people infected with HTLV in the UK is low and restricted to specific subgroups of the population
- the accuracy of screening tests in pregnant UK women is not known eg how many women would receive a false positive or false negative result on a screening test
- the risk of a mother passing HTLV to their child through breastfeeding is low unless breastfeeding is continued beyond 6 months
- most infants infected with HTLV do not develop symptoms and the risk of developing a serious illness appears to be low
- there is no treatment for HTLV and the only approach to prevention is the avoidance of breastfeeding, particularly breastfeeding after 6 months
- the potential for harm cannot be underestimated. Women with HTLV infection will be identified, there is no treatment, and about 90% will not develop HTLV related disease in later life. This situation may cause significant anxiety and stress to the women and their families.

As no new evidence to change the current recommendation was found, the review concluded that an antenatal population screening programme for HTLV infection should not be introduced in the UK.

Executive Summary

This document reviews evidence published between January 2011 and January 2017 about antenatal population screening for HTLV infection.

Background

Human T-cell lymphotrophic virus (HTLV) types I and II are retroviruses that can be transmitted vertically from mother to child or through sexual or blood-borne routes. Transmission from mother to child can occur before birth through the placenta or during caesarean delivery but most commonly occurs through breastfeeding. Longer duration of breastfeeding and high maternal proviral load increases the risk of infection.

Most individuals infected with HTLV remain asymptomatic but, after a long latent period, it can lead to severe illness such as adult T–cell leukaemia/ lymphoma (ATLL) and HTLV-associated myelopathy (HAM)/ tropical spastic paraparesis (TSP). This is thought to occur in about 10% of infected individuals. However, previous UK NSC reviews have reported that there is little information on the natural history of the infection acquired through breastfeeding. There is no cure or vaccine for HTLV so strategies to prevent infection focus on avoiding transmission, for example, though avoiding or limiting the duration of breastfeeding.

HTLV-I is endemic in some regions of the world including Southern Japan, West and Central Africa, the Caribbean, Central and South America and Melanesia. The prevalence of HTLV-II is highest in some African populations, Native Americans and injecting drug users. A UK study of 126,010 newborn dried blood spot samples predicted an overall prevalence of 3.1 per 10,000 for HTLV for the UK with prevalence ranging considerably for sub groups of the population.

Antenatal screening of pregnant women takes place in some countries where HTLV is endemic, for example Japan. The screening tests used in Japan are considered to have high sensitivity and specificity but still generate a substantial number of false-positive results, especially in non-endemic areas. Antenatal screening for HTLV in the UK was proposed during the 1990s as a means of preventing ATLL by promoting avoidance of breastfeeding by mothers identified as HTLV positive.

Previous findings

This is the fourth time that the UK NSC has considered antenatal screening for HTLV infection. The current UK NSC policy is that systematic population screening for HTLV infection in pregnancy is not recommended. The previous 2012 UK NSC review concluded that there was no new evidence that an antenatal screening programme for HTLV-I or HTLV-II would be effective in reducing mortality or morbidity. The conclusions of the previous review stated that:

- “the prevalence of HTLV infection in the UK is low and restricted to specific subgroups
- the risk of mother-to-child transmission through breastfeeding is low unless breastfeeding is prolonged beyond 6 months
- most infected infants remain asymptomatic and the life time risk of subsequent serious disease appears to be low
- there is no treatment for HTLV and the only approach to prevention is the avoidance of breastfeeding, particularly prolonged breastfeeding
- the potential for harm cannot be underestimated. Women with HTLV infection will be identified, there is no treatment, and most will not develop HTLV related disease in

later life. This situation may cause significant anxiety and stress to the women and their families."

The current review

The current review explores the volume, quality and direction of the literature published since 2011 and focuses on key questions relating to the conclusions of the previous review. The aim of the review is to inform discussion on whether recent evidence suggests the current recommendation should be reconsidered.

The key questions considered in this review are:

1. what is the prevalence of HTLV-I and II in the pregnant population in the UK?
2. what is the accuracy of antenatal screening tests for HTLV?
3. what is the effectiveness of breastfeeding avoidance in the prevention of HTLV transmission?

The review found that the volume, quality and direction of new evidence published since January 2011 does not indicate that there have been any significant changes in the evidence base since the previous review. The conclusions of the previous UK NSC review should be retained.

This update review also found no studies providing details about the performance of HTLV screening tests in a UK antenatal population.

Recommendation

The review concluded that there has been no significant change in the evidence base since the previous UK NSC review. The current recommendation not to introduce a UK systematic antenatal population screening programme for HTLV infection should be retained.

The UK NSC does not recommend screening for HTLV I or II in pregnancy.

Introduction

Human T-cell lymphotrophic virus (HTLV) types I and II are retroviruses discovered in the 1980s[1]. HTLV can be transmitted vertically from mother to child or between adults through sexual or blood-borne routes. Transmission from mother to child can occur before birth through the placenta or during caesarean delivery but most commonly occurs through breastfeeding. Longer duration of breastfeeding and high maternal proviral load increases the risk of infection[2;3].

Once acquired, HTLV infection is life-long[1]. Most individuals infected with HTLV remain asymptomatic but it can lead to severe illness such as adult T-cell leukaemia/ lymphoma (ATLL) and HTLV-associated myelopathy (HAM)/ tropical spastic paraparesis (TSP) in about 10% of infected individuals[2;3]. Most cases of ATLL occur after infection in childhood[4]. There is no cure or vaccine for HTLV[3]. Strategies to prevent infection focus on avoiding transmission, for example, through avoiding or limiting the duration of breastfeeding[2].

HTLV-I is endemic in some regions of the world including Southern Japan, West and Central Africa, the Caribbean, Central and South America and Melanesia[2]. The prevalence of HTLV-II is highest in some African populations, Native Americans and injecting drug users[5]. HTLV-1 is uncommon in the general European population, but is reported in specific populations such as immigrants from endemic areas, sex workers and intravenous drug users[1]. Prevalence decreases in subsequent generations migrating from endemic areas[1]. A prevalence of 4.4 per 10,000 (95%CI 3.5 to 5.2) was identified in a study of HTLV-I and HTLV-II in 234,078 pregnant women in Western Europe from Belgium, France, Germany, Italy, Portugal, Spain and the UK[6]. A UK study of 126,010 newborn dried blood spot samples predicted an overall prevalence of 3.1 per 10,000 for HTLV for the UK with prevalence ranging considerably for sub groups of the population[7]. For example, the prevalence estimates ranged from 169 per 10,000 for babies born to women who were born in the Caribbean and 1.1 per 10,000 for non-Black Caribbean babies born to mothers who were born in non-endemic, non-inner city areas[7]. Further details of this study are provided in the next section.

Antenatal screening of pregnant women takes place in some countries where HTLV is endemic. In Japan, women are screened for HTLV-1 by either a chemiluminescent enzyme immunoassay or particle agglutination screening test[2]. These screening tests are considered to have high sensitivity and specificity but still generate a substantial number of false-positive results, especially in non-endemic areas[2]. Western blot and/or polymerase chain reaction are used as confirmation tests[2]. Pregnant women who test positive for HTLV-I are advised to formula-feed their infants, use frozen-thawed breast milk or breastfeed for a maximum of 3 months[2].

Universal antenatal screening for HTLV in the UK was proposed during the 1990s around the same time that antenatal screening for HIV was being considered[5]. This was proposed as a means for preventing ATLL by promoting avoidance of breastfeeding by mothers identified as HTLV positive[5]. This approach has been reported in selected population groups in endemic areas[5]. Around this time, it was suggested that an initial screening sensitive test, such as a particle agglutination assay could be followed by a more specific enzyme linked immunosorbent assay (ELISA)[4].

