UK National Screening Committee

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Evidence map on antenatal screening for HTLV

Date: 09 November 2022 (updated following the Committee discussion)

Contents

Aim

To ask the UK NSC to make a recommendation, based on the contents of the evidence map and consultation responses, on antenatal screening for HTLV.

Current Recommendation

The UK NSC does not currently recommend antenatal screening for HTLV. The previous recommendation was made in 2017 following a review carried out by Solutions for Public Health in 2017.

The 2017 review found that although HTLV I is associated with ATL and HAM most infants infected do not go on to develop symptoms and the risk of developing serious illness appeared 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). Previous UK NSC reviews found that there is little information on the natural history of the infection acquired through breastfeeding. It is unlikely that the mother will pass the infection 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. It was not known how well the test performed in pregnant women particularly in areas of lower prevalence which could be a concern in the UK. In addition, there was no treatment for the adverse outcomes of the infection, or vaccine, for HTLV and the only approach to prevent mother to child transmission (MTCT) was avoidance of breastfeeding, especially after 6 months. There was also not enough evidence on whether the benefits of screening outweighed the harms. Although the prevention of MTCT is possible, there was no

treatment for women identified as having HTLV and most do not go on to develop ATL or 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. The UK NSC also noted that early discussion on screening for HTLV had suggested that a targeted approach may be better than whole population antenatal screening from a clinical and cost effectiveness perspective. The Committee therefore suggested that the stakeholders might explore this option with the relevant decision making / standard setting bodies.

Evidence Map

The 2022 evidence map on universal, or whole population, antenatal screening for HTLV was carried out by the Evidence Team in accordance with the UK NSC's evidence review process.

The aim of this evidence map was to address the following question:

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

A further aim of the evidence map was to help the Committee consider archiving this topic until significant evidence is published which justifies re-evaluating whole population antenatal screening.

Summary of findings

No relevant systematic reviews or RCTs were retrieved. Only one prospective cohort, that looked at issues of infant feeding for postnatal prevention of MTCT of HTLV-1, met the inclusion criteria.

This study found that there was a problem of compliance with the recommended intervention (complete avoidance of breast feeding) since only around 35% of pregnant HTLV-1 carriers chose to follow this. In addition, the risk of MTCT with short-term breast feeding was reportedly not significantly different to exclusive formula feeding.

Less than half of the children born to positive mothers were followed up to the age of 3 years and tested for HTLV themselves. The follow-up of babies born to HTLV positive mothers is needed to more clearly assess the effectiveness of MTCT prevention strategies.

This does, therefore, provide some information on outcomes but 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 breastfeeding patterns may be different.

Consultation

A three-month consultation was hosted on the UK NSC website. Direct emails were sent to 10 stakeholders. (Annex A)

20 comments were received from the following stakeholders (see Annex B for comments):

1. Royal College of General Practitioners
2. Professor Richard Tedder (Medical Virologist, xxxx xxxx)
3. xxxx xxxx
4. Mark Zuckerman (Consultant Medical Virologist)
5. Public Health Scotland
6. xxxx xxxx
7. xxxx xxxx
8. xxxx xxxx
9. xxxx xxxx
10. Professor Sara Rankin (xxxx xxxx)
11. xxxx xxxx
12. xxxx xxxx
13. xxxx xxxx
14. xxxx xxxx
15. xxxx xxxx
16. Professor Graham Taylor (Head of Section of Virology, Imperial College London and Honorary Consultant Physician, National Centre for Human Retrovirology, St Mary's Hospital, London) co-signed by 13 colleagues:
    Professor Charles Bangham FRS, Co-Director Institute of Infection, Imperial College London.
    Dr Carolina Rosadas, Research Associate, Section of Virology, Imperial College London
    Professor Jonathan Weber F MedSci, Dean, Faculty of Medicine, Imperial College London
    Professor Hermione Lyall, Head of Paediatric Infectious Diseases, St Mary's Hospital, London
    Dr Divya Dhasmana, Clinical Lead, National Centre for Human Retrovirology, London
    Dr Dan Bradshaw, Consultant Virology. UKHSA, London
    Ms Adine Adonis, Senior Neurophysiotherapist, National Centre for Human Retrovirology, London
    Dr Lucy Cook, Consultant in Onco-haematology, National Centre for Human Retrovirology, London
    Dr Meg Boothby, Consultant GU/HIV Physician, Queen Elizabeth Hospital, Birmingham
    Professor Anastasios Karadimitris, Co-director, Centre for Haematology, Hammersmith Hospital, London
    Ms Hollie Mortimer, Lead Nurse, National Centre for Human Retrovirology, London
    Dr Nicholas Davies, Consultant Neurologist, Chelsea and Westminster Hospital, London
    Dr Eleni Nastouli, Consultant Virologist, University College London
17. xxxx xxxx
18. xxxx xxxx
19. Dr Andrea Thoma-Kress (International Retrovirology Association (IRVA))
20. Professor Ricardo Ishak (Universidade Federal do Pará, Brazil), co-signed by 31 colleagues:

Prof Abelardo Araújo (Fiocruz-RJ, UFRJ)
Prof. Adele Caterino de Araújo (Instuto Adolfo Lutz)
Ms Adjeane Oliveira de Jesus (HTLVida, patients' association)
Dr Ana Lúcia Borges Starling (HTLV- GIPH)
Prof Ana Rita Coimbra Motta de Castro (UFMS, Fiocruz-MS)
Prof Antônio Carlos Rosario Vallinoto (UFPA)
Prof Bernardo Galvão Castro (EBMSP)
Dr Carla Bressi (SVS-BA)
Prof Carlos Brites (UFBA)
Dr Carolina Rosadas (HTLV Channel)
Dr Clarice Neuenschwander (Fiocruz-PE, UFPE)
Dr Denise Arakaki-Sanchez (CEDIN-DF)
Prof Edel Figueiredo Barbosa Stancioli (UFMG)
HTLV Channel
Dr Joanna Ramalho (SES, PB)
Prof Jorge Casseb (USP)
Dr Larissa Bandeira (UFMS)
Ms Laura Lee (Vitamore, patients`s association)
Prof Maria Alice Queiroz (UFPA)
Prof Maria Fernanda Grassi (Fiocruz-Bahia)
Prof Marzia Puccioni-Sohler (UNIRIO, UFRJ)
Prof Ney Boa-Sorte (EBMSP)
Ms Nivania dos Santos Pereira Carneiro (HTLVida, patients' association)
Prof Paula Loureiro (UPE)
Dr Paula Machado Ribeiro Magalhães (HUOC, UPE)
Prof Regina Rocco (UNIRIO)
Dr Renata Olivia Gadelha Romero (SESAP-RN)
Ms Sandra do Valle (Vitamore, patients`s association)
Prof Silvia Uehara (UFMS)
Dr Tatiane Assone (USP, HTLV Channel)
Dr Youko Nukui (HC, USP)

21. British Society for Immunology

Comments were received from 11 members of the public, and 10 professionals or organisations representing healthcare professionals.

In general, stakeholders did not agree with the conclusions of the evidence map.

The Royal College of General Practitioners, Public Health Scotland and the Consultant in Public Health all agreed that antenatal screening for HTLV should not be introduced.

The remaining 6 professional respondents and the 11 members of the public believed that antenatal screening for HTLV should be recommended in the UK.

The majority of responses from professional organisations and individuals challenged the review and the proposal to archive the universal, population, screening recommendation. A summary of the key points and the Committee's response to them follows.

1 The consultation document did not adequately address the full range of issues relating to population screening for HTLV in pregnancy. Some respondents suggested that this did not meet the standards of the UK NSC ethical framework.

Response: The UK NSC refers to four ethical principles in its decision making. The first ethical principle in the UK NSC ethical framework is that screening should improve the health and wellbeing of the population. To this end screening programmes should not be recommended unless the potential benefits outweigh any potential harms. The evidence map aimed to identify studies which could directly inform a discussion of the benefits and harms of whole population screening in pregnancy. This was identified as a key uncertainty in a UK analysis published in 2000.[1]

The analysis estimated that there would be approximately 233 maternal HTLV infections annually. In the absence of screening and advice to avoid breastfeeding, there would be 22 mother to child transmissions (MTCT) to the newborn. Of these 1% - 5% would develop adult T cell leukaemia / lymphoma (ATLL) and 0.25% - 3% would develop HTLV associated myelopathy (HAM / TSP). As such 0.1% - 1 % of maternal infections would lead to serious disease in the child. Against this rate of transmission and burden of disease, the analysis considered that the potential for a negative quality of life impact from screen detected maternal infection was a critical, but unexplored, factor. The analysis concluded that population screening on the model of HIV screening was unlikely to be the optimum approach.

This analysis informed the initial UK NSC recommendation and framed the themes of subsequent work on HTLV infection. Each time the UK NSC returned to this topic no published evidence was identified which factored in the potential for a negative impact from maternal diagnosis. After returning to the topic four times the FMCH considered it appropriate to consult on archiving the topic. Towards this end the FMCH approved the use of an evidence map to gauge the volume and type of evidence exploring the benefits and harms of screening since the previous review. The evidence map identified one paper reporting limited outcomes from a screening programme in Japan. A brief cost effectiveness analysis was also identified but the potential harms of screening were not included in the analysis. Importantly, some consultees suggest that a more substantial analysis should be undertaken following the development of evidence of a health decrement associated with asymptomatic HTLV carriage in a UK population.

2 It was suggested that the UK NSC should undertake a cost utility analysis of screening.

[1] Ades, A.E., Simon Parker, Jane Walker, Mark Edginton, Graham P. Taylor, and Jonathan N. Weber. 2000. 'Human T cell leukaemia/lymphoma virus infection in pregnant women in the United Kingdom: population study', *BMJ*, 320: 1497-501

Response: a recent paper exploring health state utility values in Brazilian and UK HTLV 1 patients using the EQ-5D questionnaire was submitted by respondents to the consultation.[2] In the 18 UK patients, this highlighted a health decrement associated with asymptomatic HTLV carriage which was comparable to that of women with a breast cancer diagnosis. The paper notes that this aspect of HTLV 1 has not been incorporated into existing cost effectiveness analyses and, as such, new analyses are needed.

2a Other comments and papers submitted by respondents might help develop an understanding of what could be expected from such an exercise. For example:

2a(i)An association between HTLV 1 and a broader range of adverse outcomes was identified by a recent systematic review.[3]

Response: while a greater burden of disease may increase the likelihood of screening to prevent HTLV transmission being cost effective, the systematic reviewers emphasise that the associations are based on evidence which is limited in terms of volume and quality. The WHO technical report suggests that further research is needed in this area.

2a(ii)Several respondents state that the rate of ATLL is 25%, rather than 1% - 5%, in those infected in the newborn period.

Response: this was an influential parameter in the cost effectiveness analysis identified in the UK NSC evidence summary. However, the WHO technical report suggests that there is no definitive evidence for an association between route of transmission and development of ATLL. The report estimates that the lifetime risk of ATLL is 5% and recommends further research to understand the factors associated with progression to this outcome.

