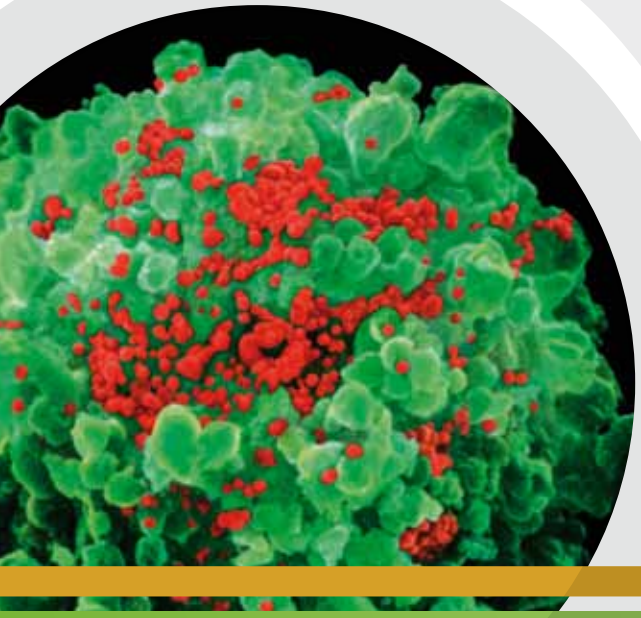

TECHNICAL REPORT

Risk assessment of HTLV-I/II transmission by tissue/cell transplantation

Part 1: Epidemiological review

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ECDC TECHNICAL DOCUMENT

Risk assessment of HTLV-I/II transmission by tissue/cell transplantation

Part 1: Epidemiological review

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Contents

Abbreviations

AATB	American Association of Tissue Banks
ATL/ATLL	Adult T-cell Leukaemia/Lymphoma
ChLIA	Chemilumisence Immune Assay
ECDC	European Centre for Disease Prevention and Control
EIA	Enzyme Immune Assay (= ELISA)
ELISA	Enzyme Linked Immune Sorbent Assay (= EIA)
EUTCD	European Union Tissues and Cells Directive
FDA	Food and Drug Administration (United States)
HAM/TSP	HTLV-I Associated Myelopathy/Tropical Spastic Paraparesis
HCT/Ps	Human Cells, Tissues, and cellular and tissue-based Products (US regulation)
HTLV	Human T-lymphotropic Virus (used to describe all types)
HTLV-I	Human T-lymphotropic Virus, type I
HTLV-II	Human T-lymphotropic Virus, type II
HTLV-Ab	Antibodies specific for HTLV
NAT	Nucleic Acid Test
PBMC	Peripheral Blood Mononuclear Cells
PTLV	Primate T-lymphotropic Virus(es)

Executive summary

Introduction

An important part of the ECDC's role is to provide its stakeholders with scientific advice upon request. On 2 August 2010 ECDC received such a request from the European Commission's Directorate General for Health & Consumers (DG SANCO) – Directorate C Public Health and Risk Assessment.

ECDC was asked to assess the epidemiological history of Human T-lymphotropic Virus (HTLV), possible risks of HTLV transmission through transplantation of human tissues and cells, and possible measures to prevent such transmission, in particular with regard to tissues and cells imported from the United States. Testing for HTLV-I/II infection among most tissue and cell donors was recently discontinued in the US.

In the EU, testing for HTLV-I is required for tissue donors living in, or originating from high-incidence areas, or with sexual partners originating from those areas, or where the donor's parents originate from such areas.

Methodology

In accordance with its internal procedures for providing scientific advice, ECDC addressed the question by setting up an ad hoc group of internal and external experts in the field. The expert group was set up in cooperation with the EU Commission's DG SANCO (Directorate C Public Health and Risk Assessment) and the EU Competent Authorities for Tissues and Cells. However, in accordance with its internal procedures, ECDC selected experts based on their individual scientific and professional qualifications.

After receiving clarifications on specific questions from the Commission, ECDC performed a comprehensive literature review to capture all evidence available. The expert group then reviewed the scientific evidence, assessing its validity and generalisability in relation to the question asked.

This report (Part 1) is the first of two separate technical reports in which ECDC presents the results of its assessment. A draft of the preliminary results for Part 1 was presented at the meeting of the EU Competent Authorities on Tissues and Cells in Brussels on 6–7 December 2010. This part of the assessment addresses the epidemiological history of HTLV.

Results and conclusions

The review of the epidemiology of HTLV-I and II revealed that the general prevalence and incidence of these viral infections in the population is unknown in most parts of the world and consequently, there is little known about the details of their epidemiology and disease burden.

This is particularly true for the European and North American geographical regions, as well as many other regions of the world which are frequently described as areas of low endemicity. Few population-representative studies have been conducted and the majority of these are from Asia, Africa and South America. None were found from the European and North American regions.

Some data do exist (mainly from blood donor populations), suggesting that the general population prevalence in both regions is likely to be comparably low and probably less than 0.1%. However, the definition of what can be considered high or low prevalence is dependent on societal, economic and value-based factors and is difficult to define objectively. In order to reduce risk in the transplantation and transfusion of substances of human origin, comparably low prevalence has often been considered sufficient to warrant testing.

Data derived from first-time blood donors show no great difference in the prevalence of HTLV-I/II infection between the US or Europe, with relatively low prevalence found in both geographical locations (approximately 1–1.5/10 000 population in the US and on average 0.46/10 000 population in the EU area). However, blood donors undergo a rigorous risk-factor exclusion programme designed to diminish the risk of blood-borne infections. Prevalence in this population therefore only constitutes a minimum estimate of the prevalence of HTLV-I/II infection in the general population. In one EU Member State (Romania), prevalence of HTLV-I among first-time blood donors (5.33/10 000) was reported to be significantly higher than in the other reporting Member States and not linked to immigrant background.

In both the US and Europe, evidence for high prevalence among high-risk groups was found, especially among injecting drug users.

Certain parts of the world have been shown to have a higher prevalence and incidence of HTLV-I and II infection. The highest prevalence has been identified in south western Japan, where general population prevalence is approximately 10% or even higher. In certain studies and sub-regions prevalence of over 30% has been reported.

In addition, there is evidence of high prevalence in Central African countries, the Caribbean and some South American countries, ranging from approximately 0.5–1% to almost 10%.

Immigration to both the US and the EU region is common and both recent first-generation immigrants and descendants of immigrants constitute sizeable proportions of the general population in both regions. Immigration from HTLV-endemic areas is common in both regions.

On the basis of the literature review findings, evidence of the epidemiology of HTLV-I/II does not support an objective classification of the US or North America as an area of high incidence or high prevalence of HTLV-I/II infection in the general population. This is in comparison with Japan, the Caribbean and some other areas of the world, where prevalence rates are very high (above 1%).

However, the literature review showed that HTLV-I/II epidemiology in the US does not substantially differ from that of the EU region. Sub-populations and regions where HTLV-I/II infection rates are high and roughly comparable exist in both parts of the world and can be classified by both ethnic and risk-behaviour factors. Different approaches to minimising the risk of transmission from donations are therefore not supported by the epidemiological evidence from the regions. If there is no HTLV-I/II testing of tissue and cell donors in the US and products derived from these donors are imported into the EU, this creates a double standard in terms of risk management.

The definition of what constitutes 'high incidence' or 'high prevalence' was extensively discussed at the ad hoc expert panel meeting organised by the ECDC. Although one expert disagreed, the rest of the panel considered that not specifying a threshold value for 'high prevalence' poses a major problem to the interpretation of the current regulation and recommended considering the introduction of a threshold.

Considerations

Based on an examination of the evidence, ECDC suggests the following for the consideration of the Commission and the EU Competent Authorities on Tissues and Cells:

In Annex II, section 1.2. of the European Union Tissues and Cells Directive (EUTCD):

- Consider replacing incidence with prevalence or inclusion of both terms in the description of endemic areas for HTLV-I/II infection.
- Motivation: this change would better reflect available data and make assessment of risk easier. Geographic areas of high prevalence, high incidence or both high incidence and high prevalence may exist depending on the epidemiological situation. Moreover, each of the situations means increased risk and circumstances may also change over time as the epidemic matures or control measures take effect.
- Consider specifying threshold values for what is considered 'high prevalence' in the regulation. The ad hoc expert panel suggests that prevalence over 1% in the general population or prevalence of over 1/10 000 among first-time blood-donors could be considered as indicators of high prevalence and endemic transmission of HTLV-I/II.
- Motivation: specifying a threshold value for 'high prevalence' would enable Member States to apply a unified interpretation and allow for the creation of objectively assessed classifications of world regions as of 'high prevalence' categories. Such a classification could also be updated regularly as new data becomes available. Specifying the threshold value would not prevent individual Member States from employing more stringent threshold values and implementing HTLV-I/II testing among tissue and cell donors based on national assessments of effectiveness and risk management.
- Consider promoting EU and national sero-survey studies of HTLV-I/II prevalence using available funding instruments.
- Motivation: in some EU countries there is no information available on HTLV-I/II prevalence and in others the study size is insufficient or studies are old and may not be adequately representative of the current situation. Moreover, increased intra-EU mobility and migration from potentially endemic areas may change the epidemiology of HTLV-I/II infection significantly over time. The very long incubation time prior to disease development suggests that monitoring for HAM/TSP and ATLL could create situations where prevalence may become high before an epidemic is detected, if sero-surveys are not conducted. Even countries where prevalence has been shown to be low in the past may benefit from systematic monitoring of prevalence through regular sero-surveys.
- Consider requiring collection and centralised reporting of test results on blood-borne viral infections in the EU region for all tissue donations using standardised protocols as part of quality assurance for tissue and cell donation establishments.
- Motivation: understanding epidemiology is a guiding principle for accurate and evidence-based assessment of the need and effectiveness of prevention and control measures. This principle has been successfully applied for blood donation services in Europe. Information on the results of screening for blood-borne viral infections has been systematically collected for many years in Europe and used to accurately assess the

residual risks of transmission for blood donations in Europe. This has had a profound influence on the improvement of blood safety and the development of better infection management procedures within the field. As screening for blood-borne infections among donors of tissues and cells is already mandatory the only additional resource requirement would be to organise the data collection and its storage, analyse the data and report the results. This would enable the effectiveness of the current screening requirement to be assessed within a few years. While the organisation of data collection is not trivial, it entails much less in terms of resources than a blanket requirement to screening all donations.

Request from the European Commission

On 2 August 2010, the ECDC Director received the following request from the European Commission's Directorate General for Health & Consumers (DG SANCO) – Directorate C Public Health and Risk Assessment (transcript):

Dear Dr Sprenger,

Subject: Request for ECDC advice on testing requirements for Human T- lymphotropic virus (HTLV) for tissue and cell donors

For a number of years the American Association of Tissue Banks (AATB) has required systematic testing for antibodies to human T-lymphotropic virus type I and type II (HTLV-I/II testing) for donations of tissues and cells occurring on US territory. Recently the AATB board agreed to change standards for tissue banking in order to remove the requirement to test donors of processed conventional human tissues (e.g. bone, tendons, ligaments, skin, heart valves etc). However, donors of viable leukocyte-rich tissue (e.g., semen, hematopoietic stem/progenitor cells) must continue to be tested and found to be negative for anti-HTLV-I and anti-HTLV-II to be considered suitable for release for transplantation. According to AATB this decision harmonises HTLV testing with US Food and Drug Administration (FDA) regulations which require HTLV test only for donors of viable, leukocyte-rich tissues and cells.

More information is available on the AATB website:

http://archive.constantcontact.corn/fs076/110205S357439/archive/I102820896575.html

Directive 2006/17/EC requires that HTLV-I antibody testing is performed for donors living in, or originating from, high incidence areas, with sexual partners originating from those areas or where donor's parents originate from those areas. Several Member States have thus HTLV testing required for human tissues and cells imported from the United States.

The recent change at the AATB standards was discussed at the joint meeting of the Competent Authorities and Regulatory Committee on tissues and cells which was held in Brussels on 20-21 May 2010 and several Member States expressed concerns about the change of AATB's testing requirements for HTLV and the potential impact on the safety of human tissues imported to the EU from the United States. In addition it became clear that different EU Member States apply different testing requirements regarding HTLV. Several Competent Authorities have therefore agreed to meet later this year in order to assess this situation and the potential consequences for tissue collection in Europe.

We herewith send you a letter prepared by the Human Tissue Authority (HTA, UK) summarizing the problem and listing some questions for discussion, as well as background information collected by HTA.

We would like ECDC to contribute to this discussion later this year and therefore to assess the situation and questions in the letter by HTA. These cover the epidemiological history of HTLV, the possible risks for HTLV transmission through transplantation of human tissues and cell, and the possible measures to prevent such transmission, in particular regarding tissues and cells imported from the United States. Considering the planned timing we would appreciate if ECDC could complete its assessment by 15 October 2010.

Yours sincerely,

Andrzej Rys
[signed]

Background and methods

Legal authority

According to the founding regulation of ECDC, Regulation (EC) No 851/2004[1] Art 9(2), 'the Centre may be requested by the Commission, the Member States, third countries and international organisations (in particular the WHO) to provide scientific or technical assistance in any field within its mission. Scientific and technical assistance provided by the Centre shall be based on evidence-based science and technology.'

ECDC shall:

- search for, collect, collate, evaluate and disseminate scientific data (Art 3(2)(a));
- provide scientific opinions and timely information (Art 3(2)(b),(c));
- exchange information, expertise and best practices (Art 3(2)(e)); and
- facilitate the development and implementation of joint actions (Art 3(2)(e)).

Evidence-based public health

Evidence-based decision-making in a public health setting has to incorporate the best available scientific evidence from research and other reliable sources with considerations of values and perceived needs in the given context. Evidence-based medicine is often defined as the integration of expertise, values, and the best available evidence into the decision-making process [1].

A public health decision may be rather complex and need to take several health determinants into account, such as genetic factors, lifestyle, physical environment, socio-economic conditions, biological environment and health services at different levels [2].

Only some of these factors are relevant to the prevention and control of HTLV I/II in tissue and cell donations.