Recently, the need for universal antenatal screening in the UK has been reasserted due to the lack of interventions to prevent ATLL in HTLV-1 carriers and the poor prognosis in people affected by ATLL[5]. However, the strategy has not been recommended in studies which have considered it in non-endemic countries[5].

Guidance from the National Institute of Health and Care Excellence on donor breast milk banks includes HTLV as one of the conditions that potential donors should be tested for[8].

Basis for current recommendation

This is the fourth time that the UK NSC has considered antenatal screening for HTLV infection. The current UK NSC policy is that systematic population screening for HTLV infection in pregnancy is not recommended. The previous UK NSC external review of antenatal screening for HTLV infection was produced in 2012[1]. The previous review concluded that there was no new evidence that an antenatal screening programme for HTLV-I or HTLV-II would be effective in reducing mortality or morbidity. The previous review concluded that screening for HTLV-I and HTLV-II is not recommended because[1]:

- "prevalence of infection in the UK is low and restricted to specific subgroups
- risk of mother-to-child transmission through breastfeeding is low, unless breastfeeding is prolonged beyond 6 months
- most infected infants remain asymptomatic and the life time risk of subsequent serious disease appears to be low
- there is no treatment and the only approach to prevention is the avoidance of breastfeeding, particularly prolonged breastfeeding
- the potential harm cannot be underestimated. Women with HTLV infection will be identified, there is no treatment, and most will not develop HTLV related disease in later life. This situation may cause significant anxiety and stress to the women and their families."

Current update review and approach taken

The current review considers antenatal screening for HTLV infection and was prepared by Solutions for Public Health (SPH) in discussion with the UK NSC evidence team.

The current evidence summary was developed using a rapid review methodology and assessed using the UK NSC reporting checklist for evidence summaries. The key questions addressed in the current update review were developed by the UK NSC and are based on the key areas where HTLV infection did not meet the criteria for a screening programme in the last 2012 UK NSC review. The aim of the current review is to update the evidence in these key areas, namely around the prevalence of HTLV-I and II in pregnant women in the UK, the accuracy of antenatal screening tests for HTLV and the effectiveness of breastfeeding avoidance in the prevention of HTLV transmission. The key questions and the UK NSC criteria that they relate to are presented in Table 1 below.

A systematic literature search of 3 databases was conducted by the UK NSC evidence team in December 2016 for new evidence published since January 2011. The search was structured around the issues raised in the 2012 UK NSC external review. A total of 158 unique references were identified and sifted by title and abstract by the UK NSC evidence team for potential relevance to the review. Fifty references were sent to SPH for further appraisal and possible inclusion in the final review.

A supplementary search was conducted by the UK NSC evidence team in January 2017 for background and contextual information published between 1990 and 2017. This additional search was performed because of the lack of UK epidemiological studies identified in the first search. A total of 2,579 unique references were identified and sifted by title and abstract by the UK NSC evidence team for potential relevance to the review. Two hundred and ninety-eight references were sent to SPH for further appraisal.

Details of the databases searched, search terms and a flow diagram summarising the references identified are presented in the Search Strategy section at the end of this report. Selection and appraisal of studies was undertaken by one reviewer. Any queries were resolved through discussion with a second reviewer.

Forty studies were identified as potentially relevant during title and abstract sifting and further assessed at full text. This includes papers where relevance could not be determined from the title or abstract alone. Twenty-six of these studies came from the first search and 14 from the second search. Only studies published between 2011 and January 2017 were considered for full inclusion in the evidence summary. Any older relevant papers identified from the supplementary search were eligible for inclusion in previous UK NSC reviews of HTLV and are therefore only used in this update evidence summary as references to provide context for discussion.

Reasons for excluding studies at the abstract stage included:

- studies with non-UK, non-pregnant populations ie blood donors, general populations, dialysis patients, transplant patients
- studies focusing on changes in prevalence in non-UK countries
- studies about the monitoring of HTLV carriers
- studies focusing on testing for other infectious diseases
- studies on the treatment of ATLL, HAM or TSP
- guidelines/discussion about feeding methods
- discussion papers.

Each section below provides information on the evidence selection process and number of included studies for the given criterion.

The review was quality assured by a second senior reviewer who was not involved with the writing of the review in accordance with SPH's quality assurance process.

Table 1: Key questions for current review of screening for HTLV infection

Criterion*	Key Questions	# Studies Included
1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.	What is the prevalence of HTLV-1 & 2 in the pregnant population in the UK?	0
4. There should be a simple, safe, precise and validated screening test.	What is the accuracy of antenatal screening tests for HTLV?	11
9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	What is the effectiveness of breastfeeding avoidance in the prevention of HTLV transmission?	1

* UK NSC evidence review criteria (January 2016)

Appraisal against UK NSC Criteria[†]

Each of the key questions and their associated criteria are considered in turn below.

Each criterion was summarised as 'met', 'not met' or 'uncertain' by considering the results of the included studies in light of the volume, quality and consistency of the body of evidence. Several factors were considered in determining the quality of the identified evidence, including study design and methodology, risk of bias and applicability of the evidence.

Criterion 1: The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.

Key Question: What is the prevalence of HTLV-I and HTLV-II in the pregnant population in the UK?

Sub-question: How does prevalence differ in women from endemic and non-endemic areas?

The 2012 UK NSC review found limited information on the prevalence of HTLV-I and HTLV-II in pregnant women. One study was cited which found a prevalence of 4.4 per 10,000 in 234,078 pregnant women in Belgium, France, Germany, Italy, Portugal, Spain and the UK. Another study estimated a prevalence of 3.1 per 10,000 for the UK based on 126,000 newborn blood samples[‡] in the London area. The 2012 UK NSC review concluded that the prevalence of infection in the UK is low and restricted to specific subgroups[1].

Description of the evidence

In the current review, of the 26 studies published between 2011 and 2016 that were identified as potentially relevant from the first search, 1 related to this criterion[9]. After review of the full text this study was excluded because it did not include any UK data and the non-UK incidence figures that were provided were not for pregnant women. Therefore, no papers were identified to update the UK prevalence of HTLV-I and HTLV-II in pregnant women.

The supplementary search identified 5 papers published prior to 2011 which provided prevalence data in specified UK populations of pregnant women from antenatal clinics in London or Birmingham. Table 6 in the appendix presents brief details of these studies for information. The prevalence of HTLV for these populations ranged from 5.8 per 10,000 to 27 per 10,000. The largest study including 126,010 newborn dried blood spot samples from babies born in the North Thames Regional Health Authority Area had a prevalence of 5.8 per 10,000. The authors used this figure to predict an overall prevalence of 3.1 per 10,000 for HTLV for the UK, equating to 223 pregnancies in mothers infected with HTLV in the UK per year (95% CI 113 to 347) (Ades et al 2000[7]). The authors also provided prevalence estimates for sub groups of UK women:

- born in the Caribbean: 169 per 10,000 (95%CI 92 to 283)

[†]These criteria are available online at UK NSC evidence review criteria (January 2016)

[‡] The presence of antibodies in newborns indicates maternal infection**Error! Bookmark not defined.**

- born in other endemic areas: 32 per 10,000 (95%CI 15 to 59)
- Black Caribbean born in non-endemic area: 68 per 10,000 (95%CI 31 to 129)
- not Black Caribbean, born in non-endemic areas, inner London or principle cities: 3.5 per 10,000 (95%CI 1.4 to 7.0)
- not Black Caribbean, born in non-endemic areas, rest of UK: 1.1 per 10,000 (95%CI 0.1 to 3.2)

Separate prevalence estimates for HTLV-I and HTLV-II were not reported. However, of the HTLV cases identified 88% were HTLV-I; 3% were HTLV-II and 9% were un-typed[7]. This study was included in the previous 2012 NSC review and represents the latest available figure for the prevalence of HTLV in the UK.