2a(iii) Several respondents dispute that there is uncertainty about the performance of screening tests (immunoassays) in the pregnant population. A recent paper exploring this in samples taken from 21 women when pregnant and not pregnant was submitted.[4] The study reported that biological changes during pregnancy did not impair the sensitivity of the test.

Response: the previous (2017) review acknowledged that available testing methods have high sensitivity and specificity. The concern raised in the review related more to the predictive values of screening tests in low prevalence settings. This was not addressed by the submitted paper. In addition, the WHO technical report

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[2] Rosadas, C., T. Assone, M. Yamashita, A. Adonis, M. Puccioni-Sohler, M. Santos, A. M. Paiva, J. Casseb, A. Oliveira, and G.P. Taylor. 2020. 'Health state utility values in people living with HTLV-1 and in patients with HAM/TSP: the impact of a neglected disease on the quality of life ', *PLoS Negl Trop Dis*, 14.

[3] Schierhout, G; McGregor, S; Gessain, A; Einsiedel, L; Martinello, M, Kaldor, J. 2019. 'The association between HTLV-1 infection and adverse health outcomes:a systematic review and meta-analysis of epidemiologic studies', *Lancet Infect Dis*.

[4] Rosadas, C., J. H. Tosswill, R. Tedder, and G. P. Taylor. 2019. 'Pregnancy does not adversely impact diagnostic tests for HTLV-1/2 infection', *PLoS Negl Trop Dis*, 13

recommends that testing strategies should be designed to fit the context of use and that cost effectiveness should be a consideration in this. This is not clear in relation to antenatal screening in the UK. For example, the submitted cost effectiveness analysis estimated that a pooled sampling strategy was more likely to be cost effective than testing individual samples. This would be a major break from antenatal infectious disease screening practice in the UK. It has also been suggested that this testing strategy may reduce test sensitivity.[5]

Summary of 2 / 2a: It is not possible for the Committee to take a position on all of these points without a comprehensive review of all the papers submitted in the consultation. However, consideration of the papers suggests that a modelling exercise would be likely to encounter both controversy and limited evidence in key areas. A modelling exercise may help quantify the potential for screening for HTLV infection to be cost effective. However, it may be more useful as a mechanism to identify research priorities than to generate a definitive estimate of the clinical and cost effectiveness of antenatal screening.

3. Some respondents suggested that the UK NSC should consider a targeted approach to screening in the antenatal period, and this relates to the UK NSC's third ethical principle, to promote equality and inclusion

Response: In previous review cycles, the Committee's focus was on universal, population, screening. This was consistent with its remit which, respondents note, now includes targeted screening. Consultees were encouraged to discuss a targeted approach with commissioners in the Committee's response to them.

The analysis published in 2000 suggests that a targeted approach may be a more appropriate option than population screening. Approximately 30% of maternal infections were estimated to be in women from endemic areas and breastfeeding patterns in these groups suggest that a higher rate of transmission to newborns is likely to occur in them. The WHO technical report highlights that, in France, targeted antenatal screening is recommended for women from endemic areas.

However, it is recognised that respondents may favour a targeted strategy which differs from the approach in France. To understand more, the Committee would welcome a proposal through the Annual Call for Topics and the Secretariat has written to the British Society for Immunology to this effect following their direct contact with the Chair of the UK NSC.

It might be noted that, in England, there is an OHID recommendation that testing for HTLV should be considered in primary care for migrants from endemic areas.[6] A publication suggests that only a small number of tests were undertaken in primary

[5] Rosadas C, Taylor GP. Mother-to-child HTLV-1 transmission: unmet research needs. Front Microbiol. 2019;10:999

[6] Office for Health Improvement and Disparities, Sexually transmitted infections (STIs): migrant health guide - GOV.UK (www.gov.uk)

care between 2008 and 2013.[7] It is unclear whether the situation has changed since the recommendation was made.

4. It was suggested that the UK NSC had not engaged sufficiently with stakeholders in previous review cycles. This meant the evidence review process had not treated experts in the field of HTLV infections with respect (the second ethical principle in the UK NSC framework) and, again, had not met the standard of the Committee's ethical framework.

Response: The UK NSC periodically reviews recommendations it has made on screening for over 100 conditions. Once key issues and evidence gaps have been identified, evidence summaries and evidence maps are used to address these. The purpose of this is to establish whether there have been significant developments in the evidence base relating to the issues and evidence gaps. Public consultation offers the opportunity for stakeholders to comment on these documents. The process aims to help the UK NSC identify and prioritise topics which would benefit from more in-depth analysis.

The fourth ethical principle underpinning decision making is that of proportionality and good use of resources. The use of evidence maps is intended to be an efficient mechanism to handle a large volume of topics. It is acknowledged that a focus on efficiency can limit opportunities to engage closely with groups of stakeholders who disagree with the Committee's recommendation. However, constructive feedback on the issue of targeted screening was provided to stakeholders. This was consistent with the conclusions of the 2000 BMJ analysis and with the remit of the Committee at the time. The request to consider targeted screening for HTLV infections is also addressed above.

The responses to the current consultation indicate that there is an increasing level of interest in HTLV infections. This is particularly evidenced by the larger number of responses compared to previous consultations. Some respondents highlight the World Health Organisation (WHO) recommendation to eliminate HTLV 1 infection by 2030. The WHO produced a technical report which provides an overview of the evidence on a broad range of issues including the global epidemiology of HTLV 1 infection, the burden of disease associated with it and prevention activity in WHO regions.[8]

We thank the respondents for bringing this, and other papers, to the Committee's attention.

[7] Ireland G, Croxford S, Tosswill J, Raghu R, Davison K, Hewitt P, Simmons R, Taylor G. Human T-lymphotropic viruses (HTLV) in England and Wales, 2004 to 2013: testing and diagnoses. Euro Surveill. 2017;22(21)

[8] Human T-lymphotropic virus type 1: technical report. Geneva: World Health Organization; 2021.

5 The 11 members of the public were all either directly or indirectly affected by HTLV. One member of the public, whose partner had died from HTLV, also provided a video and petition with 1,295 signatures.

Response: the UK NSC is grateful to these stakeholders for sharing their experiences in their contribution to the consultation process and acknowledges the pain and suffering that HTLV has caused. The Committee has noted the increased interest in screening for HTLV compared to previous review cycles. However, the current evidence does not support a universal population screening programme for HTLV in pregnant women. The Committee recognises that a targeted approach may be more suitable and since this has not been considered before, would welcome a proposal through the Annual Call for Topics. The Secretariat has written to the British Society for Immunology to this effect following their direct contact with the Chair of the UK NSC.

Action

The Committee is asked to consider and approve the proposed recommendation

Proposed recommendation

It is proposed that:

- stakeholders should be encouraged to submit a proposal for a targeted antenatal screening programme to prevent adverse outcomes from HTLV infection through the annual call for topics
- the value of a modelling exercise should be considered as part of the discussion on the proposal for a targeted screening programme
- the current recommendation on universal, population, screening for HTLV should be archived. Uncertainty and controversy remain in key areas which undermine confidence that the benefits of screening, in terms of disease prevention, would outweigh the potential harms from detecting HTLV infection in the pregnant population. If significant evidence which changes this is published, stakeholders can request that the topic is revisited by the Committee.

Annex A: List of Stakeholders Contacted

1. British Society for Immunology
2. Faculty of Public Health
3. National Centre for Human Retrovirology
4. Royal College of General Practitioners
5. Royal College of Midwives
6. Royal College of Obstetricians and Gynaecologists
7. Royal College of Physicians
8. Royal College of Physicians and Surgeons of Glasgow
9. Royal College of Physicians of Edinburgh
10. Professor Graham Taylor

Annex B: Consultation Responses

Note: Personally identifiable information has been redacted from certain comments, where individuals have chosen not to have personal details made public.

1.

Organisation: Royal College of General Practitioners

The RCGP agrees with the proposal to remove screening for HTLV from the NSC list of topics and agrees with the NSC findings, not to screen the population for this condition.

2.

Name: Prof Richard Tedder

Organisation: xxxx xxxx

Role: Medical Virologist

A response to the decision not to screen in the \UK for HTLV infection in pregnancy.

Each of the DHSC bullet points are listed below as individual bullet points.

Screening is not recommended for HTLV in the UK because:

•there is not enough evidence to say that the benefits of screening outweigh the harms

This a strange way of justifying the decision not to use accurate and sensitive methods for identifying a mother who has the likelihood of transmitting this retrovirus to her child. Providing appropriate counselling support is in place before testing and accurate serology is provided there is no harm. This model has proved appropriate for other infections such as hepatitis B, human immunodeficiency virus and syphilis. The failure to prevent onward transmission of HTLV and knowledge that as a result a mother has infected her child is far more harmful to child and mother.

•the number of people with HTLV in the UK is low

From 2016 to 2020 44 HTLV infections were identified in first time blood donors attending NHSBT centres at a rate of c 6 per 100,000 such donors. Of these infections 19 were in males and 25 in females. Of the 44 infections all but one could be confirmed by sequencing. Thus 41/43 were HTLV 1 and 2/43 were HTLV 2. Ethnicity was not predictive of infection. Twenty one infected donors (seven male

and fourteen female) were of black ethnicity, eleven (eight female and 3 male) were of white ethnicity, eight (seven male and one female) were of Asian ethnicity. Twenty of the 44 (six males and fourteen females) were born in the UK. Note that selection for acceptability to be a blood donor will influence and be likely to reduce the measured prevalence below that in the UK population as a whole.

•it is not known how well the test performs in pregnant women

This has been shown not to be the case in the UK and is not reflected in other countries. See: Rosadas C, Tosswill JH, Tedder R, Taylor GP. Pregnancy does not adversely impact diagnostic tests for HTLV-1/2 infection. PLoS Negl Trop Dis. 2019 Sep 12;13(9):e0007736. doi: 10.1371/journal.pntd.0007736. PMID: 31513603; PMCID: PMC6764679.

•it is unlikely that the mother will pass on the virus to her child unless she breastfeeds for more than 6 months

In an attempt to moderate the maternal feeling of isolation in Japan a trial of a short period of breast feeding to allow maternal-infant bonding still led to transmission and confirmed that any breast feeding at all carries a risk of onward transmission, thus any breast feeding should be discouraged. The above statement is therefore incorrect.

•most infants infected with HTLV do not develop symptoms and the risk of developing a serious illness appears to be low

The incidence of the development of HTLV-related leukaemia in late adult life in Japanese populations is between 10% and 20%.

•there is no treatment for HTLV and the only approach is the avoidance of breastfeeding particularly after 6 months

Apart from the inaccuracy of breast feeding duration, long term haematological monitoring may be indicated in some patients. Monitoring of cellular viral load may allow early haematological intervention in “risk” patients.

•screening may make some women and their families feel anxious, depressed or stigmatised as there is no treatment

This may also apply to a number of antenatal viral screening tests. It is important that appropriate pre-test counselling and support is provided to mothers who are tested antenatally for HIV, HBV and HTLV. A mother who is allowed by default to transmit HTLV to her infant is likely to carry an immense burden of guilt.

Prof The Hon Richard Tedder FRCP FRPath

West Buckland

Kent

27 July 2022

3.

