UK National Screening Committee

HUMAN T-CELL LYMPHOTROPIC VIRUS

An evidence map to outline the volume and type of evidence related to antenatal screening for HTLV for the UK National Screening Committee

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Author: Evidence Team, UK NSC Secretariat

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The UK National Screening Committee secretariat is hosted by The Office for Health Improvement & Disparities (OHID).

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About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.

Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

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UK NSC, OHID, Department of Health and Social Care, 39 Victoria Street, London, SW1H 0EU

www.gov.uk/uknsc

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Summary

This document discusses the findings of the evidence map on universal antenatal screening for human T-cell lymphotropic virus (HTLV).

Evidence maps are a way of scanning published literature to look at the volume and type of the evidence base in relation to a specific topic. They inform whether the evidence is sufficient to commission further work on the topic under consideration.

Based on the findings of this evidence map, no further work on universal antenatal screening for HTLV should be commissioned in line with the UK NSC evidence review process.

As this is the fifth time that this topic has been reviewed and the evidence base on key issues remains static, it is proposed that this recommendation be removed from the UK NSC's list of universal screening conditions.

Introduction and approach

Background & Objectives

The UK National Screening Committee (UK NSC) external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Antenatal screening for human T-cell lymphotropic virus (HTLV) is a topic currently due for an update external review.

Human T-lymphotropic virus type 1 (HTLV I) and Type 2 (HTLV II) are retroviruses (like HIV) which affect the immune system and are associated with severe illness such as adult T-cell leukaemia/lymphoma (ATL) and HTLV-associated myelopathy (HAM)/tropical spastic paraparesis (TSP), these are thought to happen in around 10% of infected cases. Most individuals with HTLV remain asymptomatic. There is currently no cure or vaccine for HTLV.(UK NSC, 2017)

HTLV 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, during a caesarean birth or through breastfeeding for longer than six months. Once acquired HTLV infection is lifelong. HTLV is endemic in some parts of the world but is rarer in Western Europe. A UK study of 126,020 newborn dried blood spot samples estimated an overall prevalence of 3.1 per 10,000 for HTLV in pregnant women, with the prevalence ranging considerably between sub-groups of the population within the UK. (Ades, 2000) This is the most recent estimate of maternal prevalence and meets current definitions of low prevalence (European Centre for Disease Prevention and Control (ECDC), 2015.).

Some countries, such as Japan where HTLV is endemic, recommend universal antenatal screening. Although the screening tests used in Japan are considered to have high sensitivity and specificity, they do generate a substantial number of false positives, particularly in low prevalence areas. (UK NSC, 2017)

The Japanese antenatal screening programme began in 2010, however, it is unknown whether it has been effective at reducing mother-to-child transmission (MTCT) of HTLV. To establish this, babies born to infected mothers would need to be followed-up to find out if they themselves also become infected. Although it is recommended that these babies are tested at age 3 years, this does not routinely happen (Itabashi et al, 2020). As such the clinical value of screening might be considered uncertain.

Due to the low prevalence of HTLV in the UK and the lack of new evidence retrieved following the last four review cycles it is proposed that HTLV might be removed from the UK NSC review cycle for population screening.

Previous review on screening for HTLV

The UK NSC has considered antenatal screening for HTLV four times.

The UK NSC currently recommends against screening for HTLV. The Committee based this recommendation on the evidence provided by the 2017 review carried out by Solutions for Public Health.

The 2017 review recommended against the introduction of a screening programme due to the following:

1. **Epidemiology and natural history**. Although HTLV I and II are associated with ATL/HAM most infants infected do not go on to develop symptoms and the risk of developing serious illness appears to be low. Using the European Centre for Disease Prevention and Control (ECDC) as a reference, the UK remained a low prevalence area at the time of the last review (ECDC, 2015). Ades et al. (2000) estimated an overall UK maternal prevalence of 3.1/10,000. This is within the ECDC threshold of <1% of the general population defining low prevalence. Previous UK NSC reviews have found that there is little information on the natural history of the infection acquired through breastfeeding. It is unlikely that the mother will pass on to her child unless she breastfeeds for more than 6 months, therefore there is a risk of over detection and the potential for lifelong anxiety for the mother.
2. **Test.** It is not known how well the test performs in pregnant women particularly in areas of lower prevalence which could be a concern in the UK.
3. **Treatment.** There is currently no treatment, or vaccine, for HTLV and the only approach to prevent MTCT is avoidance of breastfeeding, especially after 6 months.
4. **Potential negative impact on the mother.** There was not enough evidence on whether the benefits outweighed the harms. Although the prevention of MTCT is possible, there is no treatment for women identified as having HTLV and most will not go on to develop ATL/HAM in later life. This may cause significant anxiety and stress.

The 2017 review found that the volume, quality, and direction of new evidence published since January 2011 did not indicate there had been any significant changes in the evidence base. It was agreed that the conclusions of the previous UK NSC reviews should be retained.

Aims of the evidence map

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic.

The aim is to address the following question:

1. What is the volume and type of evidence on the benefits/harms of screening for HTLV during pregnancy?

The findings of this evidence map will provide the basis for discussion to support decision making on whether HTLV can be removed from the UK NSC's list of conditions.

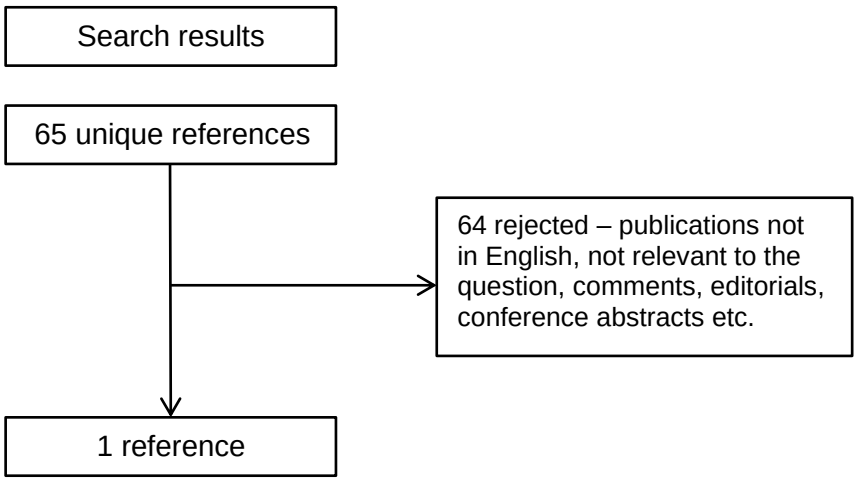
The aim of this document is to present the information necessary for the UK NSC to decide this.

Search methods and results

The searches were conducted on 2 September 2021 on 3 databases: Ovid Medline, Ovid Embase and the Cochrane Library. The search period was restricted to 2016 – September 2021. The detailed search strategies, including exclusion and inclusion criteria are available in appendix 1. One reviewer sifted all titles and abstracts. All references were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertain pieces of information. A formal quality appraisal of the evidence was not required, given the remit of the evidence map.

The search returned 107 results. After automatic and manual de-duplication, 65 unique references were sifted at title and abstract level by one reviewer for relevance to the question. 12 potential references were then reviewed at full text by 2 reviewers and 1 reference was included in the final evidence map. A flow diagram summarising the number of studies included and excluded is presented in figure 1.

Figure 1: Summary of included and excluded publications



Summary of findings

Question 1: What is the volume and type of evidence on the benefits/harms of screening for HTLV during pregnancy?

No systematic reviews or RCTs relevant to the question were retrieved. One study met the inclusion criteria.

The included study is a prospective cohort study by Itabashi et al. (2021) that looked at issues of infant feeding for postnatal prevention of MTCT of HTLV-1. They found that there was a problem with compliance since only around 35% of pregnant HTLV-1 carriers chose complete avoidance of breast feeding, which is the recommended intervention. Although in this study, the risk of MTCT with short-term breast feeding was reportedly not significantly different to exclusive formula feeding. Since less than half of the children born to positive mothers were followed up to the age of 3 years and tested for HTLV an increase in the follow-up of babies born to HTLV positive mothers is needed to more clearly assess MTCT preventive options. .