Additional information on the prevalence of HTLV in other countries is provided in the next section which considers test performance in antenatal populations. Briefly, the prevalence in these studies ranged from 10 per 10,000 to 130 per 10,000. Eight of these 10 studies were from populations in different regions of Japan and Brazil which are both areas of the world where HTLV is considered to be endemic. The populations of the other 2 studies were immigrants to Spain, including women from endemic countries.

Discussion

No new studies on the prevalence of HTLV in pregnant women in the UK were published between 2011 and January 2017. The UK prevalence of 3.1 per 10,000 for HTLV from a UK study published in 2000 and reported in the previous NSC review remains the latest available figure. This study also reported estimated prevalence figures for sub groups of the UK population which ranged from 169 per 10,000 for women born in the Caribbean to 1.1 per 10,000 for women who were not of Black Caribbean ethnicity, were not born in non-endemic areas and were not from inner London or a principle city. This study estimated that there would be 223 pregnancies in mothers infected with HTLV in the UK per year (95% CI 113 to 347). These authors also estimated that between 10 and 20 women infected with HTLV would need to be diagnosed to prevent one paediatric infection.

No separate prevalence figures for HTLV-I and HTLV-II in the UK were identified. The UK prevalence is lower than that found in areas of the world where HTLV is considered endemic.

Summary: Criterion 1 not met

The previous NSC review concluded that the prevalence of HTLV infection in the UK is low and restricted to specific subgroups. No studies were published between 2011 and January 2017 that provide an updated figure for the prevalence of HTLV in the UK. In the absence of any new information the conclusion of the previous review is retained and this criterion is not met.

Criterion 4: There should be a simple, safe, precise and validated screening test.

Key Question: What is the accuracy of antenatal screening tests for HTLV?

The UK NSC review protocol states that the purpose of this question is to explore the accuracy of tests reported in studies of pregnant women. It also states that studies of consecutively enrolled women should be prioritised.

The 2012 UK NSC review stated that testing for HTLV is well established as blood donors are routinely screened to avoid contamination of blood supplies. The 2012 review stated that diagnosis in blood donors is made by detecting the presence of HTLV antibodies by ELISA and

Western blot analysis and that 2 sequential screening tests with inconclusive results are confirmed by Western blot test. No details on test performance (ie sensitivity and specificity) were reported.

Serum samples were used to test for HTLV in 4 of the 5 papers assessing prevalence in UK populations of pregnant women published prior to 2011 as discussed in response to the previous key question. The fifth paper used a dried bloodspot[7].

Description of the evidence

In the current review, of the 26 studies published between 2011 and 2016 that were identified as potentially relevant from the first search, 21 related to this criterion. After review of the full texts 11 studies were included. The second search did not identify any further studies on screening test performance in antenatal populations.

Reasons for excluding studies at this stage included:

- studies that did not provide separate details of screening and diagnostic test results
- studies that did not use a consecutively enrolled or general antenatal population

None of the identified studies were designed to assess the accuracy of antenatal screening tests for HTLV and therefore do not provide information to fully answer the key question.

Ten studies assessing the prevalence of HTLV in consecutively enrolled populations of pregnant women were included. These studies were not designed to assess test performance but do provide details on the screening and diagnostic tests used, the number of positive screening tests and the number that were subsequently confirmed as positive. As previously stated, these populations were from Japan and Brazil or were immigrants to Spain. The populations were from areas of the world where HTLV is considered endemic, however the prevalence of HTLV in different regions in these countries varied. An indication of whether the study population was from an endemic or non-endemic area is given where this information was stated by the study authors.

The proportion of screen positive women who were confirmed as HTLV cases ranged from 25% to 100%. In 7 of the 10 studies the proportion of screen positive women with a confirmed diagnosis was over 80%. In 3 studies the proportion of positive screening tests with a confirmed diagnosis was around 50% or less. In 2 of these 3 studies the prevalence of HTLV was lower compared to the other studies included in this section. The third study was from a non-endemic region of Japan. The prevalence of HTLV was higher in all of these studies compared to the UK which reduces their potential applicability to a UK screening population.

A range of different screening tests were used, using serum and dried blood spot samples. Western blot was most commonly used as the confirmation test. In 3 studies not all women received the confirmation test. It is therefore possible that some cases were missed. As these studies were not designed to assess test performance, only women with a positive screening test were offered confirmation testing. As there was no follow up of women who received a negative screening test it is possible that some HTLV cases were missed (ie false negatives).

The results of these studies are summarised in Table 2 and in Appendix Tables 7 to 16.

Table 2: Studies testing for HTLV in populations of pregnant women

Study and Country	Tests performed	Population and number tested	Number positive on screening test (% of tested)	Number of confirmed diagnoses (% of screen positives)	Prevalence HTLV per 10,000
Moura et al (2015)[10] North-Eastern Brazil	**Tested for:** HTLV-I and HTLV-II **Screening test:** ELISA (dried blood spot) **Confirmation test:** Western blot	54,798 pregnant women attending a health clinic between 2007 and 2012	129 (0.2%)	118 (91%)	20 (95%CI 18 to 26)
Yamada et al (2014)[11] Hokkaido, Japan	**Tested for:** HTLV-I **Screening test:** PA or CMIA (serum) **Confirmation test:** Western blot or PCR	33,617 pregnant women receiving antenatal screening for HTLV-I at 111 facilities in 2012	81 (0.2%)	34 (54% of 63 who had a confirmation test) Confirmation test results not available for all screen positive tests	10 95% CI not reported
Suzuki et al (2014)[12] Japan	**Tested for:** HTLV-I **Screening test:** EIA or PA (serum) **Confirmation test:** Western blot	Data from 707,711 women screened for HTLV-I at 1,883 obstetrical facilities in 2011	2,259 (0.3%)	942 (50% of 1,894 who had a confirmation test) Confirmation test results not available for all screen positive tests	16 (data used to provide estimate for Japan) 95% CI not reported
Monteiro et al (2014)[13] Rio de Janeiro, Brazil	**Tested for:** HTLV-I and HTLV-II **Screening test:** CMIA (serum) **Confirmation test:** Western blot	1,204 pregnant women attending 2 hospitals between 2012 and 2013	10 (0.8%)	8 (80%) (7 HTLV-I; 1 HTLV-II)	66 HTLV-I and II prevalence not reported separately 95% CI not reported

Mello et al (2014)[14] Southern Brazil (endemic area)	**Tested for:** HTLV-I **Screening test:** ELISA (serum) **Confirmation test:** Western blot and PCR	2,766 pregnant women attending antenatal clinics at 2 health centres between 2008 and 2010	34 (1.2%)	29 (85%)	105 95% CI not reported
Nerome et al (2014)[15] Kagoshima, Japan (endemic area)	**Tested for:** HTLV-I **Screening test:** PA or CLIA (serum) **Confirmation test:** Western blot or IA	8,719 pregnant women attending 36 obstetric facilities in 2012	119 (1.4%)	112 (94%)	130 95% CI not reported
Sequiria et al (2012)[16] Northern Brazil	**Tested for:** HTLV-I and HTLV-II **Screening test:** EIA (dried blood spot) **Confirmation test:** Western blot	13,382 pregnant women attending healthcare units for prenatal care in 19 districts in 2008	43 (0.3%)	41 (95%) (39 HTLV-I; 1 HTLV-II; 1 indeterminate)	30 95% CI not reported
Hanaoka et al 2012[17] Tokyo, Japan (non-endemic area)	**Tested for:** HTLV-I **Screening test:** CLEIA (serum) **Confirmation test:** Western blot	11,352 women who gave birth at 1 centre between 2002 and 2009	37 (0.3%)	9 (25% of 36 who had a confirmation test) Confirmation test results not available for all screen positive tests	33 95% CI not reported
Ramos et al (2011)[18] Immigrants to Spain (including women from endemic countries)	**Tested for:** HTLV-I and HTLV-II **Screening test:** EIA (serum) **Confirmation test:** Western blot	1,439 pregnant women attending a hospital between 2006 and 2009	3 (0.2%)	3 (100%) (1 HTLV-I; 2 HTLV-II)	21 (95%CI 5 to 66) (HTLV-I: 7 (95%CI 1 to 45); HTLV-II: 14 (95%CI 2 to 56)