Name: xxxx xxxx

Member of the public

Affected Comment:

I was wrongly diagnosed with MS in 2010. When my disease didn't progress as expected I got tested for HTLV in 2019 which was positive. I have developed HAM and have limited mobility, chronic back pain as well as bladder and bowel issues. This was very difficult for me as I had been living as a person with MS with all the support which is available and was propelled into a world with a disease nobody has heard of with little information or support. Luckily I was referred to a specialist clinic at xxxx xxxx hospital who have been amazing at providing the care and support I need

This has all been extremely difficult for my family and friends who have all been very supportive. I am limited with what I can do socially and everyone has to tailor things to suit me. I feel very guilty about this and am always worried that I would appear 'difficult'. I often decide not to go as each outing requires such a lot of planning and organisation.

Discussion comment:

How do you know that there aren't many people in the population with HTLV if very few people have been tested? There may be many asymptomatic people in the population. Also some people may only have mild symptoms such as tripping over which has been attributed to something else without knowing they have HAM

As few people are tested there are many patients diagnosed with a neurological condition who may, like myself, be wrongly diagnosed. There is no test for something like MS so it's a process of elimination. If it isn't anything else it must be MS. Many patients in fact may have the HTLV virus

You also say that Mothers may find it distressing to find that they have HTLV and they may stay asymptomatic so it's not worth the stress as there is no treatment anyway. If more people are tested it may be discovered that more mothers have it and may develop symptoms in later life. Also there baby might catch it and develop symptoms. I know for a fact that getting a diagnosis for an array of symptoms which could be any number of neurological conditions is distressing and time consuming and also often inconclusive unless an HTLV blood test is done. If the mother tests positive at screening she should be supported and given information so she can make an informed decision on what to do with her baby such as breast feeding. It is no more stressful than finding they have any other condition they've been tested for as long as they get the right support.

There may be no treatment for the virus but there are many treatments for the related health issues such as bladder, bowel and mobility. People need and can access specialist support and information

Recommendation comment:

Definitely. See above

Alternatives comment:

More people need to be screened in the first place. It should be routine in Sexual Health clinics

There should be more education for medical staff regarding HTLV so they can make informed decisions on whether or not to test patients and what to do if the test is positive.

More research needs to be done on aspects of disease progression, management and treatment and also work on anti virals. It is perceived that there are so few people in the population with the virus it's not worth bothering. Unless more people are tested this is speculation. For those of us with HTLV with symptoms (of which I'm convinced are many undiagnosed) much more needs to be done.

4.

Name: Mark Zuckerman

Email: xxxx xxxx

Organisation: xxxx xxxx

Role: Consultant Medical Virologost

Page 3 of Plain English Summary:

Screening is not recommended for HTLV 1 in the UK because:

There is not enough evidence to say that the benefits of screening outweigh the harms

Please see:

Association between HTLV-1 infection and adverse health outcomes: a systematic review and meta-analysis of epidemiological studies

Gill Schierhout, Skye McGregor, Antoine Gessain, Lloyd Einsiedel, Marianne Martinello, John Kaldor

Lancet Infect Dis 2019

Published Online October 21, 2019

https://doi.org/10.1016/

S1473-3099(19)30402-5

Summary

Background Human T-cell lymphotropic virus type 1 (HTLV-1) is a human retrovirus that causes a lifelong infection.

Several diseases, including an aggressive form of leukaemia, have been designated as associated with HTLV-1,

whereby having HTLV-1 is a necessary condition for diagnosis. Beyond these diseases, there is uncertainty about other health effects of HTLV-1. We aimed to synthesise evidence from epidemiological studies on associations between health outcomes and HTLV-1.

Methods For this systematic review and meta-analysis, we searched Embase, MEDLINE, MEDLINE In-Process, and Global Health for publications from their inception to July, 2018. We included cohort, case-control, and controlled cross-sectional studies that compared mortality or morbidity between people with and without HTLV-1. We excluded

studies of psychiatric conditions, of symptoms or clinical findings only, of people who had undergone blood transfusion or organ transplant, and of population groups defined by a behavioural characteristic putting them at

increased risk of co-infection with another virus. We extracted the risk estimates (relative risks [RRs] or odds ratios [ORs]) that reflected the greatest degree of control for potential confounders. We did a random-effects meta-analysis for groups of effect estimates where case ascertainment methods, age groups, and confounders were similar,

presenting pooled estimates with 95% CIs and prediction intervals.

Findings Of the 3318 identified studies, 39 met the inclusion criteria, examining 42 clinical conditions between them.

The adjusted risk of death due to any cause was higher in people with HTLV-1 when compared with HTLV-1-negative counterparts (RR 1·57, 95% CI 1·37–1·80). From meta-analysis, HTLV-1 was associated with increased odds of seborrheic dermatitis (OR 3·95, 95% CI 1·99–7·81), Sjogren's syndrome (3·25, 1·85–5·70), and, inversely, with lower relative risk of gastric cancer (RR 0·45, 0·28–0·71).

There were a further 14 diseases with significant associations or substantially elevated risk with HTLV-1 from single studies (eczema [children]; bronchiectasis, bronchitis and bronchiolitis [analysed together]; asthma [males]; fibromyalgia; rheumatoid arthritis; arthritis; tuberculosis; kidney and bladder infections; dermatophytosis; community acquired pneumonia; strongyloides hyperinfection syndrome;

liver cancer; lymphoma other than adult T-cell leukaemia-lymphoma; and cervical cancer).

Interpretation There is a broad range of diseases studied in association with HTLV-1. However, the elevated risk for death among people with HTLV-1 is not explained by available studies of morbidity. Many of the diseases shown to be associated with HTLV-1 are not fatal, and those that are (eg, leukaemia) occur too rarely to account for the observed

mortality effect. There are substantial research gaps in relation to HTLV-1 and cardiovascular, cerebrovascular, and metabolic disease. The burden of disease associated with the virus might be broader than generally recognised.

Funding Commonwealth Department of Health, Australia.

Lancet Infect Dis 2019

the number of people with HTLV in the UK is low

In 2000, we published the following in the BMJ:

We found the seroprevalence of antibody to human T cell leukaemia/lymphoma virus was 0.39% among pregnant women in southeast London over a 36 month period. This result probably reflects the ethnic composition of the local residents of Lambeth, Lewisham, and Southwark, about 18% of whom are black (1991 census data).

The policy of not screening for HTLV antibody in pregnant women and in blood and organ donors is partly based on its perceived low prevalence and the low lifetime risk of associated disease. Although the cost of antenatal screening could be limited by selecting those women thought to be at high risk, this would require knowledge of the ethnicity details of current and previous sexual partners in order to be comprehensive. Such information might be difficult to obtain. In our study HTLV infection was not limited to women who described themselves as black African or black Caribbean, a finding that was also reported in the West Midlands.3 Three white women were infected, of whom two were born in Britain and one in Jamaica, and all three had black Caribbean partners. We also found HTLV antibody in 10 women born in Britain who described themselves as either black African of black Caribbean.

The prevalence of HTLV antibody was similar to that reported for HIV in the same population at the same time. With appropriate counselling, screening for HTLV should be accepted in the same light as testing for HIV, which has recently been recommended as part of the routine antenatal screening programme. However, unlike HIV infection, infection with HTLV is less likely to become clinically apparent, and the factors conferring a high risk of developing associated disease have not been defined. In the mean- time, antenatal screening could help limit vertical transmission.

It is not known how well the test performs in pregnant women

This is incorrect and has been reported: Pregnancy does not adversely impact diagnostic tests for HTLV-1/2 infection.

Rosadas C, Tosswill JH, Tedder R, Taylor GP. PLoS Negl Trop Dis; 2019 09; 13(9):e0007736. PubMed ID: 31513603.

It is unlikely that the mother will pass on the virus to her child unless she breastfeeds for more than 6 months

Data from colleagues in Japan indicate that this is incorrect.

simply completely wrong.

Most infants infected with HTLV do not develop symptoms and the risk of developing a serious illness appears to be low

A 5% life-time incidence of HTLV-associated leukaemia is relevant. Other causes of significant morbidty include HTLV associated myelopathy and please see the Lancet IP paper from 2019.

There is no treatment for HTLV and the only approach is the avoidance of breastfeeding particularly after 6 months

This is incorrect as bone marrow transplants are becoming part of the management of individuals with HTLV associated T cell leukaemia (ATLL). Preventing exposure to breast milk is key from day 1 not after 6 months.

Screening may make some women and their families feel anxious, depressed or stigmatised as there is no treatment

Antenatal screening requires early support for those individuals found to be infected. This support has to be in place prospectively. However no expectant mother would wish to put their children at risk of infection and subsequent illness in their adulthood if this can easily be prevented.

5.

Name: Public Health Scotland

Email: xxxx xxxx

Condition: HTLV

Public Health Scotland acknowledges the severity of illness associated with Human T-cell Lymphotrophic Virus (HTLV) infection and welcomes UK National Screening Committee (NSC) work to assess whether antenatal screening is effective in reducing associated mortality or morbidity.

The UK NSC has reviewed the evidence base related to antenatal screening of HTLV four times. UK NSC recommends against screening for HTLV based on the findings of these reviews. It is noted that the current evidence map found no new evidence to change the conclusions of the previous reviews on which this recommendation is based.

In the absence of high-quality evidence that antenatal screening for HTLV would be effective and cost-effective in reducing mortality or morbidity, and that the benefits of screening would outweigh potential harms, PHS supports the UK NSC position that antenatal screening is not currently recommended for this condition.

6.

Name: xxxx xxxx

Email: xxxx xxxx

Organisation: xxxx xxxx

Role: xxxx xxxx

Condition: HTLV

Agree that the new evidence identified does not provide information that would support a change to the current position that screening is not recommended.

7.

Name: xxxx xxxx

Member of the public

Email: xxxx xxxx

I lost my partner, xxxx xxxx from Adult T-cell leukaemia lymphoma directly caused by HTLV. We were new parents to a little boy, who was only 5 months old at the time of xxxx xxxx diagnosis. Exactly a year and a week after the diagnosis, xxxx xxxx passed away, leaving my son with no father, and myself as a single parent. HTLV destroyed our family. The suffering xxxx xxxx endured was nothing short of horrific. Seeing someone you love in such pain, knowing that the virus continues to be invisibly transmitted is extremely difficult to deal with.

Immediately after xxxx xxxx diagnosis I learnt that I may also have HTLV transmitted through sexual intercourse, and I may have passed this on to our son who I was breastfeeding at the time. My primary concern wasn't that of myself, but the health of our son. Whilst dealing with the terminal prognosis of my partner, as well as being a new mother, I had to be tested for HTLV. I immediately stopped breastfeeding, something I had struggled with, but was pressured through the NHS to do.

In the following 2 weeks we were told by the consultant that xxxx xxxx was not expected to live past 6 months. He was in a lot of pain and started treatment straight away. Plans of further children were snatched away. I divided time between home and the hospital. Awaiting my test results, I had extreme guilt and stress that I may very well have given the same virus to our son, who may then have the same fate as xxxx xxxx. This was unbearable to comprehend.