Evidence-based methodologies

ECDC has tried to compile this risk assessment in accordance with the following procedure based on evidence-based methodologies:

- Formulate questions.
- Search for evidence.
- Assess the evidence.
- Formulate an answer.
- Disseminate and implement
- Evaluate.

[1] Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European centre for disease prevention and control. OJ L 142, 30.4.2004, p. 1.

Questions from the European Commission

After a request for clarification, the following re-phrased questions were posed by DG SANCO's Directorate C Public Health and Risk Assessment:

Question 1

What is the epidemiology of HTLV-I/II viruses, including distribution by geographic region, risk group, and other factors?

Question 2

Do the risks of virus transmission differ by type of tissue/cell or processing and if yes, how do they differ?

Question 3

What is the evidence for effectiveness of measures used to prevent virus transmission through transplantation of tissues/cells?

For this part of the ECDC risk assessment (Part 1), only Question 1 above is addressed. Questions 2 and 3 will be addressed in the second part of the ECDC risk assessment (Part 2), as agreed with the Commission services.

Search strategies

This part of the risk assessment involved an exploratory search, followed by a comprehensive search strategy (Annex 1) and examination of the entire accessible published evidence base.

To ensure that the questions posed by the Commission were searchable in electronic databases, they were split into the following subcategories:

Population: Donors of cells and tissues, living and cadaveric. (In addition, donors of blood/blood products and pregnant women were identified as additional populations for which screening programmes in many countries may have produced relevant comparative data).

Interventions: Testing for HTLV-I/II infection, exclusion by clinical and risk factor criteria, exclusion by lymphocyte content.

Comparison: US/North American versus EU donors, donors in the rest of the world.

Outcome: infection due to transfusion, cell/tissue donation or receipt of blood products, prevalence of HTLV-I/II infection, implications for safety of human tissue- and cell-derived products imported to the EU.

Reviews and original research articles were retrieved from PubMed, Embase and the Cochrane Library bibliographic databases on 24 January 2011.

The concepts used in the search were taken from the controlled vocabulary available in the bibliographic databases (i.e. MeSH and Emtree terms). These were complemented with multiple field search combinations by using natural vocabulary (i.e. keywords). The retrieved records were in several languages, but with a majority in English. Some more relevant studies were selected from reading reference lists.

Results from primary searches were screened by reading titles and abstracts (when available). Studies were selected for full reading according to relevance for the different questions. Selection criteria were decided by a group of reviewers. One reviewer read the articles, but questions and uncertainties were discussed by a group of reviewers. Due to time constraints it was not possible to retrieve all potentially relevant articles from reference lists. Some relevant articles without English abstracts as well as reports in the grey literature might also have been missed.

The primary searches for Question 1 (which were conducted in several separate phases) and removal of duplicates resulted in a screening library of 1 104 potential publications. After screening, this left 181 potentially relevant manuscripts which were obtained and reviewed. Relevant studies were used for the risk assessment review.

Studies included in the evidence tables were chosen for their representativeness and for making a significant addition to the description of the epidemiology in North America, Europe and other regions of the world. Recent representative reviews were prioritised and complemented with separate individual studies. Studies were categorised according to study designs: reviews, trials and observational studies. The observational studies were sub-classified into the following categories: cohort studies, case series, case–control studies, case studies, cross-sectional studies, time series, 'before and after' studies.

The following sections were included in the evidence tables (Annex 2) for the risk assessment:

- Bibliographic citation
- Type of study
- Number of patients or size of population
- Study outcome
- Strengths of study
- Limitations of study.

Assessment of the evidence

Validity. To assess the validity of a study is to evaluate whether the results are trustworthy. In this study one of the problems was that comprehensive incidence and prevalence data on HTLV-I/II is currently not available in Europe or the US/North America since infection by this virus is not subject to systematic surveillance in either region. Few studies on HTLV-I/II transmission risks are available for the population under review (donors of cells and tissues), especially from Europe. Tests used for sero-epidemiological studies may provide inflated prevalence due to low test specificity, particularly if there is no confirmatory testing in the very low prevalence populations.

Generalisability (external validity). To assess external validity or generalisability is to evaluate whether the studies are transferrable to other settings or circumstances. In this assessment the challenges were connected to uneven comparability of different studies on HTLV-I/II and lack of epidemiological studies on the exact study population.

Grading of evidence according to strength of documentation. An evidence-based approach implies trying to draw explicit conclusions and building on the best available evidence, thus giving more weight to the studies which are of the highest quality and employ the most robust methods. The problems faced in this risk assessment were connected to a lack of studies and systematic reviews for the regions concerned. For some of the questions, the reviewers had to start by examining studies assessing populations (i.e. blood donors) different to the study population.

Obtaining expert advice: ECDC ad hoc expert panel

While performing initial evidence assessment based on explorative and systematic literature searches for Questions 1-3 as described above, the ECDC internal review group recognised that expertise within the Agency was insufficient to properly address certain elements of Questions 2 and 3. Preliminary results were presented to the EU Commission Competent Authorities on Tissues and Cells at a meeting in Brussels on 6–7 December 2010. At this meeting, it was agreed that the Commission (Directorate C Public Health and Risk Assessment) would request nominations for national experts from the Competent Authorities on Tissues and Cells to support the ECDC risk-assessment work.

The Commission (DG SANCO Directorate C Public Health and Risk Assessment) made a request for potential experts and nominations by the Competent Authorities on Tissues and Cells were sent directly to the ECDC. On the basis of its internal procedures[2,3] ECDC selected nine experts by reviewing their scientific and professional qualifications and ruling out any potential conflicts of interest. Following their appointment by the ECDC Director, the selected experts were invited to review ECDC work and attend an expert meeting in Stockholm on 4 March 2011. Seven experts attended the ECDC meeting and their advice has been incorporated into this risk assessment. A separate meeting report will also be made available.

References: Background and methods

- Straus SE, Richardson WS, Glasziou P, Haynes RB. Evidenced-based Medicine: How to Practice and Teach Evidence-based Medicine. 3rd ed. Churchill Livingstone; 2005.
- Muir Gray JA. Evidence-based healthcare and public health: How to make decisions about health services and public health. 3rd ed. Churchill Livingstone; 2009.

2 Internal procedure on handling requests for scientific advice at the European Centre for Disease Prevention and Control. ECDC/SAU/001 – rev. 1. Issue date (revised): 1 February 2011

3 ECDC policy on declarations of interest and handling of potential conflicts of interest. Draft endorsed by the ECDC Management Board at its 20th meeting, Stockholm, 9–10 November 2010 (Agenda item 14)

HTLV-I/II infection and disease

Etiological agents

Human T-lymphotropic virus types I and II (HTLV-I and II; also denoted HTLV-1 and 2) are two closely related retroviruses belonging to the Retrovirus family and the *Deltaretrovirus* genus. They belong to the Primate T-lymphotropic viruses (PTLVs), along with a number of simian counterparts. Although HTLV-I and II are retroviruses, they differ from the *Lentivirus* genus to which the more common human immunodeficiency virus types 1 and 2 (HIV-1 and 2) belong. Recently, two new genetically distinct, but closely related viruses have been described from Africa (and named HTLV-III and IV), but their epidemiology and disease-causing properties are as yet unknown [1]. For this reason, and since they seem very rare, they are not included in this risk assessment.

HTLV-I and II are RNA viruses which can reverse transcribe their genome into DNA and integrate into their host T-lymphocyte cells. Infection with both viruses is chronic and lifelong and only a fraction of those infected eventually develop disease (see below). No vaccine exists against infection by either of the viruses.

Infection can be detected in the laboratory for diagnosis and epidemiological studies using a variety of methods, most commonly by demonstrating anti-HTLV I and II antibodies through serological assays. The serological screening assays do not distinguish between HTLV I and II infection and confirmatory testing is necessary to distinguish the variants and diagnose infection. Polymerase Chain Reaction (PCR) based tests have also been developed. Virus isolation is possible but labour intensive.

Disease presentation

Infection with HTLV-I has been linked to two major diseases: HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T-cell leukaemia/lymphoma (ATL/ATLL) [2,3] as well as several other inflammatory conditions. Clinical presentation of HAM/TSP includes muscle weakness in the legs, hyperreflexia, clonus, extensor plantar responses, sensory disturbances, various urinary manifestations, impotence and lower back pain [3]. High titers of HTLV-specific antibodies are found in the blood and cerebrospinal fluid (CSF) of those with the disease. Other uncommon inflammatory disease associations include infective dermatitis, uveitis, myositis, and HTLV-associated arthropathy [3]. Adult T-cell leukaemia/lymphoma is associated with the malignant proliferation of transformed leukocytes carrying HTLV-I provirus.

Development of HTLV-I/II associated disease is generally slow and most of those infected remain asymptomatic for life. The average age of diagnosis is 40 which is commonly preceded by adult-acquired infection. The lifetime risk of HTLV-I carriers developing HAM/TSP varies according to geographic and ethnic determinants. Lifetime risk of HAM in Japan has been estimated at 0.25% [4], in Jamaica and Trinidad at 1.8% [5] and in the UK at 3%, based on incidence/prevalence data [6]. Prevalence of HAM (including incident cases) among US blood donors during follow-up for up to 10 years was 3.7% [7]. The risk of disease development is increased among transfusion and transplant recipients, who may develop the disease with a much shorter incubation time, particularly in the case of immune suppression [8-10]. The age-standardised incidence rate is 2/100 000 person-years, with a higher risk in females [8].

It is estimated that 2–7.3% of those infected with HTLV-I develop ATLL during their lifetime, although the proportion varies in different parts of the world and by gender [8, 11–14]. Infection in early life appears to be important for the development of ATLL [8,11]. The incidence rate is 2–4/100 000 person years, with a higher risk in males than females, the direct opposite to the sex-ratio of HAM/TSP [8]. In Japan, average age of onset is 60 years, while in Trinidad, Jamaica and Brazil it is 40 years [8]. The difference is unexplained but has been suggested as being dependent on host factors, among other possibilities [8].

Infection with HTLV-II has not been associated with malignancies; however, it has been associated with a neurological disease resembling HAM/TSP. The estimated lifetime risk of disease development for HTLV-II-infected persons is unknown but appears to be less than that estimated for persons with HTLV-I infection. While the majority of HTLV-II-infected persons remain asymptomatic (>95%) from the virus infection *per se*, recent studies report an increased incidence of other infectious diseases (e.g. bronchitis, kidney or bladder infections) in HTLV-1- and HTLV-II-infected persons [15].

HAM/TSP is a progressively disabling disease which frequently can have a severe impact on the quality of life of those affected. Secondary complications may lead to death after many years. No effective treatment exists against HTLV-I and II infection. Symptomatic or targeted treatment is still the main approach for HAM/TSP patients. Although zidovudine (AZT) and alpha interferon (IFN-α) in combination yield some response and improve ATL prognosis, better treatments need to be developed [16]. Antiretroviral treatment does not seem to have a sustained effect on proviral loads [16]. ATLL carries a poor prognosis in Europe, with a life expectancy of 5 months following diagnosis [17].

Transmission mechanisms and tissue/cell tropism

Both HTLV-I and II have been shown to be transmitted by blood contact, mother-to-child transmission (breastfeeding) and sexual contact, although the role of sexual transmission is less clear for HTLV-II. Unlike HIV-1/2, transmission of HTLV-I/II is more dependent on cell-to-cell contact. In the case of HIV it is possible to infect target cells using purified virions in vitro, whereas HTLV-I/II requires the co-culture of infected cells with target cells for efficient transmission. Moreover, cell-to-cell contact appears to be more important for transmission in vivo, as free virions cannot be demonstrated in plasma or serum and cell-free blood products have been shown not to transmit the infection. This is in stark contrast to HIV and Hepatitis viruses, where plasma products are infectious and high levels of virions are frequently found in the cell-free blood components of infected individuals.

For HTLV-I/II, models of transmission rely on the presence of infected cells, of which the most prominent seem to be CD4 and CD8 positive T-lymphocytes. These cells, which are part of the white blood cell (leucocyte) family, are carriers of the virus in infected individuals. In vitro models suggest that transmission between infected and uninfected cells requires physical contact and involves specific receptor molecules that interact with viral surface proteins. There is evidence that multiple cell types, such as dendritic cells and other monocyte/macrophage lineage cells may be important for transmission between individuals, even if infected CD4+ T-cells are most frequently detected in vivo [18-20]. The virus expands in vivo both by transformative proliferation of the infected cells and by re-infection of new cells through direct cell-to-cell contact.

The main cellular receptor of HTLV-I has recently been described and shown to be the ubiquitous glucose transporter protein GLUT-1, which is present on a wide variety of cells [21]. In addition, other cellular molecules, such as heparan sulfate proteoglycans (HSPGs), neuropilin-1 (NRP-1) and DC-specific intercellular adhesion molecule-3 (ICAM-3)-grabbing non-integrin (DC-SIGN), may contribute to the transmission mechanisms [18, 22–26]. To be able to transfer the infection from one cell to another, a specific structure dependent on cell-to-cell direct contact, sometimes called a viral synapse, needs to form [25]. This may explain the apparent inability of a free virus to confer infection in vivo.

HTLV-I is readily detected in CD4+ T-lymphocytes in vivo. However, the virus has also been shown to be present in other cells of the leukocyte lineage, such as CD8+ cells, monocytes and B-lymphocytes [24]. In addition, in vitro infection has been successful for a wide variety of cells types from non-haematopoietic lineages and even non-human cells. There are models for persistent HTLV-I infection in the rat, rabbit, mouse and squirrel monkey. In these models, the virus infects and can be detected in a wide variety of haematopoietic and non-haematopoietic cells and tissue types, including brain, lung, kidney, heart, liver, thyroid, as well as thymic and endometrium epithelia [24]. In the monkey model, the most frequently infected cells were peripheral blood mononuclear cells (PBMC), but infection of thyroid and salivary glands, lung, liver, pancreas, intestine, muscle and spinal cord were sporadically detected in some monkeys [24].

While these observations have not been verified by human studies, and their significance for HTLV-I pathogenesis is uncertain, it is likely that they are partly explained by the very common occurrence of the GLUT-1 receptor on multiple cell types. Some models of HTLV-I infection suggest that many cell types are infected in vivo, but that this infection is non-productive due to intra-cellular constraints on replication which can only be avoided in activated T-cells [24].