Treviño et al (2011)[19] Immigrants to Spain (including women from endemic countries)	**Tested for:** HTLV-I and HTLV-II **Screening test:** EIA (serum) **Confirmation test:** Western blot or PCR	3,337 pregnant women attending 14 clinics between 2009 and 2010	8 (0.2%)	7 (88%) (6 HTLV-I; 1 HTLV-II)	20 (HTLV-I: 17; HTLV-II: 2) 95% CI not reported

CLEIA – chemiluminescent enzyme immunoassay; CLIA – chemiluminescent immunoassay; CMIA – chemiluminescent microparticle immunoassay; EIA – enzyme immunoassay; ELISA – enzyme-linked immunosorbent assay; IA – immunofluorescence assay; PA – particle agglutination; PCR – polymerase chain reaction

One study set in Brazil (Boa-Sorte et al 2014[20]) compared the performance of screening using dried blood spot compared to serum in pregnant women. The performance of screening using a dried blood spot as an alternative to serum was of interest due to advantages regarding ease of collection, transportation and storage, room temperature sample stability and lower risk of contamination[20]. It should be noted that this study compares the 2 screening methods against each other rather than against an established gold standard confirmation test. Women attending for prenatal checks at 11 primary healthcare units in Brazil between November 2009 and March 2010 were invited to take part and 692 consented. Samples were screened using ELISA from a dried blood spot and serum sample. One woman tested positive for HTLV on both testing methods, a prevalence of 14 per 10,000 (95%CI 1 to 71). There were no conflicting results between the 2 tests. The authors reported a sensitivity of 100% (95%CI 20.6% to 100%) and a specificity of 100% (95%CI 99.4% to 100%).

The quality of this study was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) framework. The QUADAS-2 framework is used to assess the quality of primary test accuracy studies and includes 5 domains on patient selection, the index test, the reference standard, test strategy flow and timing and applicability[§]. The areas in which this study was at high risk of bias were around the absence of a confirmation test and the applicability to a UK screening population, as the prevalence of 14 per 10,000 observed in this population is higher than that found in the UK. Further details on the QUADAS-2 scores are provided in Appendix Table 17.

Discussion

No studies were identified to answer the key question on the accuracy of antenatal screening tests for HTLV. Of the studies included, none were conducted in the UK and very few in Western European or non-endemic populations. The previous UK NSC review noted that testing for HTLV is well established as blood donors are routinely screened but did not provide details of test performance metrics (ie sensitivity, specificity, positive predictive value (PPV) or negative predictive value (NPV)).

One study provided sensitivity and specificity results but compared 2 screening methods against each other rather than assessing the performance of a screening test using an established confirmation test. Sensitivity and specificity were 100% in this study, although the 95% confidence intervals around the sensitivity score were wide reducing confidence in the result.

In the other 10 included studies, only women with a positive screening test were offered confirmation testing and in 3 of these studies, including the study with the largest sample size, not all women received a confirmation test. These studies provide some information on the number of screening tests that were positives and true positives although gaps in the

[§] The patient selection domain considers the study design, the population sample and the patient exclusions; the index test domain considers assessor blinding and the process for determining the threshold to be used; the reference standard domain considers test performance and assessor blinding; the test strategy and flow and timing domain considers the interval between the test and reference standard and whether all patients received the reference standard and were included in the analysis; the applicability domain considers applicability to a UK screening population and the relevance of the test and reference standard to the UK.

confirmation testing suggests that positive cases could have been missed. In addition, no confirmation testing was conducted on women who received a negative screening test therefore the number of true negatives and false negatives (ie missed cases) are not known. Details of true negatives and false negatives are required to calculate sensitivity, specificity PPV and NPV.

In all of the included studies, the prevalence of HTLV was higher than the latest available estimate for the UK. One of the included studies (Hanaoka et al 2012[17]) included a comparison of the ratio of positive screening and confirmation tests in endemic and non-endemic countries. The authors concluded that the rate of false positive screening tests is lower in areas where prevalence is high (endemic areas) but that false positive rates will be higher in areas with lower prevalence.

Summary: Criterion 4 not met

Insufficient information was available to calculate the performance of HTLV screening tests in a UK antenatal population. The number of false positive tests tends to be higher in populations with lower prevalence of HTLV which is a consideration for a non-endemic area like the UK. In the absence of information to address the key question this criterion is not met.

Criterion 9: There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.

Key Question: What is the effectiveness of breastfeeding avoidance in the prevention of HTLV transmission?

Sub-question: Has the impact on prevention of adult T-cell leukaemia/ lymphoma been established in studies of breastfeeding avoidance?

The 2012 UK NSC review reported transmission rates from mother to infant of "2.7% in formula fed infants, 5% in infants breast fed for 3 months and 20% where breastfeeding is prolonged"[1]. The previous UK NSC review concluded that the risk of mother-to-child transmission is low, unless breastfeeding is continued beyond 6 months[1].

Description of the evidence

In the current review, of the 26 studies published between 2011 and 2016 that were identified as potentially relevant from the first search, 4 related to this criterion. After review of the full texts 1 study was included. The other 3 studies were discussion papers. The second search did not identify any further recent studies on breastfeeding avoidance.

Ribeiro et al (2012)[21] conducted a 1 year follow-up of 42 infants whose mothers were screen positive for HTLV as part of a newborn screening programme in Brazil and were counselled to avoid breastfeeding. Forty of the 42 mothers were screen positive for HTLV-I and 35 consented to have their infants tested at 12 months. Of these, 1 infant was confirmed to have HTLV-I (2.8%). Five of the 40 mothers with HTLV-I in the screening programme did not consent to have their infants tested at 12 months. It is possible that further HTLV-I cases might have been

identified in these 5 infants. Two mothers were confirmed to have HTLV-II and both infants of these mothers tested negative for HTLV-II at 12 months.

The mean duration of breastfeeding by the HTLV-I positive mothers was 27 days (range 0 to 60 days). The mother of the HTLV-I positive infant reported that they had breast fed for 7 days. The mean duration of breastfeeding by the HTLV-II positive mothers was not known. Further details of this study are presented in Appendix Table 18.

Discussion

The rate of transmission from mother to infant in Ribeiro et al's[21] study (2.8%) was the same as the 2.7% transmission rate from mother to infant in formula fed infants cited in the previous UK NSC review.

No studies providing updated information on the rate of transmission in mothers breastfeeding for longer periods were identified.

No studies were identified addressing the sub-question concerning the impact on prevention of adult T-cell leukemia/ lymphoma in studies of breastfeeding avoidance.

Summary: Criterion 9

No new evidence was identified to change the conclusion of the previous UK NSC review which was that the risk of mother-to-child transmission is low, unless breastfeeding is continued beyond 6 months.

Conclusions and implications for policy

This report is an update review on systematic population screening for HTLV infection against select UK NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme. This review assessed key questions to determine whether new evidence published since 2011 suggests that reconsideration of the current recommendation for screening for HTLV infection in the UK is required.

The volume, quality and direction of new evidence published since January 2011 does not indicate that there have been any significant changes in the evidence base since the previous review. The conclusions of the previous UK NSC review are retained. The key concerns are:

- the prevalence of HTLV infection in the UK is low and restricted to specific subgroups of the population
- no studies providing details on the performance of HTLV screening tests in a UK antenatal population were identified. However, it is probable, given the low prevalence of HTLV in the UK, that an antenatal screening programme in the UK would produce a high number of false positive tests
- the risk of mother-to-child transmission through breastfeeding is low unless breastfeeding is continued beyond 6 months
- most infected infants remain asymptomatic and the life time risk of subsequent serious disease appears to be low
- there is no treatment for HTLV and the only approach to prevention is the avoidance of breastfeeding, particularly breastfeeding after 6 months

- the potential for harm cannot be underestimated. Women with HTLV infection will be identified, there is no treatment, and about 90% will not develop HTLV related disease in later life. This situation may cause significant anxiety and stress to the women and their families.