Why was I not offered screening during pregnancy? If I was tested to be positive, studies show based on my age of transmission, ethnicity, and gender, I would have been unlikely to develop ATLL. I could have not breastfed. But here I was, waiting to know if I had risked my son's life unknowingly due to lack of screening and awareness. My son's age, ethnicity, gender and method of transmission would have made him at high risk to develop ATLL if he was to have found to have contracted

the virus from myself. I was having to comprehend that possibility whilst watching the man I had planned to spend the rest of my life with, die from the very virus I may have given my son. All due to lack of antenatal screening.

Even though my result was negative, HTLV has changed everything.

I now raise awareness of HTLV and campaign for antenatal screening to be introduced. I own the channels, 'HTLV Action and Awareness' and have a petition with 1300 signatures calling for the introduction of antenatal screening for high-risk expectant mothers. The link is here: https://www.change.org/p/uk-national-screening-committee-introduce-screening-for-htlv-1-in-high-risk-expectant-mothers

xxxx xxxx campaign videos are found here:
https://www.youtube.com/channel/UCPZm6Q2lAZdj6J7FkS_qSpQ

I am also on Twitter as 'HTLVAction', and Facebook as "HTLV Action and Awareness".

Losing xxxx xxxx and waiting for test results was traumatic for everyone who knew us. Everyone was powerless to help. Prevention is the only way to stop HTLV.

Evidence Comment:

There was an abundance of evidence missed, or overlooked as being subjectively labelled as "inconclusive" or "not enough".

Firstly, stating as a reason to not screen is that "screening may make women and their families feel anxious, depressed or stigmatised as there is no treatment", is speculative.

As a mother who was not screened, the guilt and stress that I went through awaiting my test results after breastfeeding was traumatic. I was told my partner may not survive the week, and the same virus killing him, may also be in me, and I may have passed it to my son. If I was offered screening during my pregnancy, all this stress would have been avoided. There has been no consideration in your review of the women who would be tested negative, or the women who would be tested positive who could then be empowered to protect their babies. Every mother I know would do anything for their child. You are taking away their right, my right, to protect our children by not offering screening.

You state "most infants infected with HTLV do not develop symptoms and the risk of developing a serious illness appears to be low". Again, this is speculative; "appears to be low" is based on lack of data since no screening is in place. Sufferers of HTLV-1 Associated Myelopathy (HAM) are often misdiagnosed as suffering from multiple sclerosis. HAM is not commonly known in the medical profession. Moreover, HTLV causes (HTLV-1)-associated infective dermatitis in children. This is very likely to be more common than expected as the lack of awareness of HTLV means children may simply be diagnosed with severe eczema. Eczema they may be hospitalised with. Your 'review' does not acknowledge any of this. It is selective of information that fits the pre-emptied recommendation to not screen.

The review also fails to acknowledge that antenatal tests offered to women are voluntary. The test for HTLV would be alongside tests and scans already offered.

Most women do not know what they are being tested for, they simply have confidence in the medical profession that the tests are going to be for the good of themselves, and their unborn baby. Adding a 'new' test for HTLV, that is already tested for in blood donations is, in my opinion, extremely unlikely to add any more stress to the mother than what she would already be feeling being pregnant. The difference with the HTLV test, as opposed to the genetic tests, is that a positive HTLV test result can result in a change of behaviour of the mother to protect the baby, whereas with an undesired genetic test result, the mother is powerless to do anything. Why are genetic tests offered, but HTLV is not?

Discussion comment:

In addition to my comments from the previous question, I have found the review to contain an extreme level of subjectiveness, including defining what studies can and cannot be deemed as conclusive.

You state "the number of people with HTLV in the UK is low". This is based on poor data, as without a screening program you cannot definitively declare this. "Low" is ambiguous. The communities most likely to have HTLV are also those less likely to seek medical help. We cannot use blood donations as an accurate portrayal of prevalence when those from the BAME communities are less likely to donate than those of a white British background.

You state "there is not enough evidence to say that the benefits of screening outweigh the harms", yet there is ample evidence you have subjectively declared "is not enough". I am living evidence. Evidence that does not support screening, you state as fact, yet if it does support screening, you suggest it is weak.

You state "it is not known how well the test performs in pregnant women", by ignoring all international studies that confirm the reliability of screening. Without a screening program in place, and ignoring international studies, you will forever pose this weak argument as a reason to not recommend screening.

You state "it is unlikely that the mother will pass on the virus to her child unless she breastfeeds for more than 6 months" yet you ignore evidence that the Royal College of Midwives, and the NHS actively promote and pressure women to breastfeed for more than 6 months. Essentially, the same government who refuses to set up an antenatal screening program to check for HTLV, that is passed on primarily through breastfeeding for more than 6 months ALSO encourages women to breastfeed for more than 6 months.

You state "there is no treatment for HTLV and the only approach is the avoidance of breastfeeding particularly after 6 months". Stating that the "only approach" is to avoid breastfeeding is incorrect. The most effective 'approach' to avoid contraction of HTLV is for women to be screened during pregnancy, and for those who are tested positive to opt for a c-section and to not breastfeed at all. To state the "only approach" is to avoid breastfeeding is simply incorrect, and what feels like a poor attempt to justify the recommendation to not screen from those not equipped with the scientific knowledge of HTLV.

With there being no cure for HTLV once an individual is infected, surely this is the reason to introduce a screening program to prevent transmission. Palliative

treatments are available. The cost of which is significantly higher per individual than screening.

I have made a video with several counter arguments to your conclusion. The video is found here: https://www.youtube.com/watch?v=yehi5VWRa2U

Recommendation comment:

Yes.

• HTLV causes an incurable cancer called Adult T-cell leukaemia/lymphoma, and an incurable neurological disease called HTLV-1 Associated Myelopathy (HAM).)

The only thing we can do is to prevent transmission of HTLV.

Antenatal screening is the first vital step to prevent transmission. When there is no cure, why aren't we taking steps in prevention.

• HTLV is screened for in blood donations. Blood recipients therefore have a high level of protection against contracting HTLV. Babies should be offered the same protection. By offering antenatal screening, mothers tested positive can decide not to breastfeed, thus stopping vertical transmission.

• Individuals given a positive result after donating blood do not have a point of contact to discuss their result with. Antenatal screening gives the mother a safe environment to hear the results. Their midwife can signpost them to further support, just like they do with other antenatal test results.

• Pregnant women who are tested positive are able to take action to not pass HTLV to their babies.

They may opt for a C-section, and can decide to not breastfeed.

• As part of antenatal care, women are already offered several blood tests and scans. Including HTLV in this list of optional tests would not significantly increase stress levels.

• Many women are unaware of all the tests being performed; they simply want the best for their unborn baby. Knowledge is power.

• Antenatal tests are optional.

HTLV screening should also be offered as a choice; alongside the existing tests and scans.

It is a mother's right to make their own decisions.

Not offering HTLV screening, removes her right.

• Mothers who find out they have passed on HTLV to their children have to live with guilt, shame and worry.

If screening was in place during their pregnancy, this would not happen. Transmission is preventable.

• The cost of care for those diagnosed with Adult T-cell leukaemia/lymphoma (ATLL) or HTLV-1 Associated Myelopathy (HAM) far exceeds the cost of screening.

• Pregnant women who are tested negative have reassurance that they will not pass HTLV to their babies.

• HTLV destroys families.

Children are growing up without Parents, Aunts, Uncles and Grandparents; all whilst knowing they may have the same fate.

A fate that was avoidable if antenatal screening was offered.

• Other countries such as Japan and Brazil have a successful antenatal screening program in place,

• Antenatal screening will provide more accurate data on the rate of HTLV in the population. Presently, studies can only rely on blood donation data, data from other countries, or from those with a diagnosis of ATLL or HAM.

• As HTLV most commonly affects BAME communities, by not screening, there is a strong element of discrimination.

• Immigration from countries with a higher prevalence of HTLV has significantly increased in the last decade. The rate of carriers is unknown with no screening program. A pandemic is imminent.

I have made a video describing 10 reasons to introduce antenatal screening: https://www.youtube.com/watch?v=ujMf7VY8A3g&t=5s

Alternatives comment:

HTLV sufferers face a complicated journey in the NHS as the majority of healthcare professionals are unaware of the virus's existence, never mind the conditions it causes. When I was tested for HTLV, the nurse was not sure what the virus was, it was not on her 'computer system' either. This meant she had to hand write on the vials what I was asking my blood to be tested for. Her lack of awareness heightened my fears; if they do not know what it is, then they won't be able to help me.

Medical professionals need to be taught what HTLV is. Children with (HTLV-1)-associated infective dermatitis, often mistaken as eczema face below expected levels of treatment due to lack of awareness. Those with HTLV-1 Associated Myelopathy (HAM) are often misdiagnosed as suffering from multiple sclerosis (MS). The drugs offered for MS will not help in the same way those for HAM do. Those people are let down by the NHS.

I firmly believe that the ethnicity has a huge role to play in the lack of awareness and screening. Firstly, there is a language barrier, secondly a cultural barrier in terms of accessing healthcare, and thirdly, which is in our control, the equality, or lack of, that the UK practices as a whole.

As there is no cure for HTLV, the only way to stop others from dying from conditions it causes or suffering from life debilitating symptoms, is to offer screening. When

there is no cure, this is what must be done to stop HTLV. There are no alternatives to preventing contraction of the virus.

Other comments:

I am very disappointed and worried to see that this is the final consultation for the introduction of antenatal screening for HTLV from you. By declaring this, it feels a decision to not recommend screening has already been reached. I truly hope that I am mistaken and that all evidence presented during the consultation process will be read, weighted and discussed.

I recommend watching and reading the links sent in the previous sections and understand that we are real people, here in the UK, affected by HTLV.

My final recommendation would be to acknowledge that screening would be offered to pregnant women, this does not mean they will have to accept. It should be their decision; not yours.

8.

Name: xxxx xxxx

Member of the public

Email: xxxx xxxx

Me and my family

Recommendation comment:

I think screening should definitely recommended. Myself and my siblings git it unknowingly to our mother if she was screened now we will not be dealing with this terrible virus.

Alternatives comment:

More funding to help with research

9.

Name: xxxx xxxx

Member of the public

Email: xxxx xxxx

Affected Comment:

I was diagnosed with HTLV in 2012 after a needle-stick injury at work only because I was lucky enough to work for one of the few institutions in the UK that screens for the virus. Before my diagnosis, I was not aware of HTLV, and although I am still asymptomatic I have the virus and there are no guarantees.

Evidence Comment:

Reading the UK National Screening Committee (UK NSC) recommendations for not screening for HTLV has saddened, and depressed me.

Discussion comment:

a“There is not enough evidence to say that the benefits of screening outweigh the harms”, AND “The number of people with HTLV in the UK is low”.

There is not enough evidence because of the lack of screening which will inevitably lead to the misdiagnoses of people with HTLV symptoms. Therefore, without the evidence how can you make a judgment or a definitive decision?

The numbers are low because there are people with the virus who are not aware they are infected and could be passing it on unknowingly. Therefore, stating that the numbers are low is speculation because “there is not enough evidence…”

“It is not known how well the test performs in pregnant women”.

By not screening, an opportunity is missed to establish how the test would perform.

“It is unlikely that the mother will pass on the virus to her child unless she breastfeeds for more than 6 months”.