This included study is neither a systematic review, or RCT, but does provide some information on outcomes. As the study is based in Japan, where HTLV is endemic, it is not clear on its applicability to the UK where prevalence is low and breast feeding patterns may be different.

Of note is a cost-effectiveness model on HTLV screening in the UK. (Malik et al, 2018) This was not included in the literature search primarily because, as a letter, it did not meet the inclusion criteria. However, it is of interest as it is from a UK perspective. The letter presented a brief decision tree model which estimated that HTLV-1 would be transmitted from 25 maternal carriers to their babies annually. Antenatal screening was estimated toprevent transmission of HTLV in 17 of these cases and therefore eliminate the risk of ATL and HAM. This was potentially cost-effective in the United Kingdom. The analysis was dependent upon key parameters which were uncertain. For example, the cost of the two competing testing strategies was based on expert opinion and the quality of the evidence supporting estimates of life-time risk of ATL and HAM was highlighted as a limitation. The majority of cost effective scenarios were based on a testing strategy (pooled sampling) which was not recommended for use in antenatal screening by the NHS Infectious Diseases in Pregnancy Screening Programme and which is no longer used for blood donor screening in the UK. Potential harms of screening and the lifetime cost of managing HTLV positive women and children/adults who acquire the infection despite screening were not considered in the analysis.

In summary there is an insufficient volume of evidence on HTLV to justify commissioning an evidence summary. The evidence identified by this evidence map is unlikely to lead to change in the UK NSC's current position.

Conclusions

The findings of this evidence map are unlikely to impact current recommendations on screening for HTLV as no new evidence was identified that would change those conclusions.

Recommendations

On the basis of this evidence map, it is recommended that no further work on screening for HTLV should be commissioned and the condition should be considered for removal from the list for population screening.

Appendix 1 — Search strategy for the evidence map

Databases and platforms searched

Medline (OVID), Embase (OVID) and The Cochrane Library.

Search dates

1 January 2016 – 2 September 2021

Search strategies

Ovid Medline® ALL 1946 to September 01, 2021

1. Human T-lymphotropic virus 1/ (5985)
2. HTLV-I Infections/ (3989)
3. Human T-lymphotropic virus 2/ (910)
4. HTLV-II Infections/ (904)
5. HTLV$.tw. (13442)
6. human t-cell lymphotropic virus$.tw. (2363)
7. human t-cell leukemia lymphoma virus.tw. (276)
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (14952)
9. Mass Screening/ (109399)
10. Prenatal Diagnosis/ (38316)
11. (screen$3 or detect$3 or test or tests or testing).tw. (4986356)
12. 9 or 10 or 11 (5028099)
13. Pregnancy/ (915431)
14. (pregnan$ or antenatal$ or prenatal$).tw. (613102)
15. 13 or 14 (1076319)
16. 8 and 12 and 15 (226)
17. limit 16 to yr="2016 -Current" (42)

Embase 1974 to 2021 September 01

1. Human T-lymphotropic virus 1/ (2337)

2. Human T cell leukemia virus 2/ (1597)
3. HTLV$.tw. (16525)
4. human t-cell lymphotropic virus$.tw. (2696)
5. human t-cell leukemia lymphoma virus.tw. (292)
6. 1 or 2 or 3 or 4 or 5 (17723)
7. mass screening/ (57356)
8. prenatal diagnosis/ (59683)
9. prenatal screening/ (8949)
10. (screen$3 or detect$3 or test or tests or testing).tw. (6649957)
11. 7 or 8 or 9 or 10 (6700238)
12. pregnancy/ (618216)
13. (pregnan$ or antenatal$ or prenatal$).tw. (773572)
14. 12 or 13 (1004706)
15. 6 and 11 and 14 (217)
16. limit 15 to yr="2016 -Current" (52)