Recommendation

The review concluded that there has been no significant change in the evidence base since the previous UK NSC review. The current recommendation not to introduce a UK systematic antenatal population screening programme for HTLV infection should be retained.

Limitations

Limited new evidence was identified to address the key questions in this review.

This rapid review process was conducted over a condensed period of time (approximately 12 weeks). Searching was limited to 3 bibliographic databases and did not include grey literature sources. The review was guided by a protocol developed *a priori*. The literature search and first appraisal of the results were undertaken by a UK NSC information scientist, and further appraisal and study selection by one reviewer. Any queries at both stages were resolved through discussion with another reviewer, or with the UK NSC evidence team. Studies not available in the English language, abstracts, conference reports and poster presentations were not included. Study authors were not contacted and studies that were not published in peer-reviewed journals were not reviewed.

Search strategy

A literature search on antenatal screening for HTLV-I and HTLV-II was performed by Paula Coles, Information Scientist for the UK NSC in December 2016 (search 1).

A supplementary literature search to cover background and contextual issues was performed by Paula Coles for the UK NSC in January 2017 (search 2).

Search 1

SOURCES SEARCHED: Medline, Embase, Cochrane Library

DATES OF SEARCH: January 2011 to 28th December 2016

SEARCH STRATEGY

Medline (OVID interface). Similar searches were carried out in the other databases.

1. Human T-lymphotropic virus 1/ (6043)
2. HTLV-I Infections/ 3905
3. Human T-lymphotropic virus 2/ 941
4. HTLV-II Infections/ 906
5. HTLV$.tw. 13746
6. human t-cell lymphotropic virus$.tw. (2352)
7. 1 or 2 or 3 or 4 or 5 or 6 (15250)
8. Prevalence/ 257030
9. Incidence/ (236910)
10. (inciden$ or prevalen$).ti,ab. 1358952
11. 8 or 9 or 10 (1504632)
12. UK.in. (989786)
13. (UK or United Kingdom or Great Britain or Britain or GB or England or Wales or Scotland or Ireland).ti,ab. (223937)
14. (english or welsh or scottish or irish or british).ti,ab. (211872)
15. 12 or 13 or 14 (1292186)
16. 7 and 11 and 15 (146)
17. limit 16 to yr="2011 -Current" (16)
18. Mass Screening/ (100158)
19. Prenatal Diagnosis/ (36196)
20. (screen$3 or detect$3 or test or tests or testing).tw. (4125651)
21. 18 or 19 or 20 (4167697)
22. pregnan$.tw. (464531)
23. Pregnancy/ (861661)
24. (pregnan$ or antenatal$ or prenatal$).tw. (533236)
25. 22 or 23 or 24 (992168)
26. "Sensitivity and Specificity"/ (343194)
27. (sensitiv$ or specific$).tw. (3814143)
28. "Predictive Value of Tests"/ (190173)
29. (PPV or NPV).ti,ab. (15406)
30. ((positive or negative) adj predictive value$).ti,ab. (56185)
31. 26 or 27 or 28 or 29 or 30 (4098490)
32. 21 or 31 (7089129)
33. 7 and 25 and 32 (230)

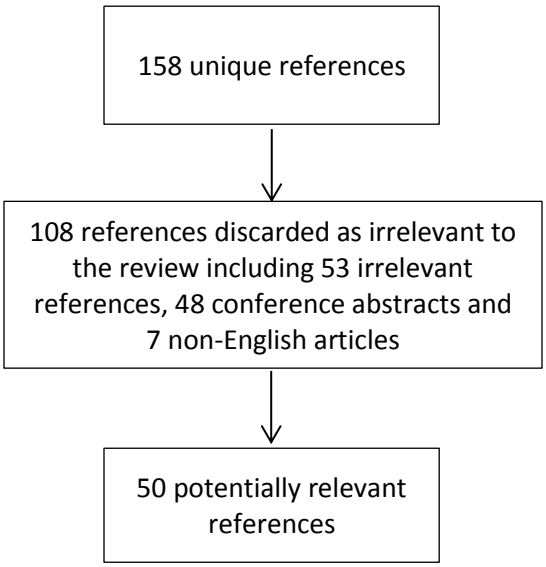
34. limit 33 to yr="2011 -Current" (38)
35. Feeding Methods/ (979)
36. feeding method$.tw. (1140)
37. ((breast feeding or breastfeeding) adj2 (avoid$ or interrupt$)).tw. (336)
38. Pregnancy Complications, Infectious/pc [Prevention & Control] (4929)
39. Infectious Disease Transmission, Vertical/pc [Prevention & Control (]6990)
40. Breast Feeding/ae [Adverse Effects] (1486)
41. mother to child transmission.tw. (4508)
42. vertical$ transmi$.tw. (6178)
43. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (21272)
44. 7 and 43 (230)
45. limit 44 to yr="2011 -Current" (41)
46. 17 or 34 or 45 (77)

Table 3: Results of literature search 1

Database	No. of citations retrieved
Medline	77
Embase	132
Cochrane Library	23
Total	**232**

After 74 duplicates were removed, 158 unique references were sifted by title and abstract, and where necessary and available the full text, for potential relevance to the review. Fifty papers remained and were passed to the SPH reviewer for further consideration.

Figure 1: Flow diagram summarising the results of the reference sifting process for search 1



These 50 references were classified as presented in Table 4

Table 4: Summary of the relevant references by category

Category	No. of citations
UK Prevalence	2
Screening test	34
Mother to child transmission prevention	14
Total	**50**

Search 2

SOURCES SEARCHED: Medline

DATES OF SEARCH: January 1990 to 5th January 2017

SEARCH STRATEGY
Medline (OVID interface):
1 Human T-lymphotropic virus 1/ (6065)
2 HTLV-I Infections/ (3920)
3 Human T-lymphotropic virus 2/ (945)
4 HTLV-II Infections/ (908)
5 HTLV$.tw. (13780)
6 human t-cell lymphotropic virus$.tw. (2357)
7 1 or 2 or 3 or 4 or 5 or 6 (15286)
8 Prevalence/ (260088)
9 Incidence/ (239503)
10 (seroprevalen$ or inciden$ or prevalen$).ti,ab. (1378803)
11 8 or 9 or 10 (1524874)
12 7 and 11 (2314)
13 limit 12 to yr="1990 -Current" (1835)
14 Mass Screening/ (100987)
15 Prenatal Diagnosis/ (36497)
16 (screen$3 or detect$3 or test or tests or testing).tw. (4158255)
17 14 or 15 or 16 (4200531)
18 pregnan$.tw. (469989)
19 Pregnancy/ (870657)
20 (pregnan$ or antenatal$ or prenatal$).tw. (539287)
21 18 or 19 or 20 (1001888)
22 "Sensitivity and Specificity"/ (346038)
23 (sensitiv$ or specific$).tw. (3841527)
24 "Predictive Value of Tests"/ (192111)
25 (PPV or NPV).ti,ab. (15633)
26 ((positive or negative) adj predictive value$).ti,ab. (56792)
27 22 or 23 or 24 or 25 or 26 (4128489)
28 17 or 27 (7142540)
29 7 and 21 and 28 (231)
30 limit 29 to yr="1990 -Current" (173)
31 Feeding Methods/ (1008)
32 feeding method$.tw. (1146)
33 ((breast feeding or breastfeeding) adj2 (avoid$ or interrupt$)).tw. (338)