What about those mothers who breastfeed beyond 6 months? Is it acceptable (if they have the virus) for them to pass it on unknowingly to the next generation?

Mothers are encouraged to breastfeed, and the majority of mothers I know breastfeed for more than 6 months.

“Most infants infected with HTLV do not develop symptoms and the risk of developing a serious illness appears to be low”

“The risk appears to be low”? Really? Are you all listening to yourselves? There is no certainty here, just speculation.

And even if the risk appears to be low, are you saying this doesn’t matter? If so, then what you are actually saying is that a few babies with an incurable virus is acceptable, collateral damage, maybe?

“There is no treatment for HTLV and the only approach is the avoidance of breastfeeding particularly after 6 months”

Are they now prepared to tell mothers that they should consider stopping breastfeeding at or before 6 months because it is possible that if they have the HTLV virus it is highly likely that it could pass to their babies if they don't?

And will they then explain to those mothers and pregnant women that the advice is due to the fact that the government is aware of the consequences of HTLV but doesn't consider it important enough to screen them, therefore, they will have to make a decision on breastfeeding as compensation?

"Screening may make some women and their families feel anxious, depressed or stigmatised as there is no treatment"

Not knowing, or finding out at a later date will cause even more stigma, anxiety, and depression. What about the women and their families that would prefer to know to be able to make informed choices? They don't matter?

Recommendation comment:

Screening must be recommended before this turns into an epidemic!

Alternatives comment:

What are the 'many' alternatives?

Stop breastfeeding at or before 6 months?

Stop having unprotected sex even if you are trying to become parents?...

If workable alternatives exist, publish them.

Other comments:

Yes, start screening for HTLV.

I am of Afro-Caribbean ethnicity and cannot help but ask this question:

If HTLV affected all ethnicity equally, would the response be different?

10.

Name: Professor Sara Rankin

Email: xxxx xxxx

Organisation: xxxx xxxx

Role: Scientist (training in pharmacology and immunology)

I write in response to the public consultation to the recent review carried out by the NSC for the antenatal screening of HTLV-1.

In am writing in my professional capacity as a Professor in Leukocyte and Stem cell Biology, who has researched in the field of immunology for over 25 years. I have reviewed the scientific literature, reports from the WHO alongside the evidence maps and meeting minutes of the NSC. In addition, I note from posts on the NSC's webpages that the NSC is currently evolving. Specifically, a new committee and work stream has recently been established for targeted screening. The 2017 evidence review for HTLV-1 concludes that "the number of people infected with HTLV in the UK is low and restricted to specific subgroups of the population". As reported in the same evidence review, the prevalence of HTLV-1 positivity in the UK is 169 per 10,000 babies born to women born in the Caribbean compared to 3.1 per 10,000 for the whole UK population. This data actually provides the evidence required for a targeted screening approach, that would also align with the NSCs third ethical principal, "Promoting equality and inclusion". A targeted screen would screen pregnant mothers born or with partners from areas of the World where HTLV-1 is endemic. This targeted antenatal screening approach for HTLV-1 has already been adopted in France.

There are some other specific points I would like to raise for the committee's consideration.

From a scientific perspective, I'd like to raise the following points.

1.I do not understand why NSC continues to question the accuracy/ robustness of the HTLV-1 test, when published data shows that it is very accurate. Furthermore, NHS Blood and Transplant consider it accurate and robust enough to use it for 'screening out' potential donors.

2.An argument has been made that HTLV-1 does not need to be screened for, as infection with HTLV-1 does not affect the health and wellbeing of the baby/child. This is at odds with the fact that the NHS offers PGD-IVF for parents known to be carries of genetic diseases such as BRAC 1/2 mutations that increase the risk of breast cancer in adult life, but have no impact on the life and well-being of the baby.

From an ethical point of view, I'd like to raise the following points

1. 25% of babies infected with HTLV-1 go on to develop ATL, an aggressive lymphoma, with no effective treatment options (1.2). Implementing antenatal screening followed by formula feeding has been shown to reduce mother to child transmission by 85%.

Having screening would therefore undoubtedly improve the life-long health and well-being of babies, born to mothers infected with HTLV-1. Not recommending screening is at odds with the NSCs first ethical principle "Improve health and well-being."

2. The published minutes of the NSC indicate that the experts (scientists and clinicians with decades of experience researching and treating patients with HTLV-1) that responded to the public consultation in 2017 have not been listened to. Indeed, the peer reviewed, published data, has not been taken into account when making previous decisions. As such I believe that the experts have been dis-respected in this process. In this respect the process appears at odds with the NSCs second ethical principle “Treat people with respect”.

3. In the 2017 assessment of HTLV-1 antenatal screening, one of the reasons cited for not recommending screening was “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.“

It is well known that Mothers put the life and well-being of their children above their own, with mothers in poverty prioritising the needs of their children over themselves and pregnant mothers with cancer, putting-off treatment during the pregnancy. The stress caused to the pregnant mother of being identified as HTLV-1 positive, will be nothing compared to the stress caused in knowing they have inadvertently infected their child with a highly oncogenic virus.

Further, this argument is at odds with how the NHS blood and transplant and the Breast milk banks operate, in that infected donors are informed by a letter, without any concern for the anxiety and stress this may cause. Another related concern I have, is that the NHS is actively recruiting Black mothers to donate Umbilical cord stem cells, this donated tissue undergoes screening for HTLV-1, and a mother would again be informed if they were HTLV-1 positive at this point, with no regard for the psychological impact. These inconsistencies in practice across the NHS need to be addressed.

From a global public health perspective I’d like to raise the following question.

1.Reports published by the WHO in 2021 outline their aspiration to eliminate HTLV-1 Worldwide by 2030 (3,4). How will this be achieved in the UK without an antenatal screening programme?

In conclusion, on the basis of the points raised above I am not in agreement with the NSCs decision to NOT recommend ante-natal screening for HTLV-1 in the UK.

References

1. Malik, B., and G. P. Taylor. 2018. ‘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’, Br J Haematol, 184: 1040-43.

2.Nosaka, K., B. Crawford, J. Yi, W. Kuan, T. Matsumoto, and T. Takahashi. 2022. ‘Systematic review of survival outcomes for relapsed or refractory adult T-cell leukemia-lymphoma’, Eur J Haematol, 108: 212-22.

3.World_Health_Organisation. 2021a. “Human T-lymphotropic Virus type 1: Technical Report.” In. Geneva, Switzerland: World Health Organisation.

4.World_Health_Organisation. “Public Health Impact and implications for future actions: WHO global consultation on the human T-lymphotropic virus type 1.” In. Geneva, Switzerland

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11.

Name: xxxx xxxx

Member of the public

Email: xxxx xxxx

Affected Comment:

Yes, myself and my son. I passed it on through breast milk. My son is 31 and has very low viral load. I have symptoms and have a high viral load

Evidence Comment:

To say that that HTLV 1 is rare in the UK is naive because there are probably a lot of people that have it and don’t know due to lack of awareness and screening.

Discussion comment:

I have had this virus for over 30 years and only found out about 2 years ago due to my son needing to find out if he had the covid antibodies.

Recommendation comment:

Screening should most certainly be done. The most natural thing is for a mother to feed her new born baby breast milk, in my case I gave my baby infected milk. I only gave my baby breast milk once but it was said in your report that baby’s only get the virus after 6 months breast feeding, not true. My baby got the virus the first day of his life.

Alternatives comment:

More awareness in schools, colleges etc. A lot of people know what HIV is but hardly any one knows about HTLV 1/2. I know HTLV 1 is more common in other countries but that could all change with a lot more nationalities coming together.

For those that have the condition, support groups and more easy to understand information on the Web sites. Also trainng for gps so they can understand and help their patients in between hospital visits.

Other comments:

The lack of screening in the UK for HTLV 1 in my view is bad. I take full responsibility for getting this virus, I'm almost sure it is from unprotected sex in the 80s. I then went on to pass it on to my son and give blood throughout the 90s, this need not have happened if their had been more screening. The most important thing for a mother is to protect her newborn baby not pass this terrible virus on. Please think again.

12.

Name: xxxx xxxx

Member of the public

Email: xxxx xxxx

Affected Comment:

Yes my friend's partner died from a cancer caused by HTLV

Evidence Comment:

No

Discussion comment:

No

Recommendation comment:

Yes, it should be recommended in order to help lives lost.

Alternatives comment:

Mental health support

Regular checks ups

Other comments:

No

13.

Name: xxxx xxxx

Member of the public

Email: xxxx xxxx

Condition: HTLV

Affected Comment:

My daughters partner got diagnosed with HTLV, she then had to be tested. She had just had my grandson, waiting for the results for my daughter wasn't a nice time. She had been breast feeding my grandson and knew if she had got it, it could have been pasted on to him. We sadly lost my daughters partner and my grandson father just after my grandson was 1.

Evidence Comment:

I have been told that if my daughter had, been tested while pregnant she would have found out if she had caught it. She wasn't tested so she breast feed my grandson, we were lucky she hadn't caught it. The government say its unlikely to be passed on to your baby through breast feeding if you breast feed for less than 6months, then the government promote breast feeding for longer. Does that mean after six months your baby will be infected? I understand that you don't screen pregnant woman in the u.k for HTLV because there isn't enough data to show screening is needed. If you don't do any screening how do you know if it's needed. What data is it based on not to screen pregnant woman. Do pregnant woman get warned about HTLV? Can they request a screening when pregnant? Because you don't screen for HTLV how do you know how prominent it is in the u.k. Isn't provent better than a cure? Oh forgot there is no cure for HTLV.

Discussion comment:

I strongly believe pregnant women should be offered the chance to be screened for HTLV. If not HTLV will increase in the u.k. Even if its done for 2 to 5 years so that data can be collected and then a proper conclusion can be made.

Recommendation comment:

Screening should be recommended. To avoid passing it on to babies, if HTLV keeps getting passed on to babies it will become more common in the u.k. If a woman is offered Screening and doesn't pass it on surly it will reduce HTLV here in the u.k

Alternatives comment:

I didn’t know anything about HTLV, until my daughter had to be tested. She herself had no awareness of it. Perhaps the government need to make people aware, help them understand what it is. We have a very diverse population in the u.k and I have spoken to some African and Asian women about HTLV and they have never heard of it.

Other comments:

It was a very hard time, waiting for the results of my daughters test. Thinking she had it and could have passed it on to my grandson. We were lucky in one sense but she lost a partner and my grandson lost his dad in a year from

HTLV diagnosis. Knowing that could have happened to my grandson when it could be avoided is unforgivable. Even if you test for two to five years and get some data to back up your not enough data your argument might be stronger but at the moment your argument is weak.

14.

Name: xxxx xxxx

Member of the public

Email: xxxx xxxx

Affected Comment:

This condition has affected the partner of my daughter’s friend.

Evidence Comment:

I think the UK NSC has covered all aspects.

Discussion comment:

I believe very firmly that targeted screening should be available for women who are at risk of passing on the condition to their babies.

This would alleviate the fear and anxiety of these mothers. The cost of screening is cheaper than the cost of following treatments, not to mention the human cost in terms of illness or death.

Recommendation comment:

I think screening should be recommended because it gives pregnant mothers the opportunity to discover the risk of passing on the condition.