Manel et al. suggest that HTLV-I infection through the GLUT-1 receptor may play a direct role in a variety of the pathophysiological effects of the viral infection, including infection of basal cells of the corneal epithelium and some endothelial cells [24].

Relevance for donations of cells and tissues

There is a risk that HTLV-I/II may be transmitted through the use of donated human tissues for transplantation or other human medicinal use as transmission through blood donations and bone transplantation has been described in the past [9, 27-30]. The recent discovery of the main HTLV-I/II receptors [21, 24], the potential role of dendritic cells for transmission [18, 23] and animal models in which HTLV infects a number of tissues and cells of non-leukocyte lineage [24] raise questions on the relevance of infection in other tissues/cells than those of the haematopoietic lineage which could be transmitted in the context of human material donation. Moreover, cells of the haematopoietic lineage are known to be present in multiple tissue types in man, but their exact concentration is not known for all tissue types relevant for transplantation [21, 24].

EU legal requirements on HTLV testing of tissue donations

COMMISSION DIRECTIVE 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells (EUTCD)[4] sets down requirements for technical procedures which are designed to exclude donors of tissues and cells which would constitute a risk for transmission of infectious diseases. The Directive specifies both general and specific exclusion measures, including exclusion based on clinical signs of disease, medical history examination, review of behavioural and social risk factors and screening of evidence for previously undiagnosed infections by specific tests.

The legal requirements for testing tissue donations state that 'HTLV-I antibody testing must be performed for donors living in, or originating from, high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas' (2006/17/EC, Annex II, point 1.2). Therefore, the Directive does not make HTLV I/II screening compulsory for all tissue donations, but only if the donor evaluation (Directive 2006/17/EC, Annex II, point 1.2) reveals that the donor falls into the category described above.

Some Member States have more stringent national requirements for application of the HTLV-I/II test. Moreover, preliminary review of the interpretation of the 'high incidence areas' for HTLV-I/II indicates that the areas/countries considered to belong to this category vary among Member States (information provided to the ECDC by the UK Human Tissue Authority – HTA).

Detailed criteria of donor evaluation relevant for controlling the risk of HTLV-I/II infection are described in the extract of Directive 2006/17/EC in Annex 3.

Recent changes in tissue donor testing requirements in the US concerning HTLV-I/II infection

The American Association of Tissue Banks (AATB)

The following section is modified from the web page of the AATB (http://www.aatb.org/About-AATB):

The AATB is a voluntary, professional, scientific and educational organisation founded in 1976. The AATB's mission is public health. It is the only national tissue banking organisation in the United States and its membership totals more than 100 accredited tissue banks and 1 000 individual members. These banks recover tissue from more than 30 000 donors and distribute in excess of two million allografts for more than one million tissue transplants performed annually in the US. The overwhelming majority of the human tissue distributed for these transplants comes from AATB-accredited tissue banks.

The AATB publishes standards and accredits tissue banks. It certifies personnel and operates a tissue network. The association also interacts with regulatory agencies and conducts educational meetings.

First published in 1984 and presently in its 12th edition, the AATB's *Standards for Tissue Banking* are recognised in both the United States and around the world as the definitive guide for tissue banking. These standards are the only private tissue-banking standards published in the United States, and they are the most comprehensive and detailed tissue-banking standards in the world. As such, the AATB's *Standards* have served as the model for federal and state regulations as well as several international directives and standards. While the AATB's *Standards* have no direct legal regulatory force by themselves, the statutes or regulations of more than 20 [US] states make reference to AATB's *Standards*, institutional accreditation, or individual certification. At least six states require AATB accreditation for any tissue bank operating in their state.

In 1986, the AATB initiated a mandatory accreditation programme for its institutional members to ensure that tissue-banking activities are performed in a professional manner in compliance with its standards. Today, the AATB Accreditation Program remains the only private accreditation programme for tissue banks in the US.

[4] COMMISSION DIRECTIVE 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

Removal of requirement for HTLV I/II testing of tissue donations

On 11 November 2009, the American Association of Tissue Banks (AATB) issued a news release stating that its Board of Governors had approved changes to AATB's *Standards for Tissue Banking* to remove the requirement to test all tissue donors for antibodies to human T-lymphotropic virus type I and type II (anti-HTLV-I and anti-HTLV-II) (Annex 4)[5]. The changes were recommended by the AATB's Physicians' Council and Standards Committee. On 20 October 2009, the Board of Governors voted to approve these changes[6]. This represented a reversal of a requirement for HTLV I/II testing introduced on 18 March 1993 by the AATB's Board of Governors.

According to the news release on its website, the AATB evaluated relevant scientific literature as well as current state, federal, and international requirements for the screening and testing of HTLV-I and HTLV-II tissue donors. The press release also states that due to administrative and operational considerations, there is no requirement to implement these changes by a specific date and they can be made at any time at the discretion of the Tissue Bank. The press release refers to the direct paragraphs of the AATB's *Standards for Tissue Banking* for the exact content of the change in the standards. The lifting of the requirement is not total, for some tissue and cell components that are 'viable, leukocyte-rich cells/tissues', the testing must still be performed.

Since the standards were amended, Florida and California have lifted their state requirement for HTLV testing of tissue donations (news releases posted on the AATB website).

Reasons for the change

There are several reasons for the AATB decision to change its standards and remove the requirement for HTLV-I/II testing. The rationale behind the changes has been described in an AATB document[7] provided to the ECDC by the AATB on 4 August 2010 (Annex 5).

US FDA requirements

The US Food and Drug Administration (FDA) regulations for human cells, tissues, and cellular and tissue-based products (HCT/Ps) described HTLV infection and risk as relevant only for donors of 'viable, leukocyte-rich cells and tissues' and has only required testing for donations falling into this category. The AATB considers that the change in their standards reflects a fallback to the FDA requirements.

Test withdrawal

In the US only tests approved for human diagnostic use by the FDA may be marketed and used for purposes other than research. At present, three test kits are licensed by the FDA, but only one remains in production[8].

The table of FDA licensed assays for Human T-Lymphotropic Virus Types I & II lists three test kits with the following trade names and testing formats:

- Abbott HTLV-I/HTLV-II EIA (EIA);
- Abbott PRISM HTLV-I/HTLV-II Assay (ChLIA); and
- Vironostika* HTLV-I/II Microelisa System (EIA) (*Licensed for donor screening, but may not be available).

At present the Vironostika HTLV Ab kit is no longer commercially available. Similarly, in February 2009 Abbott gave notification that the last shipment date of the Abbott HTLV-I/HTLV-II EIA kit was 31 December 2009. The expiration date of this kit was 18 April 2010. In the past, this test was widely used for tissue and donor testing as a result of its reasonable performance characteristics and applicability for relatively small sample series.

Poor performance of the only available test on cadaveric materials

In US only one test kit manufactured by one company is currently available for HTLV screening of tissue donors. This test kit, the Abbott PRISM HTLV-I/HTLV-II Assay (ChLIA), is only licensed for the testing of blood samples

[5] http://archive.constantcontact.com/fs076/1102056357439/archive/1102820896575.html

[6] HTLV TESTING Recommendation from the Physicians' Council & Regulatory Review Document. Compiled by Scott Brubaker/AATB August 18, 2009

[7] Rationale for Changing the Requirement to Test Tissue Donors for HTLV, AATB document, May 10, 2010

[8] http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm095440.htm#approved

from 'living' donors (see FDA website link cited above.) The kit has not been approved for the testing of blood specimens from cadaveric donors and use of this sample type is not recommended. It is a high-throughput assay system which is only suitable for running large numbers of samples.

No alternative test available

The performance of a CE-marked test kit for use on cadaveric blood specimens is still being evaluated by a testing laboratory in the US. This test kit has not been evaluated by the FDA and is not licensed in the US.

Risk assessment – transmission of HTLV and need to screen certain tissues

AATB considers, in line with the US FDA, that as HTLV I and II are retroviruses infecting CD4 and CD8 positive lymphocytes, and transmission has been linked exclusively to exposure to living lymphocytes/leukocytes and not to non-cellular blood products such as plasma, transmission risks will only be relevant for those tissue products containing viable leukocytes. Studies of HTLV virus transmission following blood transfusion have found that a sufficient number of viable leukocytes must be present for transmission to occur, and this is where the term 'rich in viable leukocytes', used by FDA, is derived from to describe a tissue type that is relevant for HTLV risk. The AATB refers to a threshold of $1x10^8$ viable leukocyte cells as the minimum number of cells that can result in transmission of the virus.

Therefore, the AATB concludes that HTLV testing is only relevant for donors of tissues 'rich in viable leukocytes'. Tissue types not considered 'rich in viable leucocytes' and for which HTLV-I/II testing is not required are processed conventional human tissues (i.e. bone, tendons, ligaments, skin, fascia, nerves, cartilage, heart valves, cardiac conduits and vessels/vascular tissue).

The AATB change of recommendations does not cover certain other tissue/cell types regarded as falling into the category 'rich in viable leucocytes', for which testing is still required by the AATB and the US FDA. These include hematopoietic stem/progenitor cells and semen.

HTLV-I/II infection in US donor populations

According to the AATB, the prevalence of HTLV infection is low in the United States and the country is not considered an endemic area. In certain population groups infection is more common, but these individuals are not eligible for cell or tissue donation (e.g. injecting drug users, sex workers).

However, US guidelines for tissue and cell donor selection contain no reference to other US population groups for which there is evidence of a higher prevalence than in the general population (see Section 7 for review of epidemiology).

Implications of changes in US HTLV-I/II testing requirements on tissue and cell donors for the EU

In its list of questions the Commission asked the ECDC to determine whether the changed testing requirements for HTLV-I/II for tissue and cell donors in the US represent an obstacle to importation and use of tissue and cell products of US origin in terms of compliance with the requirements of the EUTCD. This is particularly relevant for the risk of HTLV-I/II transmission.

Directive 2006/17/EC, Annex II, point 1.2 stipulates that 'HTLV-I antibody testing must be performed for donors living in, or originating from high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas'. The Commission asked the ECDC to examine the epidemiology of HTLV -I/II, to evaluate in which geographical areas of the world HTLV-I/II infections are most common and to establish the status of North America in this regard and how it compares with the EU/European region.

In US documentation on the change of requirements for HTLV-I/II testing, factors affecting the transmission of HTLV-I/II form part of the motivation for testing fewer categories of materials with human tissue cell origin. In particular, the restriction of HTLV-I/II transmission risk, and therefore the need for testing, to materials that are 'rich in viable leukocytes' and for a threshold value of 10^8 leukocytes is applied in the US for classification into this category.

In the initial question and subsequent clarifications, ECDC was asked to examine the evidence for classification of materials into risk categories based on their leukocyte content and especially the threshold mentioned in the US rationale documents for the change of HTLV-I/II testing requirements. It was agreed that the ECDC would not try

to examine this through a comprehensive review of tissue types, as this would require extensive tissue-specific expertise which was not readily available to the ECDC. Instead, ECDC will concentrate on evaluating the evidence as to whether transmission is possible only by exposure to sufficient numbers of infected leukocytes and whether the threshold for transmission risk is 10^8 leukocytes.

ECDC was also asked to examine whether measures used to prevent HTLV-I/II transmission during transplantation of tissues/cells are effective even after the change in US testing requirements.

Results of ECDC review

Epidemiology of HTLV-I/II

Global epidemiology

HTLV-I and II virus infections are not among the infectious diseases under regular systematic surveillance in accordance with EU legislation[9] (2000/96/EC) as applied at the European level by ECDC under the terms of its mandate[10] (2004/851/EC). Therefore, systematically collected data based on case notification are not available for the European Union. A broadly cited estimate of the number of individuals worldwide infected with HTLV-I (10–12 million) is now 25 years old and was not based on data from representative epidemiological studies [1].

A recent systematic review of the literature [2] was only able to identify 17 studies worldwide meeting stringent inclusion criteria for epidemiological representativeness and general validity, and none of them was designed to report incidence. Similarly, none of them provided any data on general population prevalence in Europe or North America [2,3].

Therefore, HTLV-I/II prevalence estimates are usually based on serological screening of blood donors, pregnant women or selected population groups at increased risk, such as injecting drug users and migrants from endemic countries. Studying the prevalence in blood donors is likely to produce underestimates of the population prevalence, while studies among injecting drug users will provide overestimates. Data from pregnant women may better reflect prevalence in the general population, but is biased in relation to gender and age profile. A further concern relates to errors in the laboratory tests used for seroepidemiological studies. The low positive predictive values for the screening tests can result in overestimates of the true prevalence, especially in low endemic settings using early generations of HTLV laboratory tests in combination with non-validated testing algorithms. A few comprehensive recent reviews of HTLV-I/II epidemiology have attempted to capture and critically assess the existing data from targeted or low prevalence studies [3-5]. The sections below summarise information from those reviews and additional original studies.

Globally, there is a clear difference between the distribution of HTLV-I and HTLV-II infection. HTLV-I, which was the first of the two viral variants to be described, is mainly found in selected geographically endemic pockets, the most significant of which are south western Japan, the Caribbean, Central Africa and some areas of South America. In these populations, transmission occurs mainly through the sexual and mother-to-child transmission route. HTLV-II infection is endemic among native Americans throughout North and South America. This endemicity is believed by many to be of ancient origin and linked to the migration of human populations to the American continents over the Bering land bridge thousands of years ago, although some studies have suggested a later introduction [6]. In addition, HTLV-II infection has been found among European and North American injecting drug users as a relatively recent event.

Epidemiology in Europe and the Americas

Europe

A general review of HTLV I/II epidemiology in the European region only addresses data from blood donors, pregnant women and injecting drug users and other specific groups at increased risk [7, 8]. New data on prevalence among blood donors in Europe is available, but is unlikely to accurately reflect general population prevalence due to the highly selective nature of the donor pool [9, 10]. Prevalence among first-time blood donors in Europe was between 0–0.17/10 000 population in Scandinavia and Ireland, between 0.45–0.48/10 000 population in France, the Netherlands and the UK and 5.33/10 000 in Romania [9, 11]. Except for Romania, HTLV-positive blood donors either came from an endemic area or declared that they had had a sexual partner coming from an endemic area [9]. Of the HTLV-positive donations that could be characterised, 6.6% were caused by HTLV-II [9].