34 Pregnancy Complications, Infectious/pc [Prevention & Control] (5004)
35 Infectious Disease Transmission, Vertical/pc [Prevention & Control] (7105)
36 Breast Feeding/ae [Adverse Effects] (1498)
37 mother to child transmission.tw. (4591)
38 vertical$ transmi$.tw. (6241)
39 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 (21566)
40 7 and 39 (234)
41 limit 40 to yr="1990 -Current" (205)
42 13 or 30 or 41 (2016)
43 HTLV-I Infections/dt, th [Drug Therapy, Therapy] (164)
44 HTLV-II Infections/dt, th [Drug Therapy, Therapy] (7)
45 43 or 44 (166)
46 Treatment outcome/ (862079)
47 (treat$ or therap$).ti. (1987063)
48 46 or 47 (2613121)
49 7 and 48 (537)
50 45 or 49 (630)
51 limit 50 to yr="1990 -Current" (539)
52 Disease Progression/ (148602)
53 Prognosis/ (466994)
54 (disease adj2 (predict$ or course or progress$ or outcome$)).ti,ab. (145064)
55 (natural adj (course or history)).ti,ab. (53779)
56 52 or 53 or 54 or 55 (746068)
57 7 and 56 (709)
58 limit 57 to yr="1990 -Current" (615)
59 51 or 58 (1087)
60 42 or 59 (2922)

After 343 duplicates were removed, 2,579 unique references were sifted for potential relevance to the review.

Inclusions:

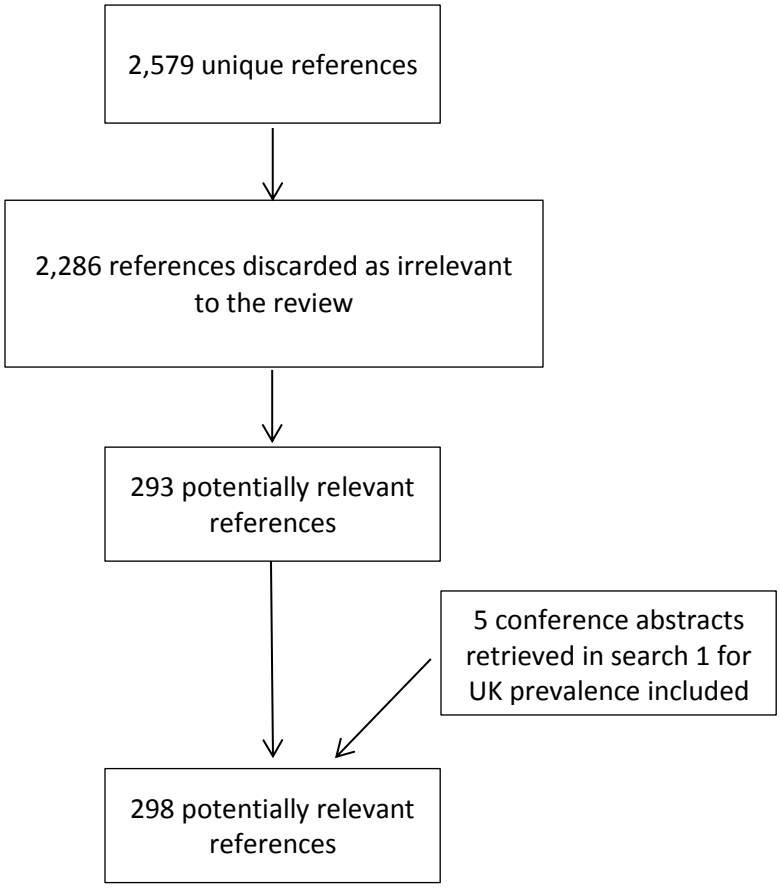
- any article referring to UK epidemiological data (including high-risk groups and recent conference abstracts)
- prevalence in comparable populations to the UK (Europe, Canada, USA, Australia and New Zealand)
- global and European epidemiology
- systematic and non-systematic reviews on natural history, screening and treatment of HTLV-I and HTLV-II (for background and context)

Exclusions:

- articles not in English
- high-risk groups (except for UK prevalence)

Two hundred and ninety-eight papers remained and were passed to the SPH reviewer for further consideration.

Figure 2: Flow diagram summarising the results of the reference sifting process for search 1



These 298 references were classified as presented in Table 5

Table 5: Summary of the relevant references by category

Category	No. of citations
UK prevalence (1990 to 2017)	26
UK prevalence conference abstracts from first search (2011 to 2017)	5
Global/ European prevalence (1990 to 2017)	20
Prevalence in comparable populations (1990 to 2017) Antenatal (8) Blood/ tissue donors/ recipients (73) General populations (32) Populations originating from endemic areas (7)	120
Context/ background (1990 to 2017) Systematic reviews (3) Reviews (72)	75
Treatment (1990 to 2017) Systematic reviews (1) Reviews (51)	52
Total	**298**

Key question PICOS[**]

Question	What is the prevalence of HTLV-1 & 2 in the pregnant population in the UK?
Sub-questions	How does prevalence differ in women from endemic and non-endemic areas?
Population	Pregnant women in the UK
Intervention	N/a
Comparator	N/a
Outcomes	Prevalence stratified by country of origin

Question	What is the accuracy of antenatal screening tests for HTLV?
Comments	The previous review noted that tests for HTLV were established through testing donated blood. Concerns about the false positive rate have been reported in some contexts such as donated cord blood. The purpose of this question is to explore the accuracy of tests reported in studies of pregnant women. Studies of consecutively enrolled women should be prioritised. Predictive vales should be reported with particular reference to the geographical location of the study.
Population	Pregnant women in any country
Intervention	Any antibody test for HTLV infection (eg EIA, particle agglutination)
Comparator	Any reference standard (eg usually Western Blot or line immunoassay (LIA) +/- PCR)
Outcomes	Sensitivity / Specificity Positive/ Negative Predictive Value

Question	What is the effectiveness of breastfeeding avoidance in the prevention of HTLV transmission?
Sub-questions	Has the impact on prevention of ATLL been established in studies of breastfeeding avoidance?
Comments	Prospective studies of this intervention in women identified by screening should be prioritised. Studies in non-endemic areas should be prioritised. Studies in endemic areas should be considered less direct level of evidence in relation to the UK setting.
Population	Pregnant women identified by screening or proxy populations where applicable (eg HTLV carriers identified by testing newborn bloodspots)
Intervention	Promotion of breastfeeding avoidance
Comparator	Any comparator if comparative studies are identified
Outcomes	HTLV positive status of infants born to women identified through screening

[**] Population, Intervention, Comparator, Outcomes

Appendix

Table 6 presents brief details of 5 papers published prior to 2011 which provided prevalence data in specified UK populations of pregnant women from antenatal clinics in London or Birmingham.