It should be voluntary so that women can choose.

Alternatives comment:

There should be more information published and accessible. Perhaps pupils could be made aware of the condition, especially those in the high risk groups. GPs and GP surgeries ought to contact those in the target group, offering more consultations.

Other comments:

I would advocate a greater awareness of the condition.There should be an informative programme using schools and community groups.

15.

Name: xxxx xxxx

Member of the public

Email: xxxx xxxx

Affected Comment:

I was diagnosed with the HTLV-1 virus 6 years ago. It took a long time and many appointments with various doctors to establish my condition. Prior to the appointments it was not obvious what was causing my illness or why it was deteriorating at such a rapid rate. This obviously escalated the worry for me, family and friends. It all started with me falling over for no apparent reason and this could happen anytime and anywhere which became extremely frightening and increased my anxiety levels. I just could not understand why this was happening to me all of a sudden. I thought maybe I had sciatica as I was also experiencing pain in my lower back. I became very nervous about leaving the house as I felt I could not control my movements or determine if or when I would fall. This in turn affected my mood and relationship with family, friends and work colleagues. It even affected how I did my job. For nearly two years the doctors thought I had arthritis. It was only when the falls became more frequent and I was injuring myself was I referred to a neurologist. I then had regular appointments with the neurologist and MRI Scans for over a year before it was determined that I may have the HTLV virus. The neurologist referred me to the HTLV Clinic at St Mary’s Hospital where I was diagnosed with the HTLV virus and that is where I have been receiving treatment to this date.

Evidence Comment:

No.

Discussion comment:

No.

Recommendation comment:

I believe screening should be recommended. I believe any and every opportunity that is available to capture the possibility of any illness at the earliest stage should always be utilised. This would give everyone a fighting chance and rule out so many other possible illnesses with similar symptoms that are not life threatening. Allowing those affected based on the outcome, to make life changing decisions much earlier on therefore reducing the possibility of stumbling across this this diagnosis (or not) much later in life.

Alternatives comment:

I do not think there should be an alternative to screening but running in conjunction to the screening, an awareness campaign of this debilitating illness, specifically targeting those demographics likely to be affected.

Other comments:

I hope you will reconsider the decision to not screen for this illness because this decision will make an immense difference to our quality of life and everyone who is affected by how this condition impacts us.

UK National Screening Committee

16.

UK National Screening Committee

Antenatal screening for HTLV infection – an evidence map

Consultation comments pro-forma

Name:	Graham P Taylor and others	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Imperial College London and others		
Role:	**Head of Section of Virology, Imperial College London and Honorary Consultant Physician, National Centre for Human Retrovirology, St Mary's Hospital, London**		

Do you consent to your names being published on the UK NSC website alongside your response?

Yes - I and the co-signatories give this consent

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
6	Epidemiology and Natural History	Please see the detailed, referenced response to each component of this section on Pages 3-5 of this response below. References on Pages 8-9
6	Test	Please see the detailed, referenced response to this section on Page 5 of the document attached below. References on Pages 8-9

6	Treatment	Please see the detailed, referenced response to this statement on Page 7 of the document attached below. References on Pages 8-9
6	Potential negative impact on the mother	Please see the detailed, referenced response to this statement on Page 6-7 of the document attached below. References on Pages 8-9
8	Summary of findings	This is addressed, in detail, with references, throughout the document drawing attention to the errors of the 2011 review which continue to be perpetuated.
9	Conclusion and Recommendation	The document attached below provides ample evidence of the case for antenatal screening which have been omitted from the present review and addresses again the concerns that we presented to the public consultations of 2011 and 2017 but were not taken into account. The signatories call for a comprehensive review of all data.

Response to the National Screening Committee HTLV Evidence Map.

This is the third response from UK experts on HTLV-1 infection to the National Screening Committee during the Consultation process. The first, following the 2011 review, identified significant errors in that review: this identification was substantiated by published evidence. These errors have been perpetuated in the subsequent reviews.

Here, we therefore set out the pertinent facts relating to HTLV-1 infection and antenatal screening based on the published literature. We request that each point is considered by the Committee before reaching a decision on whether to recommend antenatal screening for HTLV-1 infection in the UK or to recommend further targeted work to improve health and reduce health disparity in the UK.

An unexpected and counterintuitive argument of the 2017 review, which we draw to the attention of the Office of Health Improvement and Disparities, was that HTLV-1 infection was only found in certain sections of the UK population, viz. Black, Asian and minority ethnic (BAME) groups.

The 2022 review relies on the 2017 being fair and accurate and then focuses on a single question *"What is the volume and type of evidence on the benefits/harms of screening for HTLV during pregnancy?".* The review includes only 1 paper published since the last review to address the potential of antenatal screening in the UK. A second paper, which is acknowledged to be pertinent, was excluded on the grounds that it was presented as a letter. As a result, the potential benefits and harms of HTLV antenatal screening have not been appropriately or adequately taken into account.

In 2022, at the 75th World Health Assembly HTLV-1 was included in WHO`s Global Health Sector Strategies on, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030 (GHSS), as a Sexually Transmitted Infection, and the WHO published the detailed meta-analysis of the burden of HTLV-1-associated diseases which they had commissioned in 2019. The 2022 review should take these new developments into account.

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. As outlined above, the 2017 review did not take into account either previous inaccuracies in the earlier review, or the significant new evidence published in the intervening period. Here, we address the findings in each of the four areas identified in the 2022 review:

Updated response to 2017 review

1.Epidemiology and natural history - 1. *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*.

The review must include the latest data on the significant burden of disease associated with HTLV-1 infection. We draw attention to the evidence that HTLV-1 infection is associated:

- a range of conditions, not just ATL/HAM (Schierhout 2019; World_Health_Organisation 2021a);
- a 57% increase in adjusted mortality rate (Schierhout 2019; World_Health_Organisation 2021a);
- increased risk of diabetes mellitus and chronic renal disease (Talukder et al. 2021)
- increased risk and worse outcomes of a range of co-infections (Ye, Taylor, and Rosadas 2022; Rosadas and Taylor 2022);
- reduced Health State Utility values in asymptomatic carriers (Rosadas et al. 2020);
- very low Health State Utility values in patients with HAM (Rosadas et al. 2020).

Furthermore, most importantly from the prevention of vertical transmission perspective, ATL:

- is strongly associated with infection in infancy (Bartholomew et al. 1998): most of the lifetime risk of 5% for ATL in people with HTLV-1 affects the 20% who are infected in infancy through vertical transmission, and who thus have a 25% lifetime risk of ATL (Malik and Taylor 2018);
- has a median overall survival life of less than 8 months in most recently reported studies, regardless of treatment strategy (Nosaka et al. 2022).

In summary, the burden of disease associated with HTLV-1 is high and the review to inform the NSC should be corrected.

Epidemiology and natural history -2***.*** *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.*

We note that the prevalence of the target infection or disease is not a criterion per se of the need for screening but would inform the cost utility analysis. Screening for diseases with much lower prevalence is currently recommended in the UK e.g. Maple Syrup Urine Disease (1 per 150,000). The current wording is somewhat prejudicial. However, it is important to emphasise that the prevalence of HTLV-1 with the Black African and Caribbean population high (according to the ECDC threshold) being >1% (Ades et al 2000).

Epidemiology and natural history -3***.*** *Previous UK NSC reviews have found that there is little information on the natural history of the infection acquired through breastfeeding.*

Contrary to this statement there is a long history of published evidence not only of the association of ATL with infection acquired in infancy as discussed above, but also of development of the HTLV-1-associated conditions HAM, uveitis and Infective Dermatitis occurring in children. Breastfeeding is one of the two main routes of transmission in HTLV-1-endemic areas, and there is extensive published evidence concerning the development of HTLV-1-associated diseases in those infected in infancy (Bittencourt, Primo, and Oliveira 2006; K et al. 1997; LaGrenade et al. 1990; La Grenade 1994; Umeki et al. 2009).

Epidemiology and natural history -4***.*** *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.*

The basis and intent of this statement is unclear. The rate of acquisition of HTLV-1 infection increases with duration of breastfeeding beyond **3 months,** reaching 33% after 2 years (Ando et al. 2003) . Indeed, in the 2021 systematic review and meta-analysis by Itabashi and Myazawa short-term breast feeding for less than 6 months was associated with a risk ratio of 2.91 (95% CI 1.69 – 5.03) compared with exclusive formula feeding (Itabashi and Miyazawa 2021). Prolonging the duration of breast-feeding in the general population is encouraged and longer duration of breastfeeding is observed in black and minority ethnic communities in the UK (https://files.digital.nhs.uk/publicationimport/pub08xxx/pub08694/ifs-uk-2010-chap2-inc-prev-dur.pdf accessed 04/10/2022) – the very communities with higher rates of HTLV-1 (Ades et al. 2000). This was incorporated into the cost-benefit analysis pertaining to UK HTLV screening (Malik and Taylor 2018).

The term “over detection” here is highly inappropriate: the implication is that detection is unnecessary – that is, that ignorance is preferable. A position that is morally indefensible. Detection of HTLV-1 infection in the mother will allow her to make informed choices not only about infant-feeding but also about her own health and reducing risk of adult-to-adult transmission. The relief a mother experiences to be able to reduce the risk of HTLV-1 transmission (Zihlmann KF, Mazzaia MC, and AT. 2017) has also been vocalised in the Pan-American Health Organisation’s (regional office for the Americas of the World Health Organisation) 2022 webinar on the Public Health response to HTLV, focusing on the prevention of HTLV-1 mother-to-child transmission(https://www.youtube.com/watch?v=opthFTcjcRA). In the UK all HTLV-1 infected persons are able to access care which includes information about disease risk, access to further investigations to clarify disease risk and appropriate monitoring. A major limitation to management of HTLV-associated diseases currently is delayed diagnosis due to lack of awareness of HTLV-1 infection. The national policy must consider the benefits to the mother and not focus entirely on potential anxiety.

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.*

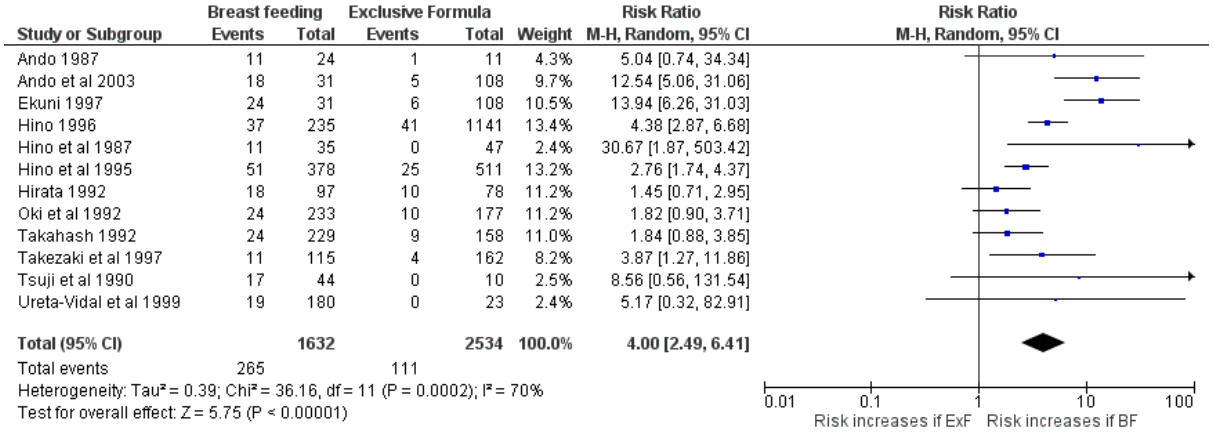
This statement is inaccurate; it was formally addressed prior to the 2022 review. The published study cited (Rosadas et al. 2019) found that both serology and molecular diagnostics were unaffected by pregnancy – comparing the tests in the same women when they were pregnant and when not pregnant . Furthermore the sensitivity and specificity of current assays for the detection of anti-HTLV-1/2 antibodies such as the Abbott Architect rHTLV-I/II, (100% and 99.95% respectively) (Kapprell et al. 2010) which is commonly used in UK, are extremely high, giving few false positive results. In the UK all reactive samples whether from screening (as in the NHSBT) or patient investigation are confirmed and typed prior to reporting. Antenatal screening at booking allows ample time to complete the analysis before decisions need to be made and eliminates the mother’s uncertainty of her diagnosis.