A recent large prospective study among pregnant women in Europe covering 7 EU countries (Belgium, France, Germany, Italy, Portugal, Spain and England as part of the UK) revealed confirmed seroprevalence rates of 0.7-11.5/10 000 population (mean 4.4/10 000), on average six times higher than in the blood donor populations of

[9] Annex I of Commission Decision 2000/96/EC of 22 December 1999 on the communicable diseases to be progressively covered by the Community network under Decision No 2119/98/EC of the European Parliament and of the Council, as amended by Decisions 2003/534/EC, 2003/542/EC, 2007/875/EC and 2009/312/EC.

[10] Regulation (EC) No 851/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 21 April 2004 establishing a European centre for disease prevention and control.

the same geographic areas [12]. The same study showed that rates of HTLV-I infection were higher among pregnant women with an immigrant background from endemic areas, as expected. In the UK part of the study the seroprevalence of HTLV infection was 17-fold higher (57/10 000 vs. 3.3/10 000) among mothers born in endemic regions compared with mothers born in the United Kingdom [12].

Another recent study among blood donors in Israel presents evidence of increased prevalence among residents of Eastern European origin [13]. In this study, prevalence among migrants from Romania, Russia and some countries in the former Yugoslav region was found to be higher than in the average population and higher than among people born in Israel. In this study, the prevalence was reported to be 5.4/10 000 among donors born in the Russian Federation, 1.5/10 000 among donors born in Romania and 6.3/10 000 among donors born in the region of the former Yugoslavia [13].

HTLV-II infection is more common among drug users in Europe and has been identified in several countries [8, 14, 15].

North America

HTLV-I infection is likely to be relatively rare in North America. Although population-representative studies are not available for the region, relatively well-defined data exists for blood donors and some studies have been performed among tissue donors [16-18]. In the blood donor population, HTLV-I infection among first-time blood donors in the US was found at a prevalence of 1–1.6/10 000 population [16–18], approximately two to three times higher than the European average [9]. HTLV-II prevalence among first-time blood donors (reported in two of the studies) was found to be 2.4–4.6/10 000 population.

One of the studies (involving 1.7 million first-time and repeat blood donors in five US blood centres between 1991 and 1995) also examined seroprevalence for HTLV-I among all donors. This was found to be 0.9/10 000 population for HTLV-I and 2.2/10 000 population for HTLV-II [16]. The study also examined geographic and population determinants among the donors.

According to the study, HTLV-I seroprevalence was higher among women (1.2/10 000) than men (0.6/10 000). Ethnic subpopulations with relatively increased seroprevalence were African-American/black (4.4/10 000), Hispanic (1.3/10 000) and Asian donors (1.4/10 000) [16]. In contrast, seroprevalence among Caucasian/white donors was found to be relatively low (0.4/10 000) [16]. Further analysis of risk factors revealed relatively increased seroprevalence among donors born outside the US compared to US-born donors (2.1 versus 0.7/10 000, respectively) [16]. HTLV-I seroprevalence increased steadily with age in both sexes, reaching a maximum of 2.4/10 000 in women and 1.6/10 000 in men [16]. In two studies from Canada, the prevalence was estimated to be approximately 5–10 times lower than that in the US: 0.09–0.17/10 000 [19, 20].

The epidemiology of HTLV-II infections on the North American continent is in many respects similar to that in Europe since the majority of cases occur in individuals with a migrant background from endemic areas and among current or previous injecting drug users, with a seroprevalence of 20% being observed in injecting drug users living in US metropolitan areas [4,15,17,18,21]. A clear cohort effect is also visible through a peak prevalence in some age groups and relatively increased prevalence among African-American/black ethnic groups. However, one difference from the European situation is that infection seems to be endemic among some Native American populations [4]. Serologic studies of Native American blood donors for HTLV-II in New Mexico revealed a seroprevalence of 1.0–1.6% [15, 22], 30–40 times higher than the seroprevalence of 2.2–3.3/10 000 for HTLV-II in first-time blood donors coming from the general US population [16, 18].

Endemic areas

The area of the world which has the highest prevalence rate of HTLV infections (HTLV-I) is south-western Japan. Extensive screening from blood donors and pregnant women indicates that prevalence in this area is close to 10% [4]. The highest prevalence was reported in the Japanese islands of Okinawa and Tsushima, 36.4% and 17.8% in 1980, and 17.1% in 1989/1990 [2]. Relatively high population prevalence has also been reported from the Caribbean, some African countries and some areas in South America. For example, in Haiti the prevalence was 3.8% and in selected African studies between 6.6% and 8.5% [2], while in other studies from West-Africa the figures ranged from 0.5% in pregnant women in Burkina Faso [23] to 3.6% in a population-based survey in Guinea Bissau [24]

In Oceania a single-centre study carried out in Papua New Guinea reported a prevalence of 1.9%, whilst a multi-regional study conducted in New Guinea from both Papua New Guinea and Irian Jaya, Indonesia, reported an overall prevalence of 3.76%.

In South America, prevalence rates vary greatly, both between and within countries. In Brazil, the Amazonian population had a seroprevalence of 1.15% and blood donors showed rates of 0.1–1.0% [25-27], while the population in the city of Salvador had the highest rate of 1.8% [28]. Prevalence rates in other studies conducted in Latin America were 0.8% and 2.1% within the Columbian Indian tribes, 0.70% among the Mapuche of Chile and 0.45% among native populations from different regions of Argentina [2].

In the Caribbean (i.e. Jamaica, Martinique, Guyana, French Guyana, Colombia, and the north of Brazil) HTLV-I is particularly frequent among the descendants of African slaves, whereas in other areas such as Peru and the north of Argentina it is the indigenous people who present with the highest prevalence [5].

Recent data also suggests that some regions previously not considered endemic for HTLV-I infection may in fact carry an above-average population prevalence. In particular, some countries in the eastern parts of Europe and in the Middle East may be newly identified areas. The strongest suggestion for an endemic area in Europe is Romania, where both nationally blood donor data and indirect evidence from other studies suggest that there is a relatively high prevalence of HTLV-1 infection compared to many other European countries [9-11, 13]. Another potentially emerging area of increased prevalence may be the Middle East, particularly one region of Iran, where a prevalence among blood donors of 0.77 % and 1.61 % among tissue donors has been described [29, 30]. Other studies seem to confirm this finding [13, 31].

Populations at increased risk

Injecting drug users are at increased risk of blood-borne infections, and HTLV-II has been identified as having entered this population in multiple parts of the world [4]. Studies have shown that injecting drug users in both North America and Europe are affected. The epidemics in these populations are presumed to have been initiated in the 1960s and 1970s but the epidemiology is not very well understood [4]. One comprehensive review study specifically examined the epidemiology of HTLV-II infection [21]. In HTLV-infected individuals, a high prevalence of HTLV-II was reported among injecting drug users in Europe and the United States [21]. Reported seroprevalence rates in injecting drug users have ranged from 0.2% to 49% in the US, France, and Spain. Data from the United States, in largely urban regions, showed that HTLV-II was identified in approximately 90% of the HTLV-positive injecting drug users. Data from Italian injecting drug users reflected similar distributions [21].

Among immigrants in the European region and born outside the region, several studies using data from blood and tissue donors and pregnant mothers suggest that if there is a higher prevalence in the country of birth, this is reflected in the migrant population in the country of residence [28, 32-37]. However, data is not systematically available from all European countries.

Epidemiology among donors of cells and tissues

A limited amount of data on the epidemiology of HTLV-I/II infection among donors of cells and tissues is available from the US and Australia [17,38]. The studies show that the prevalence of HTLV-I/II infection in these populations is low, but not negligible. The prevalence was approximately 6.8/10 000 and 12.2/10 000 in tissue and cell donors in the US and Australia, respectively. The studies also show that the prevalence is significantly higher in the tissue and cell donor population than among first-time blood donors (6.8 times higher in the US study and 35 times higher in the Australian study) [17,38]. This may be explained by differences in age profile and effectiveness of the exclusion of cell and tissue donors based on socio-behavioural risk factors since a large proportion of tissue donations may be of cadaveric origin [17]. However, in the Australian study, the majority of the donations were from surgical bone donors.

European support for the apparent difference between blood and tissue donor populations was confirmed in a Scottish study where the prevalence in tissue and bone donors was 11 times higher than that for first-time blood donors [39]. Some studies reporting data from potential organ donors were identified from France and Spain. In the study from Spain, prevalence among immigrants was found to be 50/10 000 [28]. In the French study, prevalence in a similar population was found to be 4.7–6.7/10 000 [40].

Systematically collected comprehensive data on HTLV-I/II prevalence among tissue and cell donations from Europe does not exist.

Discussion and conclusions

Epidemiology of HTLV-I/II (Question 1)

The review of the epidemiology of HTLV-I and II performed as part of this risk assessment has revealed that the general population prevalence and incidence of these viral infections is unknown in most parts of the world. Consequently, there is little understanding of their epidemiology and disease burden. This is particularly true for the European and North American geographical regions, as well as many other regions of the world which are frequently described as areas of low endemicity. Of the few population-representative studies performed the majority of them have been in Asia, Africa and South America. None were found for Europe and North America. Although some data exist, these suggest that the general population prevalence in both regions is likely to be comparably low and probably less than 0.1%. The definition of what can be considered a high or low prevalence is, however, dependent on societal, economic and value-based factors and is difficult to define objectively. For the purposes of risk removal in transplantation and transfusion of substances of human origin, comparably low prevalence has often been considered sufficient to warrant testing.

The best comparability exists among studies using data from first-time blood donors, which show no great difference in the prevalence of HTLV-I/II infection between the US or Europe, and indicate that prevalence is relatively low in both geographical locations (approximately 1–1.5/10 000 population in the US and on average 0.46/10 000 population in the EU area). However, blood donors undergo a rigorous risk-factor exclusion programme which is designed to reduce the risk of blood-borne infections. Prevalence in this population therefore only constitutes a minimum estimate of the prevalence of HTLV-I/II infection in the general population. In one EU Member State (Romania) prevalence of HTLV-I among first-time blood donors was reported to be significantly higher than in the other European countries, 5.33/10 000, indicating that for some reason the infection may have become endemic in a subpopulation of blood donors in the region.

Information from other populations which are less selective, such as pregnant women and tissue and cell donors, may be more representative the prevalence of HTLV-I/II infection in the population. A study among pregnant women in six countries throughout the central and southern EU region showed that prevalence among pregnant women varied from 0.7–11.5/10 000 population (average of 4.4/10 000), six-fold higher than in the EU blood donor populations. Tissue and cell donation data from the US showed that prevalence in this group was higher than among blood donors, reaching a value of 6.8/10 000 population. In Scotland, HTLV prevalence among tissue and cell donors was recently shown to be 11 times higher than in new blood donors.

In both the US and Europe, evidence of high prevalence was found among high-risk groups, in particular injecting drug users. In Europe and the US the type of virus that has established itself in injecting drug user populations is mainly HTLV-II.

Certain parts of the world have been shown to have a higher prevalence and incidence of HTLV-I and II infection than is evident in other regions. The highest prevalence has been identified in south western Japan, where general population prevalence is approximately 10% and even higher. In selected studies and sub-regions prevalence of over 30% has been reported. In addition, there is evidence of high prevalence in Central African countries, the Caribbean and some South American countries, ranging from approximately 0.5–1% to close to 10%.

Immigration to both the US and the EU region is common and the numbers of both recent first-generation immigrants and descendants of immigrants constitute sizeable proportions of the general population in both regions. In the EU region, large-scale immigration from former colonies of European states has significantly contributed to the population in these countries. In addition, many EU countries continue to receive large numbers of immigrants. Some of these immigrants, or their parents/grandparents, originate from areas with a high-prevalence of HTLV-I/II infection. As HTLV-I/II are transmissible from mother to child or through sexual contact and cause disease in only a small proportion of those chronically infected, prevalence in the population may remain higher than among the general population for extended periods. Prevalence studies among blood-donors and pregnant women in the EU have indicated that this is indeed the case. Evidence of above-average prevalence among pregnant women with a migrant background has been noted in France, Spain and the UK.

Although immigration from multiple parts of the world, including large-scale forced migration from Central and West Africa (HTLV-I/II endemic region) as a result of the slave trade, has contributed to the US and North American populations over long periods, clear information on the prevalence of infection in populations with recent or historical migrant background could not be identified in the literature searches. Some studies, however, suggest above-average prevalence among Native American, African American and Hispanic population groups compared to Caucasian. In some Native American populations there is evidence to suggest that HTLV-II may be endemic. Based on general demographic information in North America, however, it can be assumed that sub-populations which could have above-average prevalence may have persisted in the general population. Similarly, current migration from Caribbean and South American countries may increase the prevalence in North America over time as a result of the influx from populations where HTLV-I/II infection is endemic.

According to the EUTCD, HTLV-I antibody testing must be performed for donors living in, or originating from, high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas. The use of the term 'incidence' in the Directive is problematic, as almost no information on incidence is available in the literature. A large proportion of tissue donors (with the exception of donors of reproductive cells) donate materials only once. Most studies report only on prevalence, which is easier to measure and provides a more stable description of transmission risk in the case of a chronic, mostly asymptomatic viral infection, which remains transmissible throughout its course. Therefore, the use of estimates of prevalence would constitute a better marker for defining regions of HTLV-I/II endemicity.

Based on the findings of the literature review, evidence available on the epidemiology of HTLV-I/II does not support an objective classification of the US or North America as an area of high-incidence or high prevalence of HTLV-I/II infection in the general population compared to Japan, the Caribbean and other areas of the world, where prevalence rates are very high and above 1%.

However, the literature review showed that the epidemiology of HTLV-I/II in the US does not substantially differ from that of the EU region. Sub-populations and regions where HTLV-I/II infection rates are high and roughly comparable exist in both areas and are classified by both ethnic and risk-behaviour factors. Therefore, the epidemiological evidence does not support different approaches to minimising the risk of transmission from donations. If no HTLV-I/II testing of tissue and cell donors is performed in the US and products derived from these donors are imported to the EU, a double standard will be created concerning risk management.