Table 6: Studies assessing the prevalence of HTLV in UK populations

Study	Population	Prevalence per 10,000	Comments
Ades et al (2000)[7]	126,010 babies born in the North Thames Regional Health Authority area from 1997-1998	5.8	Data used to predict an overall prevalence of 3.1 per 10,000 (95%CI 1.6 to 4.8) for UK pregnant women
Hale et al (1997)[22]	6,289 women attending an antenatal clinic in South East London between 1990 and 1992	22	
Nightingale et al (1993)[23]	3,522 women attending an antenatal clinic in Birmingham between 1990 and 1991	17 (95%CI 8 to 37)	
Bantvala et al (1990)[24]	3,760 women attending antenatal clinics at 1 hospital in London in 1988	27	
Tosswill et al (1990)[25]	2,956 women attending an antenatal clinic in London in 1980	20	

95% Confidence intervals included where reported

Appendix Tables of Included Studies

Appendix number	7
Relevant criteria	4. There should be a simple, safe, precise and validated screening test.
Relevant Key question	What is the accuracy of antenatal screening tests for HTLV?
Publication details	Moura AA. de Mello MJG. Correia JB. Prevalence of syphilis, human immunodeficiency virus, hepatitis B virus, and human T-lymphotropic virus infections and co-infections during prenatal screening in an urban Northeastern Brazilian population. International Journal of Infectious Diseases 2015, 39: 10-15
Study details	Prospective study
Study	To estimate the prevalence of HTLV infection in pregnant women in North-Eastern

objectives	Brazil
Inclusions	Pregnant women attending a health clinic between 2007 and 2012
Exclusions	None specified
Population	54,798 pregnant women
Intervention/ test	Enzyme-linked immunosorbent assay (ELISA) using a dried blood spot
Comparator	Western blot
Results	Number HTLV women screen positive using ELISA screening test: 129 Number confirmed cases using Western blot: 118 Percentage of screen positive women who are confirmed cases: 91% Prevalence of HTLV: 20 per 10,000
Comments	

Appendix number	8
Relevant criteria	4. There should be a simple, safe, precise and validated screening test.
Relevant Key question	What is the accuracy of antenatal screening tests for HTLV?
Publication details	Yamada T. Togashi T. Tsutsumi H. et al. Prevalence of human T-lymphotropic virus type 1 carriers among pregnant women in Hokkaido, Japan. Microbiology and Immunology 2014, 58: 427-431
Study details	Prospective study
Study objectives	To estimate the prevalence of HTLV infection in pregnant women in Hokkaido, Japan
Inclusions	Pregnant women attending 111 facilities in 2012
Exclusions	None specified
Population	33,617 pregnant women
Intervention/ test	Particle agglutination (PA) or chemiluminescent microparticle immunoassay (CMIA)
Comparator	Western blot or polymerase chain reaction
Results	Number HTLV screen positive women using EIA screening test: 81 Number screen positive women receiving a confirmation test: 63

	Number screen positive women confirmed as cases using Western blot or PCR: 34 Percentage of screen positive women who are confirmed cases: 54% Prevalence of HTLV: 10 per 10,000
Comments	95% confidence intervals not reported Not all of the women who were screen positive had a confirmation Western blot test so it is possible that some cases were missed

Appendix number	9
Relevant criteria	4. There should be a simple, safe, precise and validated screening test.
Relevant Key question	What is the accuracy of antenatal screening tests for HTLV?
Publication details	Suzuki S. Tanaka M. Matsudo H. et al. Current status of HTLV-I carrier in Japanese pregnant women. The Journal of Maternal-Fetal and Neonatal Medicine 2014, 27(3): 312-313
Study details	Retrospective study of pregnant women screened in Japan
Study objectives	To estimate the prevalence of HTLV-I infection in pregnant women in Japan
Inclusions	Pregnant women screened at 1,883 obstetric facilities in Japan in 2011
Exclusions	Data requested for women who delivered at ≥22 weeks gestation
Population	707,711 women screened during pregnancy
Intervention/ test	Enzyme immunoassays (EIA) or particle agglutination (PA)
Comparator	Western blot
Results	Number HTLV-I screen positive women: 2,259 Number screen positive women who had Western blot confirmation test: 1,894 Number screen positive women who were confirmed cases using Western blot: 942 Percentage of screen positive women who were confirmed cases: 50% Estimated prevalence of HTLV-I for Japan: 16 per 10,000
Comments	95% confidence intervals not reported This study used data from pregnant women who had received screening, but only requested data for women who delivered ≥22 weeks gestation. It is possible that

	some positive screening tests were not included Not all of the women who received a screen positive test had a confirmation Western blot test so it is possible that some cases of HTLV-1 were missed

Appendix number	10
Relevant criteria	4. There should be a simple, safe, precise and validated screening test.
Relevant Key question	What is the accuracy of antenatal screening tests for HTLV?
Publication details	Monteiro DLM. Taquette SR. Barmpas DBS et al. Prevalence of HTLV1/2 in pregnant women living in the metropolitan area of Rio de Janeiro. PLOS Neglected Tropical Diseases 2014, 9(8): e3146
Study details	Prospective study
Study objectives	To estimate the prevalence of HTLV infection in pregnant women in Rio de Janeiro, Brazil
Inclusions	Pregnant women attending 2 hospitals in Brazil between 2012 and 2013
Exclusions	None specified
Population	1,024 pregnant women
Intervention/ test	Chemiluminescent microparticle immunoassay (CMIA) using serum
Comparator	Western blot
Results	Number HTLV screen positive women using CMIA screening test: 10 Number screen positive women who were confirmed cases using Western blot: 8 (7 HTLV-I; 1 HTLV-2) Percentage of screen positive women who were confirmed cases: 80% Prevalence of HTLV: 66 per 10,000
Comments	95% confidence intervals not reported.

Appendix number	11
Relevant criteria	4. There should be a simple, safe, precise and validated screening test.
Relevant Key question	What is the accuracy of antenatal screening tests for HTLV?

Publication details	Mello MAG. da Conceição AF. Sousa SMB. et al. HTLV-1 in pregnant women from the Southern Bahia, Brazil: a neglected condition despite the high prevalence. Virology Journal 2014, 11:28
Study details	Prospective study
Study objectives	To estimate the prevalence of HTLV infection in pregnant women in an endemic area of Southern Brazil
Inclusions	Pregnant women attending 2 clinics between 2008 and 2010
Exclusions	None specified
Population	2,766 pregnant women
Intervention/ test	Enzyme-linked immunosorbent assay (ELISA) using serum
Comparator	Western blot and polymerase chain reaction
Results	Number HTLV screen positive women using ELISA screening test: 34 Number screen positive women who were confirmed cases using Western blot and PCR: 29 Percentage of screen positive women who were confirmed cases: 85% Prevalence of HTLV: 105 per 10,000
Comments	95% confidence intervals not reported

Appendix number	12
Relevant criteria	4. There should be a simple, safe, precise and validated screening test.
Relevant Key question	What is the accuracy of antenatal screening tests for HTLV?
Publication details	Nerome Y. Kojyo K. Ninomiya Y. et al. Current human T-cell lymphotrophic virus type 1 mother-to-child transmission prevention status in Kagoshima. Pediatrics International 2014, 56: 640-643
Study details	Prospective cohort study
Study objectives	To assess the mother-to-child transmission prevention system in Kagoshima Prefecture, Japan
Inclusions	Pregnant women attending 1 of 36 obstetric facilities in 2012
Exclusions	None specified
Population	8,719 pregnant women

Intervention/ test	Passive particle agglutination method or chemiluminescent immunoassay
Comparator	Western blot or immunofluorescence assay. Indeterminate Western blot samples tested by Polymerase Chain Reaction
Results	Number HTLV-I screen positive women: 119 Number screen positive women who were confirmed cases using Western blot or PCR: 112 Percentage of screen positive women who were confirmed cases: 94.1% Prevalence of HTLV: 130 per 10,000
Comments	95% confidence intervals not reported 2 of the 5 women who tested as indeterminate on Western blot did not consent to further testing by PCR. These women could be additional cases

Appendix number	13
Relevant criteria	4. There should be a simple, safe, precise and validated screening test.
Relevant Key question	What is the accuracy of antenatal screening tests for HTLV?
Publication details	Sequeira CG. Tamegão-Lopes BP. dos Santos EJ. et al. Descriptive study of HTLV infection in a population of pregnant women from the State of Pará, Northern Brazil. Revista da Sociedade Brasileira de Medicina Tropical 2012, 45(4): 453-456
Study details	Prospective study
Study objectives	To estimate the prevalence of HTLV infection in pregnant women in Brazil
Inclusions	Pregnant women attending healthcare units for prenatal care in 19 districts of Brazil in 2008
Exclusions	None specified
Population	13,382 pregnant women
Intervention/ test	Enzyme immunoassay using a dried blood spot
Comparator	Western blot
Results	Number HTLV screen positive women using EIA screening test: 43 Number screen positive women who were confirmed cases using Western blot: 41 (39 HTLV-I; 1 HTLV-II; 1 indeterminate) Percentage of screen positive women who are confirmed cases: 95.3%