Cost-effectiveness analysis. The additional cost of screening for HTLV-1 would be restricted to reagent costs and changes to the information provided to mothers since the process for high through-put serological antenatal screening for infection is already in place for Human Immunodeficiency Virus, Hepatitis B virus and syphilis. Ie the processed for delivering HTLV-1 screening information, collecting and processing the samples, and reporting the results to the mother is established and thus is not an additional cost. It is noted that screening for isovaleric acidaemia and for glutaric aciduria type 1 with rates of 1 per 150,000 and 1 per 300,000 respectively was recommended in 2014 and introduced as the process for testing was already in place and thus the cost implications were relatively small.
(https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/480961/UK_NSC_evidence_report_201415_online_version.pdf).

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.*

This statement from the 2017 review confirms the importance of prevention to the infant and therefore the importance of detection in pregnancy. The efficacy of prevention of HTLV-1 acquisition in infancy by avoidance of breastfeeding has been known since the 1980s: as shown in Figure 1 breast-feeding increases the risk of HTLV-1 4-fold. Mothers also benefit from knowing that they have been empowered to protect their children from life-long infection with an oncogenic virus, and thus protecting their infants from a very aggressive form of adult leukaemia, in addition to the benefits to their own health, as described above.

Figure 1



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 question here is whether mothers would value the offer of screening and, if found to be infected, the option to formula-feed their baby. In the first Japanese intervention programme 90% of mothers chose not to breast-feed in order to prevent vertical transmission (Hino 2011). It will be important to see the responses from the community to this public consultation whilst awaiting data from UKHSA on attitudes to HTLV-1 antenatal screening. Importantly, the review has not taken into account current screening in the UK both by NHSBT and the recommendations that both breast-milk donors and candidates for IVF are screened for HTLV-1. It seems unlikely that any harm from antenatal screening would be greater than in these settings. The review correctly highlights that the HTLV health risk to the mothers is lower than to their babies, although some mothers will themselves have been infected in infancy. In the UK all mothers will be offered specialised follow-up as is the case for blood donors, with a high acceptance rate.

Summary

The association of HTLV-1 with significant rates of disease and a broad impact on health and life expectancy is now widely accepted. (World_Health_Organisation 2021a, 2021b). These developments, and the associated evidence base, must be taken into account in the 2022 review. Key points include the following:

- BAME groups in the UK are disproportionately impacted by HTLV-1 infection.
- Avoidance of breast-feeding reduces HTLV infection in infancy by ~85%.
- Assays to identify those are risk of transmission are highly sensitive (100%) and specific (99.95%).
- The UK has 20 years' experience in universal HTLV-1 screening in particular in blood donors, and there is a national specialised service for the clinical management of HTLV-1 infected persons. The public health benefits of HTLV-1 screening are recognised: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/27793/annual-review-with-a4-infographics-final-accessible-features-v3.pdf

The current review fails to address the concerns raised during public consultation of the 2011 and 2017 reviews and to take into account essential previous data.
We therefore request a comprehensive review of all data. This review should include a cost-utility analysis, because the only published analysis indicates that the introduction of screening, even prior to the new data on the impact of HTLV-1 infection on the adjusted mortality rate, would meet the cost-benefit criteria (Malik and Taylor 2018).

We, the undersigned agree to the publication of our names, along with this response, on the UK NSC website

Prof Graham P Taylor, Head of Section of Virology, Imperial College London
Professor Charles Bangham FRS, Co-Director Institute of Infection, Imperial College London.
Dr Carolina Rosadas, Research Associate, Section of Virology, Imperial College London
Prof Jonathan Weber F MedSci, Dean, Faculty of Medicine, Imperial College London
Prof Hermione Lyall, Head of Paediatric Infectious Diseases, St Mary's Hospital, London
Dr Divya Dhasmana, Clinical Lead, National Centre for Human Retrovirology, London
Dr Dan Bradshaw, Consultant Virology. UKHSA, London
Ms Adine Adonis, Senior Neurophysiotherapist, National Centre for Human Retrovirology, London
Dr Lucy Cook, Consultant in Onco-haematology, National Centre for Human Retrovirology, London
Dr Meg Boothby, Consultant GU/HIV Physician, Queen Elizabeth Hospital, Birmingham
Prof Anastasios Karadimitris, Co-director, Centre for Haematology, Hammersmith Hospital, London

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Dr Nicholas Davies, Consultant Neurologist, Chelsea and Westminster Hospital, London
Dr Eleni Nastouli, Consultant Virologist, University College London.

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UK National Screening Committee

17.

Name: xxxx xxxx

Email: xxxx xxxx

Notify: False

Condition: HTLV

Affected Comment:

Having had a close friend lose a partner and her childs father to this disease I can confirm both the agonising effects on the mother and child. Not only did I watch my friend suffer the loss of her partner and the child the loss of a father but the agonising wait of screening for a born child to be screened and to be supported to save another life should they have inherited the disease.

I strongly beleive the screening of unborn children would firstly eliminate an unecessary loss of children who inherit this illness and would also highlight that one parent may be a carrier and trigger on time nhs support to prolong or save the life of the affected parent.

We talk about a multicultural and society and British values of every life equal yet our NHS is not funding or supporting the screening of a fatal illness which targets some of our ethnic minorities. Children are losing parents and parents are living with ticking time bombs wondering if their own children suffer.

Black lives really do matter, to not introduce this screening for a known disease to prevent the suffering of many families and children is negligent of the health and wellbeing of a large proportion of the population.

A loss of a child or a parent has a lifelong affect on a family. It cannot be cured and or made slightly better or controlled. A cancer can be.

The pressures on the NHS for mental health support after bereavement is inundated. Introducing this screening will eliminate some families needing access to this support.

Evidence Comment:

See above

Discussion comment:

See above

Recommendation comment:

Yes i beleive it is necessary.

Alternatives comment:

Regular check ups on those known to be affected to monitor their health.

Other comments:

See above

18.

Name: xxxx xxxx

Email: xxxx xxxx

Recommendation comment:

I feel that the opportunity for screening should be available to a known carrier mother.

Dear Sir,

the NHS makes the following statement about antenatal screening of pregnant women: „Screening is always a choice“ (1). However, this can only be a correct statement if mothers are fully informed about infections that they potentially could transmit to their babies if not tested for and counselled on.

As an expert scientist working on understanding the transmission of Human T-cell Leukaemia Virus Type-1 (HTLV-1) and the European Representative of the International Retrovirology Association (IRVA), the peak body of the international representation of HTLV-1 research and patient advocacy, I wish to bring to your attention that currently women at risk of living with HTLV-1 do not have a choice to accept or reject being tested for the sexually acquired and vertically transmitted HTLV-1, because they are not made aware of the existence of this virus in key populations living in the UK.

Currently as part of routine antenatal screening, tests for vertically transmitted pathogens are routinely offered to pregnant women between 8-12 weeks of pregnancy. These include blood tests for Human Immunodeficiency Virus (HIV),

Hepatitis B Virus, and syphilis. The tests can be offered at any time during pregnancy (1). Pregnant women can opt out from being tested for these infections, and naturally mothers rarely reduce being screened for anything that could harm their babies.

But they are not asked if they would like to opt out from being tested for HTLV-1, although we know that HTLV-1 is predominantly transmitted through prolonged breastfeeding and that 1:4 babies who acquire HTLV-1 as children will develop Adult T-cell Leukaemia (ATL) as an adult and often succumb of this horrible cancer. Chances are that if mothers where informed of this virus they would opt to have the HTLV-1 screening test. This would also mean that those who were positive could protect their sexual contacts from HTLV-1 transmission by using condoms.

Surprisingly, the Evidence Team (UK National Screening Committee (NSC) Secretariat) provided a consultation version of an evidence map, which includes novel results only from one publication and concludes that no further work on exploring the benefits of universal antenatal screening for HTLV-1 should be commissioned. Further, the authors of this evidence map state that “the evidence base on key issues remains static” and propose to remove this recommendation from the UK NSC’s list of universal screening conditions altogether (2).

IRVA membership consists of international HTLV-1 experts including Prof. Bob Gallo who discovered HTLV-1 in 1980. We are qualified to judge fundamental questions about the transmission of this virus and how to eliminate it effectively. We recommend reviewing the comprehensive open letter IRVA submitted to the World Health Organisation in 2018 which prompted the WHO to include HTLV-1 as a sexually-transmitted infection (STI) that needs to be eliminated by 2030 (3,4).

Unfortunately, so far IRVA has not been asked for advice. We are happy to offer our expertise to provide evidence-based, up-to-date and best-possible advice to the UK NSC. Please find attached a point-to-point response to the current consultation version and recommendation of the Evidence Team for further consideration, which results in a different conclusion:

Screening for HTLV-1 should also always be a choice for pregnant women in the UK!

Yours sincerely,

xxxx xxxx

xxxx xxxx

xxxx xxxx

xxxx xxxx

References:

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UK National Screening Committee

19.UK National Screening Committee

Antenatal screening for HTLV infection – an evidence map

Consultation comments pro-forma

Name:	PD Dr. Dr. Andrea Thoma-Kress	**Email address:**	xxxx xxxx
Organisation (if appropriate):	International Retrovirology Organisation (IRVA)		
Role:	**European Representative of IRVA, Scientist working on HTLV-1 transmission**		

UK National Screening Committee

Do you consent to your name being published on the UK NSC website alongside your response?

Yes x No

Dear Madam,
Dear Sir,

the NHS makes the following statement about antenatal screening of pregnant women: **„Screening is always a choice"(**1). However, this can only be a correct statement if mothers are fully informed about infections that they potentially could transmit to their babies if not tested for and counselled on.

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Screening for HTLV-1 should also always be a choice for pregnant women in the UK!

Yours sincerely,

Andrea Thoma-Kress (PD Dr. rer. nat. Dr. habil. med.)