The definition of what constitutes 'high incidence or high prevalence' was extensively discussed in the ad hoc expert panel meeting organised by the ECDC in accordance with its mandate and requested by DG SANCO – Directorate C Public Health and Risk Assessment. It was recognised that not specifying a threshold value for 'high prevalence' constitutes a major interpretation problem in the current regulation. This is evident when reviewing how the Directive is being interpreted by Member States. A pilot survey conducted among a randomly selected group of EU Member States shows very wide variation in the interpretation of the term (available on request).

One member of the expert panel expressed doubt over the usefulness of setting a threshold on the basis that this approach was too simplistic. Such a threshold should be based on a more thorough risk analysis performed on a case-by-case basis, taking into account a numbers of risk determinants. If threshold values were based on general population prevalence, there was a danger that sub-groups with a higher prevalence would be masked by being averaged across the population, especially if the sub-groups were small.

However, other experts argued that a threshold would be valuable as a starting point from which countries may then deviate and use more stringent criteria, if evidence-based risk analysis indicated such a need.

Ideally, determination of whether HTLV-I/II testing is needed for tissue and cell donations would be based on the tissue and cell donor population prevalence. Currently, information from tissue and cell donor testing is not collected in most of EU Member States or centrally analysed, as is the case for HIV, Hepatitis B and C and HTLV-I/II infections in blood donors. Specific comparisons of prevalence in tissue and cell donors in EU and the US would require separate studies or setting-based surveillance. The ad hoc expert group suggested that prevalence studies covering all EU Member States could be promoted using research and public health funding instruments as well as national funding sources.

The ad hoc expert panel concluded that a practical alternative approach to setting threshold values would be to use more readily available data, such as data collected from blood donations. As blood donors are efficiently pre-selected, prevalence of infectious diseases would be significantly lower than among unselected populations, and therefore a threshold value for this group would have to be set at a lower level. Studies show that prevalence of HTLV-I/II among first-time blood donors is generally at least 10 times lower than the general population or among the donors of tissues and cells.

However, the expert group generally agreed that an HTLV-I/II infection rate above 1% of the general population should be considered very high prevalence and that 0.1% may already be considered high. The literature review revealed that data on general population prevalence is not available from most countries, which makes it impractical to specify such a general population threshold. It was therefore suggested that prevalence among first-time blood donors could be used as a proxy to define a threshold value, taking into account the fact that prevalence in this population is lower than in tissue and cell donors or the general population.

The ad hoc expert panel came to the conclusion that a prevalence level of over 1/10 000 among first-time blood donors should be regarded as a minimum value for 'high prevalence' and could be used as a general threshold value for determining whether an area was endemic in terms of HTLV-I/II infection and as an indication for testing tissue and organ donors from the area. It was stressed that this threshold should be considered general and not only relevant for areas outside the EU region. The suggested threshold value happens to coincide with an estimate from Norway which suggests that screening for HTLV-I/II is cost-effective if prevalence exceeds 0.8/10 000 among first-time donors [1,2]. Such estimates do include significant uncertainty and are also dependent on the national underlying costs and willingness to pay for averted disease.

A threshold value for repeat blood donors is not useful as infected individuals will be identified and removed during initial testing at their first donation. This is partially true even in situations where HTLV-I/II testing is not performed systematically, as there is significant overlap with other blood-borne infections.

The ad hoc expert group also considered specifying a secondary threshold prevalence level of over 1/100 000 among first-time blood donors which could serve as an indication to consider testing for HTLV-I/II among donors of tissues and cells. However, there was not a full consensus among the panel experts as to the usefulness of such a secondary threshold value.

Donor selection by assessment of social and behavioural risk factors will be discussed separately as soon as the effectiveness of the measures has been appropriately reviewed. However, it should be noted that under the guidelines issued by the FDA for donor screening and assessment of risk factors for donor deferral, there is no requirement to assess whether the donors originate from an area of high HTLV-I/II prevalence. Instead, the FDA guidelines list individuals from several regions of the world (including the entire European region) as ineligible for donation. The rationale for all the regions listed is not immediately evident in the FDA guidelines, but for the EU region, it is to avoid the risk of transmitting variant Creutzfeldt-Jakob disease.

Since the approaches to donor exclusion differ between the EU and the US, estimating the relative risks of HTLV-I/II infection among tissue and cell donors in the two regions is a challenge. Since the prevalence among most populations in the US for which data is available is higher than in the EU region, and since sub-populations with higher prevalence exist both in the US and the EU, a different approach to testing for HTLV-I/II in the two regions is not supported by the epidemiological evidence.

Considerations

These considerations are based on the results of a comprehensive literature search, as described in Section 2 (Search strategies) and the expert advice of the ad hoc expert panel. ECDC would suggest the following for the consideration of the EU Commission and the EU Competent Authorities on Tissues and Cells.

In Annex II, section 1.2. of the EUTCD:

- Consider replacing 'incidence' with 'prevalence' or include both terms in the description of endemic areas for HTLV-I/II infection.
  Motivation: this change would better reflect available data and facilitate assessment of risk. Geographic areas of high prevalence, high incidence or both high incidence and high prevalence may exist depending on the epidemiological situation. Moreover, each of the situations implies increased risk and situations may change over time as the epidemic matures or control measures take effect.
- Consider specifying threshold values in the Directive for what is considered high prevalence. The ad hoc expert panel suggests that prevalence over 1% in the general population or prevalence of over 1/10 000 among first-time blood-donors could be considered as indicators of high prevalence and endemic transmission of HTLV-I/II.
  Motivation: specifying a threshold value for 'high prevalence' would enable Member States to apply a common interpretation and enable certain regions of the world to be objectively classified as 'high prevalence'. Such a classification could also be updated regularly as new data becomes available. Specifying the threshold value would not prevent individual Member States from employing more stringent threshold values and implementing testing for HTLV-I/II among tissue and cell donors based on national assessments of effectiveness and risk management.
- Consider promoting EU and national sero-survey studies of HTLV-I/II prevalence using available funding instruments.
  Motivation: in some EU countries, little or no information is available on HTLV-I/II prevalence, while in others the study size is insufficient or the studies are old and unrepresentative of the current situation. Moreover, the increased intra-EU mobility and migration from potentially endemic areas may change the epidemiology of HTLV-I/II infection significantly over time. The very long incubation period prior to disease development suggests that monitoring for HAM/TSP and ATLL could create situations where prevalence may increase before an epidemic is detected if no sero-surveys are conducted. Even countries where prevalence has been shown to be low in the past may benefit from systematic monitoring by means of regular sero-surveys.
- Consider requiring collection and centralised reporting of testing data on blood-borne viral infections for all tissue donations using standardised protocols in the EU region as part of quality assurance procedures for tissue and cell donation establishments.
  Motivation: a clear understanding of epidemiology is essential for an accurate and evidence based assessment of prevention and control measures. This principle has been successfully applied to blood donation services in Europe. Information on the results of screening for blood-borne viral infections has been systematically collected for many years in Europe, and has been used to accurately assess residual risks of transmission for blood donations in Europe. This has had a profound influence on the improvement of blood safety and the development of improved infection management procedures within the field. As screening for blood-borne infections among tissue and cell donors is already mandatory, the only additional resource requirement would be the organisation of the data collection and its storage, analysis of the data and reporting of the results. This would enable the effectiveness of the current screening requirement to be assessed within a few years. Although the organisation of the data collection is not a trivial matter, it represents a minor use of resources compared to a blanket requirement for all donations to be screened.

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Annex 1. Systematic literature search strategy

PUBMED: Tissue and organ donors (blood donors excluded)

Concept 1	Boolean operator	Concept 2	Boolean operator	Concept 3
OR		OR		OR
"atlv"[Title/Abstract] "t cell leukemia virus i"[Title/Abstract] "t cell leukemia virus ii"[Title/Abstract] "T Lymphotropic Virus II"[Title/Abstract] "HTLV-I Infections"[Mesh] "HTLV-II Infections"[Mesh] "Human T-lymphotropic virus 1"[Mesh] "Human T-lymphotropic virus 2"[Mesh] "Leukemia-Lymphoma, Adult T-Cell"[Mesh] "htlv i"[Title/Abstract] "htlv ii"[Title/Abstract] "htlv 1"[Title/Abstract] "htlv 2"[Title/Abstract] "human t lymphotropic virus 1"[Title/Abstract] "human t lymphotropic virus htlv i"[Title/Abstract] "human t lymphotropic virus htlv ii"[Title/Abstract] "human t lymphotropic virus 2"[Title/Abstract] "human t lymphotropic virus type 1"[Title/Abstract] "human t lymphotropic virus type 2"[Title/Abstract]	AND	((donor* or donat*) AND (organ OR organs OR cadaveric OR deceased OR "non living" OR living OR "Germ Cells"[Mesh] OR sperm OR spermatoz* OR semen OR ovum* OR "spermatic fluid" OR ovule* OR oocyte* OR cyte* OR egg* OR "reproductive cell" OR "reproductive cells")) "Tissue Donors"[Mesh:NoExp] "Living Donors"[Mesh] "cadaveric donor"[Title/Abstract] "cadaveric donors"[Title/Abstract] "deceased donor"[Title/Abstract] "deceased donors"[Title/Abstract] "living donor"[Title/Abstract] "living donors"[Title/Abstract]	AND	"Meta-Analysis "[Publication Type] "Meta-Analysis as Topic"[Mesh] "Guideline "[Publication Type] "Guidelines as Topic"[Mesh] "Practice Guideline "[Publication Type] "Evidence-Based Practice"[Mesh] "Consensus Development Conference "[Publication Type] "Consensus Development Conferences as Topic"[Mesh] "Review Literature as Topic"[Mesh] "Review "[Publication Type] "Epidemiology"[Mesh] "Cross-Sectional Studies"[Mesh] "Risk"[Mesh] "Prevalence"[Mesh] "Incidence"[Mesh] "Prospective Studies"[Mesh] "Mass Screening"[Mesh] "Epidemiologic Studies"[Mesh] "systematic review"[Title/Abstract] "cross sectional"[Title/Abstract] "meta analysis"[Title/Abstract] "screening"[Title] "screen"[Title] "risk"[Title] "prevalence"[Title/Abstract] "incidence"[Title/Abstract] "cohort study"[Title/Abstract] "cohort studies"[Title/Abstract] "guideline"[Title] "guidelines"[Title] "epidemiology"[Title] "prospective study"[Title/Abstract] "prospective studies"[Title/Abstract]

Concept 1	Boolean operator	Concept 2	Boolean operator	Concept 3	Boolean operator	Concept 4
OR		OR		OR		OR
"atlv"[Title/Abstract] "t cell leukemia virus i"[Title/Abstract] "t cell leukemia virus ii"[Title/Abstract] "T Lymphotropic Virus II"[Title/Abstract] "HTLV-I Infections"[Mesh] "HTLV-II Infections"[Mesh] "Human T-lymphotropic virus 1"[Mesh] "Human T-lymphotropic virus 2"[Mesh] "Leukemia-Lymphoma, Adult T-Cell"[Mesh] "htlv i"[Title/Abstract] "htlv ii"[Title/Abstract] "htlv 1"[Title/Abstract] "htlv 2"[Title/Abstract] "human t lymphotropic virus 1"[Title/Abstract] "human t lymphotropic virus htlv i"[Title/Abstract] "human t lymphotropic virus htlv ii"[Title/Abstract] "human t lymphotropic virus 2"[Title/Abstract] "human t lymphotropic virus type 1"[Title/Abstract] "human t lymphotropic virus type 2"[Title/Abstract]	AND	((donor* or donat*) AND (organ OR organs OR cadaveric OR deceased OR "non living" OR living OR "Germ Cells"[Mesh] OR sperm OR spermatoz* OR semen OR ovum* OR "spermatic fluid" OR ovule* OR oocyte* OR cyte* OR egg* OR "reproductive cell" OR "reproductive cells")) "Tissue Donors"[Mesh] "Living Donors"[Mesh] "cadaveric donor"[Title/Abstract] "cadaveric donors"[Title/Abstract] "deceased donor"[Title/Abstract] "deceased donors"[Title/Abstract] "living donor"[Title/Abstract] "living donors"[Title/Abstract]	AND	"Meta-Analysis "[Publication Type] "Meta-Analysis as Topic"[Mesh] "Guideline "[Publication Type] "Guidelines as Topic"[Mesh] "Practice Guideline "[Publication Type] "Evidence-Based Practice"[Mesh] "Consensus Development Conference "[Publication Type] "Consensus Development Conferences as Topic"[Mesh] "Review Literature as Topic"[Mesh] "Review "[Publication Type] "Epidemiology"[Mesh] "Cross-Sectional Studies"[Mesh] "Risk"[Mesh] "Prevalence"[Mesh] "Incidence"[Mesh] "Prospective Studies"[Mesh] "Mass Screening"[Mesh] "Epidemiologic Studies"[Mesh] "systematic review"[Title/Abstract] "cross sectional"[Title/Abstract] "meta analysis"[Title/Abstract] "screening"[Title] "screen"[Title] "risk"[Title] "prevalence"[Title/Abstract] "incidence"[Title/Abstract] "cohort study"[Title/Abstract] "cohort studies"[Title/Abstract] "guideline"[Title] "guidelines"[Title] "epidemiology"[Title] "prospective study"[Title/Abstract] "prospective studies"[Title/Abstract]	NOT	"blood"[Title] "seroprevalence"[Title] "seroepidemiology"[Title]