	Prevalence of HTLV: 30 per 10,000
Comments	95% confidence intervals not reported

Appendix number	14
Relevant criteria	4. There should be a simple, safe, precise and validated screening test.
Relevant Key question	What is the accuracy of antenatal screening tests for HTLV?
Publication details	Hanaoka M. Kubo T. Saitoh A. Discrepancy between human T-cell lymphotrophic virus type I screening test and confirmatory tests in non-endemic areas. Journal of Obstetrics and Gynaecology Research 2012, 38(5): 793-796
Study details	Retrospective cohort study
Study objectives	To examine the prevalence of HTLV-I among pregnant women in an non-endemic area
Inclusions	Pregnant women attending 1 facility between 2002 and 2009
Exclusions	Non stated
Population	11,352 pregnant women
Intervention/ test	Chemiluminescent enzyme immunoassay
Comparator	Western blot. Indeterminate Western blot samples tested by polymerase chain reaction
Results	Number HTLV -1 screen positive women: 37 Number of screen positive women who received a confirmation test: 36 Number screen positive women who were confirmed cases using Western blot: 9 Percentage of screen positive women who were confirmed cases: 25% Prevalence of HTLV: 33 per 10,000 7 indeterminate cases were tested by PCR. No further cases were identified.
Comments	95% confidence intervals not reported 1 woman did not receive a confirmation test. This could represent a missed case

Appendix number	15
Relevant criteria	4. There should be a simple, safe, precise and validated screening test.

Relevant Key question	What is the accuracy of antenatal screening tests for HTLV?
Publication details	Ramos JM. Milla A. Treviño A. et al. Seroprevalence of HTLV infection among immigrant pregnant women in the Mediterranean coast of Spain. Journal of Clinical Virology 2011, 51: 192-194
Study details	Prospective study
Study objectives	To estimate the prevalence of HTLV infection in pregnant immigrants to Spain
Inclusions	Pregnant women attending a hospital in Spain between 2006 and 2009
Exclusions	None specified
Population	1,439 pregnant women
Intervention/ test	Enzyme immunoassay (EIA) using serum
Comparator	Western blot
Results	Number HTLV screen test positive women using EIA screening test: 3 Number screen positive women who were confirmed cases using Western blot: 3 (1 HTLV-I; 2 HTLV-2) Percentage of screen positive women who were confirmed cases: 100% Prevalence of HTLV: 21 per 10,000 (95%CI 5 to 66)
Comments	

Appendix number	16
Relevant criteria	4. There should be a simple, safe, precise and validated screening test.
Relevant Key question	What is the accuracy of antenatal screening tests for HTLV?
Publication details	Treviño A. Benito R. Caballero E. et al. HTLV infection among foreign pregnant women living in Spain. Journal of Clinical Virology 2011, 52: 119-122
Study details	Prospective study
Study objectives	To estimate the prevalence of HTLV infection in pregnant immigrants to Spain
Inclusions	Pregnant women attending 14 clinics between 2009 and 2010
Exclusions	None specified

Population	3,337 pregnant women
Intervention/ test	Enzyme immunoassay (EIA) using serum
Comparator	Western blot. Indeterminate Western blot samples tested by Polymerase Chain Reaction
Results	Number HTLV screen positive women using EIA screening test: 8 Number screen positive women who were confirmed cases using Western blot: 7 (6 HTLV-I; 1 HTLV-2) Percentage of screen positive women who were confirmed cases: 87.5% Prevalence of HTLV: 20 per 10,000
Comments	95% confidence intervals not reported

Appendix number	17
Relevant criteria	4. There should be a simple, safe, precise and validated screening test.
Relevant key question	What is the accuracy of antenatal screening tests for HTLV?
Publication details	Boa-Sorte N. Purificação A. Amorim T. et al. Dried blood spot testing for the antenatal screening of HTLV, HIV, syphilis, toxoplasmosis and hepatitis B and C: prevalence, accuracy and operational aspects. Brazilian Journal of Infectious Diseases 2014, 18(6): 618-624
Study details	Prospective study of test performance
Study objectives	To assess the accuracy of screening for HTLV using a dried blood spot sample compared to a blood serum sample
Inclusions	All women attending a primary healthcare unit in Brazil between November 2009 and March 2009 for prenatal care tests
Exclusions	None specified
Population	692 pregnant women
Test	Enzyme linked immunosorbent assay (ELISA) using a dried blood spot sample
Comparator / reference standard	ELISA using a serum blood spot sample

Results	Number tested positive for HTLV: 1 Prevalence of HTLV: 14 per 10,000 (95%CI 1 to 71) Sensitivity: 100% (95%CI 20.6% to 100%) Specificity: 100% (95%CI 99.4% to 100%)

Quality appraisal

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Y	Low	Consecutive sample
Case-control design avoided?	Y	Low	Consecutive sample
Inappropriate exclusions avoided?	Y	Low	No exclusion criteria stated
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Y	Low	The study used a comparator rather than a reference standard but the testing was blind
Threshold pre-specified?	Y	Low	Commercial kits used for the assay
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	N	High	No reference standard test performed
Reference standard results interpreted without knowledge of index test results?	N	High	No reference standard test performed
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	Y	Low	The same sample was used for both tests
Did all participants receive same reference standard?	Y	Low	A comparator was used rather than a reference standard, but all patients received both tests
All patients included in	Y	Low	All patients received both tests

analysis?			
Applicability			
Applicable to UK screening population of interest?	N	High	The prevalence of 14 per 10,000 in this population is higher than that found in UK
Applicable to UK screening test of interest?	Y	Low	ELISA screening test
Target condition measured by reference test applicable to UK screening condition of interest?	N	High	No established confirmation test performed

Other comments

It should be noted that this compares the 2 screening methods against each other rather than a screening method against an established confirmation test. One case of HTLV was identified and the confidence intervals around the prevalence and sensitivity are wide reducing confidence in the result.

Appendix number	18
Relevant criteria	9: There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered
Relevant Key question	What is the effectiveness of breastfeeding avoidance in the prevention of HTLV transmission?
Publication details	Ribeiro MA. Martins ML. Teixeira C. et al. Blocking vertical transmission of human T cell lymphotrophic virus 1 and 2 through breastfeeding interruption. The Pediatric Infectious Disease Journal 2012, 31(11): 1139-1143
Study details	Prospective study
Study objectives	1-year follow up of infants whose mothers were screen positive for HTLV and were counselled to prevent transmission of HTLV through avoidance of breastfeeding
Inclusions	Mothers who tested positive for HTLV as part of a newborn screening programme and their infants
Exclusions	None stated
Population	42 mothers who were identified as screen positive through a newborn screening programme in Brazil and their infants
Intervention/	Avoidance of prolonged breastfeeding

test	
Comparator	n/a
Results	**HTLV-I** • Number of women who were screen positive: 40 • Number of infants tested at 12 months old: 35 (87.5%) • Number of infants with confirmed HTLV-I at 12 months old: 1 (2.8%) • Mean breastfeeding duration: 27 days (range 0 to 60 days) The infant who tested positive was breast fed for 7 days **HTLV-II** • Number of women who were screen positive: 2 • Number of infants tested at 12 months old: 2 (100%) • Number of infants with confirmed HTLV-II at 12 months old: 0 (0%) • Mean breastfeeding duration not available due to language barriers
Comments	5 mothers with HTLV-I did not consent to have their infants blood tested at 12 months old. Cases of HTLV infection could have been missed in these infants Infant milk formula was provided to all newborns in the study for at least 6 months

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