The Cochrane Library

#1 MeSH descriptor: [HTLV-I Infections] explode all trees (23)
#2 MeSH descriptor: [HTLV-II Infections] explode all trees (1)
#3 HTLV*:ti,ab,kw (154)
#4 "human t-cell lymphotropic virus*":ti,ab,kw (15)
#5 "human t-cell leukemia lymphoma virus":ti,ab,kw (0)
#6 #1 or #2 or #3 or #4 or #5 (162)
#7 MeSH descriptor: [Mass Screening] explode all trees (3931)
#8 MeSH descriptor: [Prenatal Diagnosis] explode all trees (847)
#9 (screen* or detect* or test or tests or testing):ti,ab,kw (457927)
#10 #7 or #8 or #9 (458339)
#11 MeSH descriptor: [Pregnancy] explode all trees (23152)
#12 (pregnan* or antenatal* or prenatal*):ti,ab,kw (71796)

#13 #11 or #12 (72066)

#14 #6 and #10 and #13 with Cochrane Library publication date Between Jan 2016 and Aug 2021 (13)

Results by database

Medline	42
Embase	52
Cochrane Library	13
Total	107

Inclusions and exclusions

Studies were included based on the eligibility criteria listed in Table 1

Table 1: Eligibility criteria

PICOS domain	Inclusion criteria	Exclusion criteria
Patient population	Pregnant women screened positive for HTLV	N/A
Intervention	Postnatal feeding practices following screening, for example, avoidance of breast feeding, exclusive formula feeding, etc.	N/A
Comparator	Any other postnatal feeding practice or none	N/A
Outcomes	Any benefits or harms, • Prevention of MTCT • Harms of intervention, such as psychological consequences of not being able to breast feed, stopping short-term breast feeding at 3 months, etc.	N/A
Study design	• RCTs • Cohort studies • Systematic reviews of these study designs	• Case reports • Narrative reviews • Editorials • Commentaries • Conference abstracts • Other publication types, such as letters, that have not been peer-reviewed

PICOS domain	Inclusion criteria	Exclusion criteria
Setting	**Tier 1:** Studies conducted in the UK **Tier 2:** Studies conducted in high-income countries where the population, screening methods and technology are expected to be similar to that of the UK (OECD and EEA countries excluding South Korea and Mexico)	Studies in ineligible countries, or international studies where outcomes for eligible countries are not presented separately to outcomes from ineligible countries
Other considerations	• Articles published in the English language • Articles published since January 2016	• Studies with abstract not in the English language • Articles published before January 2016

References

Ades AE, Parker S, Walker J, *et al*. Human T cell leukaemia/ lymphoma virus infection in pregnant women in the United Kingdom: population study. BMJ 2000;**320**(7248):1497-501

European Centre for Disease Prevention and Control. Geographical distribution of areas with a high prevalence of HTLV-1 infection. Stockholm: ECDC; 2015.

Itabashi K, Miyazawa T, Nerome Y, *et al*. Issues of infant feeding for postnatal prevention of human T-cell leukemia/lymphoma virus type-1 mother-to-child transmission. *Pediatrics International* 2021;**63**(3):284-9

Itabashi K, Miyazawa T, Sekizawa A, *et al*. A Nationwide Antenatal Human T-Cell Leukemia Virus Type-1 Antibody Screening in Japan. *Frontiers in Microbiology* 2020;**11** (no pagination)(595)

Malik B, Taylor GP. Can we reduce the incidence of adult T-cell leukaemia/lymphoma? Cost-effectiveness of human T-lymphotropic virus type 1 (HTLV-1) antenatal screening in the United Kingdom. *British Journal of Haematology* 2019;**184**(6):1040-3

UK National Screening Committee. (2017) *The UK NSC Recommendation on HTLV (Human T-Cell Lymphotropic Virus) Screening in Pregnancy. Recommendation Statement*. UK National Screening Committee, London. Available from: https://view-health-screening-recommendations.service.gov.uk/htlv/ (accessed 14 January 2022)