Limits: English, French, German, Spanish, Finnish, Swedish, Romanian

PUBMED: Blood donor and transfusion

Concept 1	Boolean operator	Concept 2	Boolean operator	Concept 3
OR		OR		OR
"atlv"[Title/Abstract] "t cell leukemia virus i"[Title/Abstract] "t cell leukemia virus ii"[Title/Abstract] "T Lymphotropic Virus II"[Title/Abstract] "HTLV-I Infections"[Mesh] "HTLV-II Infections"[Mesh] "Human T-lymphotropic virus 1"[Mesh] "Human T-lymphotropic virus 2"[Mesh] "Leukemia-Lymphoma, Adult T-Cell"[Mesh] "htlv i"[Title/Abstract] "htlv ii"[Title/Abstract] "htlv 1"[Title/Abstract] "htlv 2"[Title/Abstract] "human t lymphotropic virus 1"[Title/Abstract] "human t lymphotropic virus htlv i"[Title/Abstract] "human t lymphotropic virus htlv ii"[Title/Abstract] "human t lymphotropic virus 2"[Title/Abstract] "human t lymphotropic virus type 1"[Title/Abstract] "human t lymphotropic virus type 2"[Title/Abstract]	AND	"blood transfusions"[Title/Abstract] "blood transfusion"[Title/Abstract] "blood transfusion"[MeSH Terms] "blood donors"[MeSH Terms] "blood donor"[Title/Abstract] "blood donors"[Title/Abstract]	AND	"Meta-Analysis "[Publication Type] "Meta-Analysis as Topic"[Mesh] "Guideline "[Publication Type] "Guidelines as Topic"[Mesh] "Practice Guideline "[Publication Type] "Evidence-Based Practice"[Mesh] "Consensus Development Conference "[Publication Type] "Consensus Development Conferences as Topic"[Mesh] "Review Literature as Topic"[Mesh] "Review "[Publication Type] "Epidemiology"[Mesh] "Cross-Sectional Studies"[Mesh] "Risk"[Mesh] "Prevalence"[Mesh] "Incidence"[Mesh] "Prospective Studies"[Mesh] "Mass Screening"[Mesh] "Epidemiologic Studies"[Mesh] "systematic review"[Title/Abstract] "cross sectional"[Title/Abstract] "meta analysis"[Title/Abstract] "screening"[Title] "screen"[Title] "risk"[Title] "prevalence"[Title/Abstract] "incidence"[Title/Abstract] "cohort study"[Title/Abstract] "cohort studies"[Title/Abstract] "guideline"[Title] "guidelines"[Title] "epidemiology"[Title] "prospective study"[Title/Abstract] "prospective studies"[Title/Abstract]

Limits: English, French, German, Spanish, Finnish, Swedish, Romanian

PUBMED: Pregnant women

Concept 1	Boolean operator	Concept 2	Boolean operator	Concept 3
OR		OR		OR
"atlv"[Title/Abstract] "t cell leukemia virus i"[Title/Abstract] "t cell leukemia virus ii"[Title/Abstract] "T Lymphotropic Virus II"[Title/Abstract] "HTLV-I Infections"[Mesh] "HTLV-II Infections"[Mesh] "Human T-lymphotropic virus 1"[Mesh] "Human T-lymphotropic virus 2"[Mesh] "Leukemia-Lymphoma, Adult T-Cell"[Mesh] "htlv i"[Title/Abstract] "htlv ii"[Title/Abstract] "htlv 1"[Title/Abstract] "htlv 2"[Title/Abstract] "human t lymphotropic virus 1"[Title/Abstract] "human t lymphotropic virus htlv i"[Title/Abstract] "human t lymphotropic virus htlv ii"[Title/Abstract] "human t lymphotropic virus 2"[Title/Abstract] "human t lymphotropic virus type 1"[Title/Abstract] "human t lymphotropic virus type 2"[Title/Abstract]	AND	pregnan* gravid* "Pregnant Women"[Mesh] "Pregnancy"[Mesh]	AND	"Meta-Analysis "[Publication Type] "Meta-Analysis as Topic"[Mesh] "Guideline "[Publication Type] "Guidelines as Topic"[Mesh] "Practice Guideline "[Publication Type] "Evidence-Based Practice"[Mesh] "Consensus Development Conference "[Publication Type] "Consensus Development Conferences as Topic"[Mesh] "Review Literature as Topic"[Mesh] "Review "[Publication Type] "Epidemiology"[Mesh] "Cross-Sectional Studies"[Mesh] "Risk"[Mesh] "Prevalence"[Mesh] "Incidence"[Mesh] "Prospective Studies"[Mesh] "Mass Screening"[Mesh] "Epidemiologic Studies"[Mesh] "systematic review"[Title/Abstract] "cross sectional"[Title/Abstract] "meta analysis"[Title/Abstract] "screening"[Title] "screen"[Title] "risk"[Title] "prevalence"[Title/Abstract] "incidence"[Title/Abstract] "cohort study"[Title/Abstract] "cohort studies"[Title/Abstract] "guideline"[Title] "guidelines"[Title] "epidemiology"[Title] "prospective study"[Title/Abstract] "prospective studies"[Title/Abstract]

Limits: English, French, German, Spanish, Finnish, Swedish, Romanian

EMBASE: Tissue and organ donors (blood donors excluded)

Concept 1	Boolean operator	Concept 2	Boolean operator	Concept 3	Boolean operator	Concept 4
OR		OR		OR		OR
'human t cell leukemia virus 1'/exp 'human t cell leukemia virus 2'/exp 'human t cell leukemia virus infection'/exp 'htlv i':ab 'htlv i':ti 'htlv ii':ab 'htlv ii':ti 'htlv 1':ab 'htlv 1':ti 'htlv 2':ab 'htlv 2':ti 'human t lymphotropic virus 1':ab 'human t lymphotropic virus 1':ti 'human t lymphotropic virus htlv i':ab 'human t lymphotropic virus htlv i':ti 'human t lymphotropic virus 2':ab 'human t lymphotropic virus 2':ti 'human t lymphotropic virus type 1':ab 'human t lymphotropic virus type 1':ti 'human t lymphotropic virus type 2':ab 'human t lymphotropic virus type 2':ti atlv:ab atlv:ti	AND	'donor'/de 'kidney donor'/exp 'kidney donor' 'living donor'/exp 'living donor' 'organ donor'/exp 'organ donor' 'sperm donor'/exp 'sperm donor' 'cadaveric donor' 'deceased donor' 'living donor'/exp 'non living donor' (('organ'/exp OR 'organ' OR living OR cadaveric OR deceased OR 'non living' OR 'sperm'/exp OR 'sperm' OR spermatoz* OR 'semen'/exp OR 'semen' OR ovum* OR 'spermatic fluid' OR ovule* OR oocyte* OR cyte* OR egg* OR 'reproductive cell' OR 'reproductive cells' OR 'germ cell'/exp OR 'germ cell') AND (donor* OR donat*))	AND	'cohort analysis'/exp 'cross-sectional study'/exp 'prevalence'/exp 'incidence'/exp 'screening'/exp 'risk'/exp 'evidence based practice'/exp 'systematic review'/exp 'meta analysis'/exp 'practice guideline'/exp 'systematic review':ab 'systematic review':ti 'cross sectional':ab 'cross sectional':ti 'meta analysis':ab 'meta analysis':ti 'screening':ti 'screen':ti 'risk':ti guideline:ti guidelines:ti epidemiology:ti 'cohort study':ab 'cohort study':ti 'cohort studies':ab 'cohort studies':ti	NOT	blood:ti seroprevalence:ti seroepidemiology:ti

([english]/lim OR [finnish]/lim OR [french]/lim OR [german]/lim OR [romanian]/lim OR [spanish]/lim OR [swedish]/lim) AND [embase]/lim

EMBASE: Blood donor and transfusion

Concept 1	Boolean operator	Concept 2	Boolean operator	Concept 3
OR		OR		OR
'human t cell leukemia virus 1'/exp 'human t cell leukemia virus 2'/exp 'human t cell leukemia virus infection'/exp 'htlv i':ab 'htlv i':ti 'htlv ii':ab 'htlv ii':ti 'htlv 1':ab 'htlv 1':ti 'htlv 2':ab 'htlv 2':ti 'human t lymphotropic virus 1':ab 'human t lymphotropic virus 1':ti 'human t lymphotropic virus htlv i':ab 'human t lymphotropic virus htlv i':ti 'human t lymphotropic virus 2':ab 'human t lymphotropic virus 2':ti 'human t lymphotropic virus type 1':ab 'human t lymphotropic virus type 1':ti 'human t lymphotropic virus type 2':ab 'human t lymphotropic virus type 2':ti atlv:ab atlv:ti	AND	'blood donor'/exp 'blood transfusion'/exp 'blood donor':ab 'blood donor':ti 'blood transfusion':ab 'blood transfusion':ti	AND	'cohort analysis'/exp 'cross-sectional study'/exp 'prevalence'/exp 'incidence'/exp 'screening'/exp 'risk'/exp 'evidence based practice'/exp 'systematic review'/exp 'meta analysis'/exp 'practice guideline'/exp 'systematic review':ab 'systematic review':ti 'cross sectional':ab 'cross sectional':ti 'meta analysis':ab 'meta analysis':ti 'screening':ti 'screen':ti 'risk':ti guideline:ti guidelines:ti epidemiology:ti 'cohort study':ab 'cohort study':ti 'cohort studies':ab 'cohort studies':ti

([english]/lim OR [finnish]/lim OR [french]/lim OR [german]/lim OR [romanian]/lim OR [spanish]/lim OR [swedish]/lim) AND [embase]/lim

EMBASE: Pregnant women

Concept 1	Boolean operator	Concept 2	Boolean operator	Concept 3
OR		OR		OR
'human t cell leukemia virus 1'/exp 'human t cell leukemia virus 2'/exp 'human t cell leukemia virus infection'/exp 'htlv i':ab 'htlv i':ti 'htlv ii':ab 'htlv ii':ti 'htlv 1':ab 'htlv 1':ti 'htlv 2':ab 'htlv 2':ti 'human t lymphotropic virus 1':ab 'human t lymphotropic virus 1':ti 'human t lymphotropic virus htlv i':ab 'human t lymphotropic virus htlv i':ti 'human t lymphotropic virus 2':ab 'human t lymphotropic virus 2':ti 'human t lymphotropic virus type 1':ab 'human t lymphotropic virus type 1':ti 'human t lymphotropic virus type 2':ab 'human t lymphotropic virus type 2':ti atlv:ab atlv:ti	AND	'pregnant woman'/exp 'pregnant woman' 'pregnancy'/exp 'pregnancy' gravid:ab gravid:ti	AND	'cohort analysis'/exp 'cross-sectional study'/exp 'prevalence'/exp 'incidence'/exp 'screening'/exp 'risk'/exp 'evidence based practice'/exp 'systematic review'/exp 'meta analysis'/exp 'practice guideline'/exp 'systematic review':ab 'systematic review':ti 'cross sectional':ab 'cross sectional':ti 'meta analysis':ab 'meta analysis':ti 'screening':ti 'screen':ti 'risk':ti guideline:ti guidelines:ti epidemiology:ti 'cohort study':ab 'cohort study':ti 'cohort studies':ab 'cohort studies':ti

([english]/lim OR [finnish]/lim OR [french]/lim OR [german]/lim OR [romanian]/lim OR [spanish]/lim OR [swedish]/lim) AND [embase]/lim

COCHRANE LIBRARY

Concept 1	Boolean operator	Concept 2
OR		OR
MeSH descriptor **HTLV-I Infections** explode all trees MeSH descriptor **HTLV-II Infections** explode all trees MeSH descriptor **Human T-lymphotropic virus 1** explode all trees MeSH descriptor **Human T-lymphotropic virus 2** explode all trees	AND	MeSH descriptor **Risk** explode all trees MeSH descriptor **Epidemiology** explode all trees MeSH descriptor **Prevalence** explode all trees MeSH descriptor **Prospective Studies** explode all trees MeSH descriptor **Incidence** explode all trees MeSH descriptor **Cross-Sectional Studies** explode all trees MeSH descriptor **Mass Screening** explode all trees MeSH descriptor **Epidemiologic Studies** explode all trees MeSH descriptor **Meta-Analysis as Topic** explode all trees MeSH descriptor **Guidelines as Topic** explode all trees MeSH descriptor **Evidence-Based Practice** explode all trees MeSH descriptor **Consensus Development Conferences as Topic** explode all trees MeSH descriptor **Review Literature as Topic** explode all trees (Meta-Analysis):pt (Guideline):pt (Practice Guideline):pt (Consensus Development Conference):pt (Review):pt

Annex 2. Evidence tables

Global reviews

Citation	Title	Type of study	Area covered	Population/ sample size	Outcome	Strengths	Limitations
Hlela C, Shepperd S, et al. (2009). AIDS Rev 11(4): 205-214.	"The prevalence of human T-cell lymphotropic virus type 1 in the general population is unknown."	Epidemiolog-ical review	Global	General population, 16 745 participants (0–89 years), 1988–1999;	Prevalence rates HTLV-I: -Okinawa Island, Japan 17.1% (1989-1990); Tsushima Island, Japan 36.4% (year not specified) -Haiti 3.8% (1988) -Africa: 6.6-8.5% in Gabon (1988-1996) and 1.05% in Guinea (1992); -Oceania: Papua New Guinea 1.9% (1972-1991), Papua New Guinea and Indonesia 3.7% (different ethnic populations, year not specified); -Brazil: Amazon 1.15% (year not specified), Salvador 1.7% (1998) -Columbian Indian tribes 0.8%-2.1% (1988-1992) -Chile, Mapuches tribe: 0.7% (year not specified) -Argentina, Indians : 0.45%(1987-1992)	Strict application of objective criteria for population representative ness. Studies were only included if serological tests were confirmed by immunoblot, RIPA or IFA. One of the few literature reviews reporting HTLV-I prevalence rates in general population.	Statistical heterogeneity. Various diagnostic techniques. Study population not always clearly characterised
Proietti FA, et al. Oncogene, 2005. 24(39): p. 6058-68	"Global epidemiology of HTLV-I infection and associated diseases."	Epidemiolog-ical review	Global	Blood donors , other selected populations	Prevalence rates of HTLV-I: *0.01-0.03%* HTLV-I infection is mainly found in immigrants from endemic areas, their offspring and sexual contacts, among sex workers and injecting drug users.	Summarises a large proportion of all published studies.	Differences in age, gender and risk profiles of studied populations. Early EIAs have reduced specificity, or did not discriminate between HTLV-I and II. Biological false positivity with reactive EIAs and indeterminate WB patterns due to possible cross-reactivity with malaria antigens *(Mahieux et al.)*
Roucoux DF and Murphy EL (2004). AIDS Reviews 6(3): 144-154.	"The epidemiology and disease outcomes of human T-lymphotropic virus type II."	Epidemiolog-ical review	American continent	Amerindian tribes: Pueblo, Seminole; Amerindian blood donors in New Mexico; Non-Hispanic white blood donors in New Mexico	Prevalence rates of HTLV-II: *2-3%* Pueblo *13.2%* Seminole *1.0-1.6%* in Amerindian blood donors *0.009-0.06%* Non-Hispanic white blood donors HTLV-I/II: *0.07%* (30/41.657) in blood donors in Albuquerque, New	Adds information on HTLV-II epidemiology and disease outcomes, which previously were poorly defined. Formulates hypotheses on HTLV-II virus	Blood donor sub-population used to approximate rates in general Amerindian population. Rates in donors are likely to be lower due to selection bias. Small numbers of subjects, no

Citation	Title	Type of study	Area covered	Population/ sample size	Outcome	Strengths	Limitations
					Mexico	origins.	randomisation.
WHO and IARC (1996). International Agency for Research on Cancer (IARC) Monographs on the evaluation of carcinogenic risks to humans.67 : 447.	"Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses"	Epidemiological review and expert assessment of clinical significance of HTLV-I and HTLV-II for cancer	Global	n/a	Estimate of global prevalence. Review of links to ATLL, HAM/TSP and other possible conditions. Estimates of lifetime risks of ATLL (2 %).	Comprehensive review of epidemiology and most aspects of HTLV-I/II infection. Summary of most available data at time of production. Convincing conclusions concerning causative link of HTLV-I to ATLL.	Lack of population representative data. Does not present comprehensive conclusions concerning links to diseases other than HAM/TSP and ATLL. Does not present lifetime risks of HAM/TSP development among HTLV-I infected.