European Representative of IRVA, Scientist working on HTLV-1 transmission

Institute of Clinical and Molecular Virology

Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg
Erlangen, Germany

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 6, 1. (2)	„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.“ (website (5) „most infants infected with HTLV do not develop symptoms and the risk of developing a serious illness appears to be low“)	This statement is incorrect. First of all, HTLV-1 is associated with Adult T-cell leukemia/ lymphoma (ATL) and HAM/TSP, but HTLV-2 is not. Second, the lifetime risk to develop ATL is higher if infection is acquired early in life (e.g. by breastfeeding) and is estimated to be 25% (6). This may be explained in part by the exceptionally high oncogenicity of HTLV-1 as compared to other infectious agents causing cancer (7). Since HTLV-1-associated diseases occur after a long latency period, prevention of milk-borne transmission of HTLV-1 is one of the most efficient and feasible ways to prevent the onset of disease (8). It is also clear that HTLV-1 associated diseases are not restricted to HAM/TSP and ATL and the impact of HTLV-1 is broader still (9).
Page 6, 1. (2)	„Previous UK NSC reviews have found that there is little information on the natural history of the infection acquired through breastfeeding.“	It is clearly known from countries like Japan, who introduced antenatal screening programmes, that this measure prevents HTLV-1 mother -to-child transmission (MTCT) (8, 10). Furthermore, introduction of antenatal screening would be financially beneficial in high-prevalence countries like Brazil, but also in countries with lower prevalence like the UK since the development of incurable diseases is prevented at a very early step (6, 11). Detection of infections by screenings at early stages is far cheaper than the treatment of the disease.

		Moreover, it is also recommended to screen breast milk donations in the UK and in France, at least for donors from endemic regions (12). This recommendation would not make sense if nothing was known about the natural history of the infection acquired through breast feeding. Finally, there is no doubt that breastfeeding is one major route of HTLV-1 transmission, depending on the country even the most frequent and important route (13). Together, I disagree that there is little information on the natural history of infection acquired through breastfeeding. The listed publications and facts should urgently be considered in the final recommendation of the NSC regarding screening of HTLV-1 in pregnant women.
Page 6, 1. (2)	„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.“ (website (5): „it is unlikely that the mother will pass on the virus to her child unless she breastfeeds for more than 6 months.“)	I agree that the risk of transmission increases with the duration of breastfeeding and the majority of HTLV-1 MTCT occurs via breastfeeding (14), but breastfeeding for up to 3-6 months is already associated with increased risk of transmission compared to exclusive formula feeding (15). It is true that the level of infection among babies who are exclusively formula fed is low (13-15). In breastfed infants, MTCT occurs at rates varying from 7.4 to 32%, compared with a rate of less than 2.5–5% among bottle-fed children (11, 14). However, there are more risk factors for HTLV-1 transmission via breastfeeding than just long feeding periods, including high proviral loads (PVL) in milk and blood, low income, previous HTLV-1-infected offspring, HLA-concordance between mother and child, coinfections, and being a HAM/TSP patient (14, 16, 17).

		Mothers should have the chance to know about their HTLV-1 status to have the choice to prevent transmission of HTLV-1, e.g. by formula-feeding. Highly effective intervention methods like exclusive formula-feeding are acceptable for HIV in the UK, why not for HTLV-1? Mothers feel anxious and guilty if they get to know that they have infected their baby, but not, if they get educated about their infection status and get trained how to prevent transmission to their offspring (18). This should be possible in an industrialized country like the UK. Based on a model by Malik et al., 72 % of British women start breastfeeding, more than 50 % breastfeed for at least 3 months, and ca. 35 % for more than 6 months. The prevalence of breastfeeding for more than 6 months is much higher (61 %) amongst mothers with Black or Black British ethnicity (6). Thus, in absence of antenatal screening for HTLV-1, mothers do not have the choice to prevent their babies from a life-long persisting virus which can cause incurable and life-threatening diseases.
Page 6, 2. (2)	„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.“ (website (5): „it is not known how well the test performs in pregnant women.“)	This is a weak argument since there is no reason to assume that the test does not perform in blood from pregnant women. In fact, a study already confirmed that pregnancy does not adversely affects the diagnosis of HTLV-1 (19). Blood is taken from the mothers anyhow during weeks 8-12 of pregnancy for testing of HIV, HepB, and syphilis (1). The HTLV-1 tests used in the UK are routinely used, robust, and CE approved. Blood donors are screened for HTLV-1 in the UK since 2002 (NHS Blood and Transplant). The tests have been

		demonstrated by the manufacturers to be both highly specific and sensitive. HTLV-1 prevalence is higher in pregnant women than in the general population in the UK. There are no hints from any other countries that screening tests do not work in pregnant women. Moreover, upon positive screening, confirmatory tests are performed Thus, I disagree with the doubts of the authors that test could not perform well in pregnant women.
	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. (website (5): „there is not enough evidence to say that the benefits of screening outweigh the harms“/ „screening may make some women and their families feel anxious, depressed or stigmatised as there is no treatment.“)	I disagree with this statement. Screening is one of the most effective ways to prevent transmission of incurable HTLV-1-associated diseases. Moreover, if infants get HTLV-1-infected, they do not know whether they are the ones that will stay asymptomatic, or whether they will develop incurable inflammatory or neoplastic diseases. Their lifetime risk for disease development is exceptional high (see first comment and (6)). This causes psychological stress, which could be easily avoided by preventing HTLV-1 transmission by antenatal screening. To state that the mother might be anxious since she will be identified as having HTLV-1 as a side effect of screening does not solve the problem. She will even get more stressed an anxious when she knows that she has infected her children, which could be efficiently prevented by KNOWING about the infection status. Finally, guideline for management of mothers and infants in pregnancy and the perinatal period have been recently proposed to reduce the risk of transmission (17). Together, the listed publications and facts should urgently

		be considered in the final recommendation of the NSC regarding screening of HTLV-1 in pregnant women

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20.

Name: Ricardo Ishak

Email: xxxx xxxx

Organisation: xxxx xxxx

We read the preliminary report on the unfortunate decision to maintain the harsh, disproportionate, and discriminatory compromise to not include HTLV-1/2 antenatal screening for the pregnant women of the UK.

HTLV-1/2 infections are repeatedly left aside as they are usually regarded as of low prevalence and with a low frequency of disease outcome (two major equivocal perpetuated by equivocal information). This does not properly consider the burden of the infection and its associated diseases. The prevalence of HTLV-1 in pregnant women is high in marginalised groups in the UK, reaching 1.3% in Black Caribbeans (Ades, 2000). The number of diseases associated to HTLV-1/2 involve at least 10 target organs, including the nervous system, blood, eyes, skin, lungs and joints (Schierout et al 2019). The psychological burden imposed by HTLV-1 is similar to that caused by HIV-1, but less recognised. HTLV-1/2 research has focused in distinct areas including its biology, associated diseases, epidemiology, laboratory diagnosis and prevention. Despite limited resources, a lot has been described, and this knowledge was not considered in the present review conducted by the UKNASC (only one reference included).

The World Health Organization has started an initiative to eliminate HTLV-1/2 in 2019, and several advances were made since then. The more than 10 million people living with HTLV-1/2 worldwide are demanding that the number of infected persons does not increase unnecessarily in any population, of any country, in any continent. Low, medium and high-income countries have successful programs to prevent HTLV-1/2 infections. Brazil and Japan, leading countries in preventive measures towards HTLV-1/2, have implemented their HTLV antenatal screening programs (recommended in Brazil early this year). This is one of the main pillars to the elimination of the virus. Testing vulnerable pregnant women for HTLV-1/2 is a crucial step to achieve this goal and a vast amount of evidence, dating back the 1980s, clearly show the effectiveness of available interventions to reduce the risk of HTLV-1/2 mother-to-child transmission.

The financial burden to treat degenerative, inflammatory, leukemic and many other diseases associated to HTLV-1/2 is enormous, but most of all, the burden of HTLV-1/2 infection is not possible to be measured in financial terms. This could be reduced by implementing policies to prevent mother-to-child transmission.

It is time to listen to health managers, to understand the costs of a disease, but most of all, it is important to engage with affected persons who are living with the virus. They should be in the centre of this discussion, but their views were not considered by the committee.

At last, we would like to reinforce, that the views of this prestigious committee are considered by other countries, when they are assessing the implementation of HTLV antenatal screening in their own scenarios. This has sadly contributed to delay the implementation of HTLV-1/2 antenatal screening in our country (Brazil). Therefore, the publication of an accurate report is of utmost importance.

We sincerely hope that the decision is reconsidered, to agree with a contemporary view in which preventing HTLV-1/2 mother-to-child transmission is considered a priority and an important step to achieve the major goal to eliminate HTLV-1/2 globally, contributing to improve health equity and social justice. If the board decides not to implement this policy in the UK, we expect that, at least, a comprehensive and accurate report is produced and published by this committee.

Prof Ricardo Ishak (UFPA)

Prof Abelardo Araújo (Fiocruz-RJ, UFRJ)

Prof. Adele Caterino de Araújo (Instuto Adolfo Lutz)

Ms Adjeane Oliveira de Jesus (HTLVida, patients' association)

Dr Ana Lúcia Borges Starling (HTLV- GIPH)

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21.

Name: Professor Arne Akbar President

Organisation: British Society for Immunology

Dear Professor Richards,

I am writing on behalf of the British Society for Immunology regarding the consultation on antenatal screening for HTLV-1.

The British Society for Immunology is the leading UK charity organisation representing scientists and clinicians who study the immune system. The United Kingdom Primary Immunodeficiency Network (UKPIN) is the professional body for

clinical immunologists, specialist nurses and healthcare/academic scientists in the UK.

We felt unable to participate in the consultation on antenatal HTLV-1 screening due to inherent failings in the review process. In order for the consultation to be conducted in a fair and transparent manner, the NSC must expand the scope of the current consultation beyond simply considering new evidence from between 2016 and 2021. We believe that there were substantial flaws made in the consideration of previous literature and data that precede the current review period, i.e., the 2011/2 and 2017 screening reviews. Without reassessing the original interpretation of historic evidence, each successive evidence map/review becomes more unsound as it is based on the flawed findings of previous reviews. A dogmatic approach not to reconsider the weight and accuracy of previous evidence not only damages confidence in the review process itself but is also antithetical to the way that science should be conducted.

Of particular concern in the evidence map is the omission of how HTLV affects different communities within the UK population. Whilst the overall prevalence of HTLV is low, it is important to emphasise that the prevalence of HTLV-1 within the Black African and Caribbean population is high (as defined by the European Centre for Disease Control threshold) exceeding 1%. With the new remit of the NSC allowing the recommendation for targeted or stratified screening, and the prevalence in black Caribbean women and those from West and Central Africa in the UK, of HTLV-1/2, being 32-170/10,000, over ten times that of the general population, the decision to recommend against a screening programme is discernibly discordant to the Government's aim, through the Office of Health Improvement and Disparities of breaking the link between background and prospects for a healthy life.

We would very much like to discuss the issues raised in this letter and ensure we can best work together for patient benefit. Please contact my colleague, xxxx xxxx

(xxxx xxxx) on xxxx xxxx or at xxxx xxxx to arrange a suitable time. I look forward to hearing from you soon.

Yours sincerely,

Professor Arne Akbar President, British Society for Immunology