North America

Citation	Title	Type of study	Area covered	Population/ sample size	Outcome	Strengths	Limitations
Zou S, PhD, Dodd RY PhD, Stramer SL, PhD, Strong DM PhD for the Tissue Safety Study Group. N Engl J Med 2004; 351:751-759 August 19, 2004	"Probability of Viremia with HBV, HCV, HIV, and HTLV among Tissue Donors in the United States."	Epidemiolog -ical and modelling study	US, five tissue banks	7.4/7 857 tissues donors, 2000-2002. 160/783 651 first-time blood donors in 2001.	Prevalence rate of HTLV-I/II in tissue donors: 0.068%. Prevalence rate of HTLV-I/II in first-time blood donors: 0.010%	One of the few studies giving HTLV –I/II prevalence rates in the specific tissue donor population stratified by gender and age groups.	No differentiation between HTLV -I and HTLV-II.
O'Brien F, et al. 2009. Vox Sanguinis. 97; 37	Human T lymphotropic virus in Canadian blood donors	Epidemiolog -ical study; Cross sectional analysis	North America/ Canada	Blood donors/ all donations since 1990	Prevalence rate of HTLV-I/II: 0.0009%	This study includes all the blood donors in Canadian since 1990. A case-control study used to assess association between risk factors and HTLV positivity.	Only 50% (18/36) of the HTLV positive blood donors participated in the case-control study. No differentiation between subtypes.
Chiavetta JA, et al., 2003. CMAJ. 169; 8: 767-73	Incidence and estimated rates of residual risk for HIV, hepatitis C, hepatitis B and human T-cell lymphotropic viruses in blood donors in Canada, 1990-2000	Epidemiolog -ical and modelling study	North America/ Canada	Blood donors/2.1 million June 1990 and December 2000	Prevalence rate of HTLV-I/II: 0.00177%	Prevalence rate reported for a large study population.	No differentiation between subtypes.
Murphy EL, Watanabe K, et al. (1999). J Infect Dis 180(6): 1777-1783.	"Evidence among blood donors for a 30-year-old epidemic of human T lymphotropic virus type II infection in the United States."	Epidemiolog -ical study; Cross sectional analysis	USA – five blood centres 1991–1995.	1.7 million blood donors	Prevalence rates of HTLV-I: 0.01% HTLV-II:0.02% Significantly higher prevalence rates in: - female donors, - black donors - Hispanic donors - those with only high-school or lower education. Major risk factors among US donors: -history of injecting drug user, -sex with an injecting drug users, -history of blood transfusion;	Large study involving 1.7 million subjects from five different blood centres across the US. HTLV sub-type specific data reported.	Low-representativeness of blood donors for the general population due to self-selection and deferral. Differential deferral of subgroups could bias some demographic characteristics, such as women being overrepresented due to deferral of injecting drug users (mostly men).

Citation	Title	Type of study	Area covered	Population/ sample size	Outcome	Strengths	Limitations
Eble BE, Busch MP, et al. (1993). J Infect Dis 167(4): 954-957.	"Determination of human T lymphotropic virus type by polymerase chain reaction and correlation with risk factors in northern California blood donors."	Epidemiological study. Cross sectional analysis	Northern California	67/122 517 Blood donors	Prevalence rate of HTLV-I/II: 0.055% Characteristics of seropositive blood donors: - middle-aged, - female, and - non-white Risk factors HTLV-I: - ancestry , sexual contact, or paternal military service in Japan or the Caribbean; Risk factors HTLV-II: - past intravenous drug abuse or sex with a drug user; - a dentist Risk factors HTLV-I/II: -previous blood transfusions	HTLV prevalence data reported for a large study population. PCR used to differentiate between HTLV types. Risk factors presented for each of the HTLV types.	Donor population will underestimate the prevalence due to self-selection bias and donor screening. Blood donors are adults (>30 years) only. Epidemiological analysis describes 50% (30/60) of the HTLV positive donors.
Canavaggio M, Leckie G, Allain JP, et al./Abbott Laboratories, North Chicago, Illinois. Transfusion. 1990 Nov-Dec; 30(9):780-2.	"The prevalence of antibody to HTLV-I/II in United States plasma donors and in United States and French hemophiliacs."	Epidemiological study; Cross sectional analysis	Five regions of USA, 1988	19/6 286 plasma donors	Prevalence rate of HTLV-I/II: 0.3% Seroprevalence is 10 times higher in plasma donors compared to whole blood donors. HTLV-I/II higher rates in: -blacks (0.74%) -Hispanics (0.66%) (vs. whites 0.08%). -aged 30 years or older.	A multicentre study involving five regions of the US. HTLV prevalence rate in plasma donors compared with the HTLV prevalence rate in blood donors.	The serological test did not differentiate between HTLV-I and II. Plasma donor population had different demographic characteristics to the general population. Imbalanced ethnic distribution.

Europe

Citation	Title	Type of study	Area covered	Population/ sample size	Outcome	Strengths	Limitations
Laperche S, et al. 2009. Vox Sang. 96; 2: 104-10	Blood safety strategies for human T-cell lymphotropic virus in Europe	Review	Europe	Blood donors in Europe 2003–2008 (23 countries)	Two regions of prevalence + one outlying region identified in Europe: Scandinavia and Ireland (0 to 0.17/10 000) France, the Netherlands and	Comprehensive data from reporting countries. Large dataset.	Lack of general population representative data. Non-reporting countries.
Taylor GP, et al. 2005. JAIDS Journal of Acquired Immune Deficiency Syndromes. 38; 1: 104-09	The Seroepidemiology of Human T-Lymphotropic Viruses: Types I and II in Europe: A Prospective Study of Pregnant Women	Multicentre prospective cross-sectional epidemiological study	Selected EU countries: Belgium, France, Germany, Italy, Portugal, Spain, and UK	234 078 Pregnant women	Six-fold higher prevalence among pregnant women (4.4/10 000) than among blood donors (0.07/10 000)	Comparison of blood-donors and pregnant women. Separate estimates for HTLV-I and II.	Lack of general population representative data. Selected subset of countries in Europe. Indirect detection of maternal Ab in infant blood.
Taylor GP and H.E.R.N. 1999 .	The Epidemiology and Clinical Impact of HTLV Infections in	Review	Europe	Various populations	0.2–0.12/10 000	Review of existing data. Specialised network for	Lack of general population representative data.
Pecec M and Necula N 2010. Vox Sanguinis. 99; 304	Retroviruses (HIV-1/HIV-2, HTLV-I/HTLV-II) during 2000–2009: Residual risks	Epidemiological study	Romania	Blood donors	HTLV-I infection may be endemic in Romania. First-time blood donors prevalence 5/10 0000. In Bucharest 15.2/10 000. Incidence 0.1/10 000 in repeat blood donors.	Comprehensive data from 10 years of surveillance. Large dataset.	Lack of general population representative data. Selected population. Identifies need for better donor selection criteria.
Veelken H, et al. 1996. Leukemia. 10; 8: 1366-9	HTLV-I-associated adult T cell leukemia/lymphoma in two patients from Bucharest, Romania	Case study	Romania	n/a	Suggested Romania as endemic area for HTLV-I in Europe	Initial observation	Small dataset
Trevino A, et al. 2009. AIDS Res Hum Retroviruses. 25; 6: 551-4	Seroprevalence of HTLV-1/2 infection among native and immigrant pregnant women in Spain	Cross-sectional epidemiological study	Spain	20 518 pregnant women; 18 266 native Spaniards and 946 immigrants from HTLV-1 endemic areas (Central and South America and sub-Saharan Africa)	Overall prevalence 0.019/10 000. Immigrant prevalence 20.1/10 000.	Relatively large dataset	Small dataset for immigrants
Davison KL et al. 2009. Transfus Med. 19; 1: 24-34	The introduction of anti-HTLV testing of blood donations and the risk of transfusion-transmitted HTLV, UK: 2002–2006.	Epidemiological study	UK	Blood donors	Prevalence for first-time donors 0.4/10 000 and 0.042/10 000 for repeat donors	Separate estimates for HTLV-I and II. Trend data available.	Lack of general population representative data. Selected population.
Galea, G. and Dow, B. C., 2006. Vox Sanguinis. 91; 1: 28-33	Comparison of prevalence rates of microbiological markers between bone/tissue donations and new blood donors in Scotland	Retrospective epidemiological study/register study	UK, Scotland	Blood donors and bone/tissue donors	11-fold higher prevalence among bone/tissue donors compared to first-time blood donors	Comprehensive evaluation of registered data	

Other regions

NOTE: this section is mainly shown as a selected demonstration of data available outside of Europe and North America and is NOT intended to represent the entire or most significant evidence base.

Citation	Title	Type of study	Area covered	Population/ sample size	Outcome (prevalence, %)
Omilabu S, et al. 2010. Archives of Gynecology and Obstetrics. 282; S154	Seroprevalence of HTLV infection in a pre-pregnancy class group in Lagos	Epidemiological study; Cross sectional analysis	Africa/Nigeria Lagos	Pregnant women/252	0.79
Etenna SL, et al. 2008. J Clin Microbiol. 46; 11: 3607-14	New insights into prevalence, genetic diversity, and proviral load of human T-cell leukemia virus types 1 and 2 in pregnant women in Gabon in equatorial central Africa	Epidemiological study; Cross sectional analysis	Africa/Gabon	Pregnant women/907	2.1
Collenberg E, et al., 2006. J Med Virol. 78; 5: 683-92	Seroprevalence of six different viruses among pregnant women and blood donors in rural and urban Burkina Faso: A comparative analysis	Epidemiological study; Cross sectional analysis	Africa/Burkina Faso	Blood donors, Pregnant women/683	1.4/0.5
Apea-Kubi KA, et al. 2006. West Afr J Med. 25; 1: 17-21	HTLV-1 and other viral sexually transmitted infections in antenatal and gynaecological patients in Ghana	Epidemiological study; Cross sectional analysis	Africa/Ghana	Pregnant women/517	2.7
Armah HB, et al. 2006. J Med Microbiol. 55; Pt 6: 765-70	Seroprevalence of human T-cell lymphotropic virus type I among pregnant women in Accra, Ghana	Epidemiological study; Cross sectional analysis	Africa/Ghana Accra	Pregnant women/960	2.1
Pouliquen JF, et al. 2004. J Clin Microbiol. 42; 5: 2020-6	High seroprevalence of human T-cell lymphotropic virus type 1 in blood donors in Guyana and molecular and phylogenetic analysis of new strains in the Guyana shelf (Guyana, Suriname, and French Guiana)	Epidemiological study; Cross sectional analysis	Africa/Guyana	Blood donors/?	1.3
Candotti D, et al. 2001. J Med Virol. 65; 1: 1-5	Serological and molecular screening for viruses in blood donors from Ntcheu, Malawi: high prevalence of HIV-1 subtype C and of markers of hepatitis B and C viruses	Epidemiological study; Cross sectional analysis	Africa/Malawi	Blood donors/159	2.4
Larsen O, et al. 2000. J Acquir Immune Defic Syndr. 25; 2: 157-63	Prevalence of HTLV-1 infection and associated risk determinants in an urban population in Guinea-Bissau, West Africa	Epidemiological study; Cross sectional analysis, risk factor analysis	Africa/Guinea Bissau	Population based survey/2 127	3.6
Kwon SY, et al. 2008. J Med Virol. 80; 10: 1864-7	Seroprevalence of human T-lymphotropic virus type 1 and 2 in Korean blood donors	Epidemiological study; Cross sectional analysis	Asia/Korea	Blood donors/15 173	0.007
Kumar H and Gupta PK, 2006. Indian J Pathol Microbiol. 49; 4: 532-4	Is seroprevalence of HTLV-I/II among blood donors in India relevant?	Epidemiological study; Cross sectional analysis	Asia/India	Blood donors/10 000	0.14
Lu SC, et al. 2001. Int J Hematol. 74; 3: 333-7	Seroprevalence and demographic characteristics of HTLV-I among blood donors in Taiwan: 1996-1999	Epidemiological study; Cross sectional analysis	Asia/Taiwan	Blood donors/3 701 087	0.058
Koga Y, Iwanaga M, et al. (2010). J Med Virol **82**(4): 668-674	Trends in HTLV-1 prevalence and incidence of adult T-cell leukemia/lymphoma in Nagasaki, Japan	Epidemiological study;	Asia/Japan	Hospital-based survey	Estimated number of HTLV-1 carriers in Nagasaki City: 36 983 (approx. 8.2% prevalence)
Tanggo Y, et al. 2000. Intervirology. 43; 2: 77-9	Human T lymphotropic virus I in Indonesia. Very low seroprevalence in the Jakarta area: antibodies in healthy blood donors and in various non-	Epidemiological study; Cross sectional analysis	Asia/West Indonesia	127 healthy persons around Jakarta, 451 patients with various non-hematological diseases and 79	0

Citation	Title	Type of study	Area covered	Population/ sample size	Outcome (prevalence, %)
	hematological diseases			blood donors/657	
Arjmand B, et al. 2009. Cell Tissue Bank. 10; 3: 247-52	Seroprevalence of human T lymphtropic virus (HTLV) among tissue donors in Iranian tissue bank	Epidemiological study; Cross sectional analysis	Middle East/Iran	Tissue donors/1 548	1.61
Stienlauf S, et al. 2009. Emerg Infect Dis. 15; 7: 1116-8	Epidemiology of human T-cell lymphotropic virus type 1 infection in blood donors, Israel	Epidemiological study; Cross sectional analysis	Middle East/Israel	Blood donors/?	1/100 000
Al-Mufti S, et al. 1999. Medical Principles and Practice. 8; 1: 45-50	Seroprevalence of human T-cell leukemia/lymphoma virus type I and type II (HTLV-I/HTLV-II) infection among volunteer blood donors in Kuwait	Epidemiological study; Cross sectional analysis	Middle East/Kuwait	Blood donors/97 602	(21 persons)
Arif M and Ramia S, 1998. Ann Trop Med Parasitol. 92; 3: 305-9	Seroprevalence of human T-lymphotropic virus type I (HTLV-I) in Saudi Arabia	Epidemiological study; Cross sectional analysis	Middle East/Saudi Arabia	Blood donors/34 541	(3 persons)
Malan R, et al. 2010. Medicina (B Aires). 70; 1: 71-4	[Seroprevalence of HTLV-1/2 in blood donors from Misiones Province]	Epidemiological study; Cross sectional analysis	South America/Argentina Misiones province	Blood donors/6 912	0.072
Carneiro-Proietti AB, et al. 2010. Transfusion. 50; 207A	HTLV-1/2 prevalence in Brazilian blood donors: Regional and demographic variation	Epidemiological study; Cross sectional analysis, risk factor analysis	South America/Brazil	Blood donors/281 760	0.129
Chandia L, et al. 2010. Medical Microbiology and Immunology. 199; 4: 341-44	Seroprevalence of human T-cell lymphotropic virus type 1 and 2 in blood donors from the regional hospital of Valdivia, Chile	Epidemiological study; Cross sectional analysis	South America/Chile, Valdivia	Blood donors/6 237	0.24
Berini C, et al. 2009. AIDS Research and Human Retroviruses. 25; 11: 1281	Prevalence of HTLV-1/2 and other mandatory detections in a public setting of Buenos Aires, Argentina from 2003 to 2008	Epidemiological study; Cross sectional analysis	South America/Argentina Buenos Aires	Blood donors/23 483	0.09
Berini C, et al. 2009. AIDS Research and Human Retroviruses. 25; 11: 1284	Seroprevalence of HTLV-1/2 in blood donors from Misiones Province, Argentina	Epidemiological study; Cross sectional analysis	South America/Argentina Misiones province	Blood donors/6 912	0.09%
Gallego S, et al. 2001. Rev Argent Microbiol. 33; 3: 182-6	[HTLV-I/II seroprevalence and risk factors associated with infection in a blood donor population in Cordoba, Argentina]	Epidemiological study; Cross sectional analysis, risk factor analysis	South America/Argentina	Blood donors/5 476	0.26
Figueiro-Filho E, et al. 2009. International Journal of Gynecology and Obstetrics. 107; S181-S82	Human T-cell lymphotropic virus (HTLV) infection in Brazilian pregnant women	Epidemiological study; Cross sectional analysis	South America/Brazil	Pregnant women/32 512	0.1
Trenchi A, et al. 2007. Journal of Medical Virology. 79; 12: 1974-78	Retrospective study of the prevalence of human T-cell lymphotropic virus-type 1/2, HIV, and HBV in pregnant women in Argentina	Epidemiological study; Cross sectional analysis	South America/Argentina	Pregnant women/3 143	0.191
Alarcon JO, et al. 2006. J Acquir Immune Defic Syndr. 42; 5: 604-9	High endemicity of human T-cell lymphotropic virus type 1 among pregnant women in Peru	Epidemiological study; Cross sectional analysis	South America/Peru	Pregnant women/2 492	1.7

Citation	Title	Type of study	Area covered	Population/ sample size	Outcome (prevalence, %)
Catalan-Soares B, et al. 2005. Cad Saude Publica. 21; 3: 926-31	Heterogeneous geographic distribution of human T-cell lymphotropic viruses I and II (HTLV-I/II): serological screening prevalence rates in blood donors from large urban areas in Brazil	Epidemiological study; Cross sectional analysis	South America/Brazil	Blood donors/?	0.04–1.0
Tortevoye P, et al. 2005. Am J Trop Med Hyg. 73; 3: 560-5	Comparative trends of seroprevalence and seroincidence rates of human T cell lymphotropic virus type I and human immunodeficiency virus 1 in pregnant women of various ethnic groups sharing the same environment in French Guiana	Epidemiological study; Cross sectional analysis , risk factor and trend analysis	South America/French Guyana	Pregnant women/6 921	Noir-Marron (of African origin) 4.24% (181 of 4 266). Haitian women 4.18% (12 of 287)
Gastaldello R, et al. 2004. J Acquir Immune Defic Syndr. 35; 3: 301-8	Seroepidemiology of HTLV-I/II in Argentina: an overview	Review	South America/Argentina	Blood donors/?	1-0.1
Carles G, et al. 2004. J Gynecol Obstet Biol Reprod (Paris). 33; 1 Pt 1: 14-20	[HTLV1 infection and pregnancy]	Epidemiological study; Cross sectional analysis, risk factor analysis	South America/French Guyana	Pregnant women/1 727	4.4
Dourado I, et al. 2003. J Acquir Immune Defic Syndr. 34; 5: 527-31	HTLV-I in the general population of Salvador, Brazil: a city with African ethnic and sociodemographic characteristics	Epidemiological study; Cross sectional analysis	South America/Brazil, Salvador	Population based survey/1 385	1.76
Sanchez-Palacios C, et al. 2003. Int J Infect Dis. 7; 2: 132-7	Seroprevalence and risk factors for human T-cell lymphotropic virus (HTLV-I) infection among ethnically and geographically diverse Peruvian women	Epidemiological study; Cross sectional analysis, risk factor analysis	South America/Peru	Women/568	2.5

Annex 3. Current testing requirements in Europe for tissue donation

Extract from relevant sections of EU COMMISSION DIRECTIVE 2006/17/EC dated 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

[Preamble]

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(2) In order to prevent the transmission of diseases by human tissues and cells for human applications and to ensure an equivalent level of quality and safety, Directive 2004/23/EC calls for the establishment of specific technical requirements for each one of the steps in the human tissue and cell application process.

(3) The use of tissues and cells for application in the human body carries a risk of disease transmission and other potential adverse effects in recipients. That risk can be reduced by careful donor selection, testing of each donation and the application of procedures to procure tissues and cells in accordance with rules and processes established and updated according to the best available scientific advice. Therefore, all tissues and cells, including those used as starting material for the manufacture of medicinal products to be used in the Community, should meet the quality and safety requirements laid down in this Directive.

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ANNEX I: SELECTION CRITERIA FOR DONORS OF TISSUES AND/OR CELLS (EXCEPT DONORS OF REPRODUCTIVE CELLS) AS REFERRED TO IN ARTICLE 3(a)

Selection criteria for donors are based on an analysis of the risks related to the application of the specific cells/tissues. Indicators of these risks must be identified by physical examination, review of the medical and behavioural history, biological testing, post-mortem examination (for deceased donors) and any other appropriate investigation. Unless justified on the basis of a documented risk assessment approved by the responsible person as defined in Article 17 of Directive 2004/23/EC, donors must be excluded from donation if any of the following criteria applies:

1. Deceased Donors

1.1. *General criteria for exclusion*

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1.1.3. Presence, or previous history, of malignant disease, except for primary basal cell carcinoma, carcinoma in situ of the uterine cervix, and some primary tumours of the central nervous system that have to be evaluated according to scientific evidence. Donors with malignant diseases can be evaluated and considered for cornea donation, except for those with retinoblastoma, *haematological neoplasm*, and malignant tumours of the anterior segment of the eye.

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1.1.5. Systemic infection which is not controlled at the time of donation, including bacterial diseases, *systemic viral*, fungal or parasitic infections, or significant local infection in the tissues and cells to be donated. Donors with bacterial septicaemia may be evaluated and considered for eye donation but only where the corneas are to be stored by organ culture to allow detection of any bacterial contamination of the tissue.

1.1.6. History, clinical evidence, or laboratory evidence of HIV, acute or chronic hepatitis B (except in the case of persons with a proven immune status), hepatitis C and HTLV I/II, transmission risk or evidence of risk factors for these infections.

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1.1.9. Evidence of any other risk factors for transmissible diseases on the basis of a risk assessment, taking into consideration donor travel, exposure history and local infectious disease prevalence.

1.1.10. Presence on the donor's body of physical signs implying a risk of transmissible disease(s) as described in Annex IV, point 1.2.3.

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1.2. Additional exclusion criteria for deceased child donors

1.2.1. Any children born to mothers with HIV infection or that meet any of the exclusion criteria described in section 1.1 must be excluded as donors until the risk of transmission of infection can be definitely ruled out.

(a) Children aged less than 18 months born from mothers with HIV, hepatitis B, hepatitis C or HTLV infection, or at risk of such infection, and who have been breastfed by their mothers during the previous 12 months, cannot be considered as donors regardless of the results of the analytical tests.

(b) Children of mothers with HIV, hepatitis B, hepatitis C or HTLV infection, or at risk of such infection, and who have not been breastfed by their mothers during the previous 12 months and for whom analytical tests, physical examinations, and reviews of medical records do not provide evidence of HIV, hepatitis B, hepatitis C or HTLV infection, can be accepted as donors.

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2. Living donors

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2.2. Allogeneic living donors

2.2.1. Allogeneic living donors must be selected on the basis of their health and medical history, provided on a questionnaire and through an interview performed by a qualified and trained healthcare professional with the donor, in compliance with point 2.2.2. This assessment must include relevant factors that may assist in identifying and screening out persons whose donation could present a health risk to others, such as the possibility of transmitting diseases or health risks to themselves. For any donation, the collection process must not interfere with or compromise the health or care of the donor. In the case of cord blood or amniotic membrane donation, this applies to both mother and baby.

2.2.2. Selection criteria for allogeneic living donors must be established and documented by the tissue establishment (and the transplanting clinician in the case of direct distribution to the recipient), based on the specific tissue or cells to be donated, together with the donor's physical status and medical and behavioural history and the results of clinical investigations and laboratory tests establishing the donor's state of health.

2.2.3. The same exclusion criteria must be applied as for deceased donors with the exception of point 1.1.1. [ECDC comment: NOTE, para-truncated]

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ANNEX II: LABORATORY TESTS REQUIRED FOR DONORS (EXCEPT DONORS OF REPRODUCTIVE CELLS) AS REFERRED TO IN ARTICLE 4(1)

1. Biological tests required for donors

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1.2. HTLV-I antibody testing must be performed for donors living in, or originating from, high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas.

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2. General requirements to be met for determining biological markers

2.1. The tests must be carried out by a qualified laboratory, authorised as a testing centre by the competent authority in the Member State, using EC-marked testing kits where appropriate. The type of test used must be validated for the purpose in accordance with current scientific knowledge.

2.2. The biological tests will be carried out on the donor's serum or plasma; they must not be performed on other fluids or secretions such as the aqueous or vitreous humour unless specifically justified clinically using a validated test for such a fluid.

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2.4. In the case of a deceased donor, blood samples must have been obtained just prior to death or, if not possible, the time of sampling must be as soon as possible after death and in any case within 24 hours after death.

2.5. (a) In the case of living donors (except allogeneic bone marrow stem-cell and peripheral blood stem-cell donors, for practical reasons), blood samples must be obtained at the time of donation or, if not possible, within seven days post donation (this is the 'donation sample').

(b) Where tissues and cells of allogeneic living donors can be stored for long periods, repeat sampling and testing is required after an interval of 180 days. In these circumstances of repeat testing, the donation sample can be taken up to 30 days prior to and 7 days post donation.

(c) Where tissues and cells of allogeneic living donors cannot be stored for long periods and repeat sampling is therefore not possible, point 2(5)(a) above applies.

2.6. If in a living donor (except bone marrow stem-cell and peripheral blood stem-cell donors) the 'donation sample', as defined in point 2(5)(a) above, is additionally tested by the nucleic acid amplification technique (NAT)

for HIV, HBV and HCV, testing of a repeat blood sample is not required. Retesting is also not required if the processing includes an inactivation step that has been validated for the viruses concerned.

2.7. In the case of bone marrow and peripheral blood stem-cell collection, blood samples must be taken for testing within 30 days prior to donation.

2.8. In the case of neonatal donors, the biological tests may be carried out on the donor's mother to avoid medically unnecessary procedures upon the infant.

ANNEX IV: CELL AND/OR TISSUE DONATION AND PROCUREMENT PROCEDURES AND RECEPTION AT THE TISSUE ESTABLISHMENT, AS REFERRED TO IN ARTICLE 5

1. Donation and procurement procedures

1.2. Donor evaluation (this section does not apply to partner donation of reproductive cells or to autologous donors).

1.2.1. An authorised person must collect and record the donor's relevant medical and behavioural information according to the requirements described in section 1.4.

1.2.2. In order to acquire the appropriate information, different relevant sources must be used, including at least an interview with the donor, for living donors, and the following when appropriate:

(a) the medical records of the donor;

(b) an interview with a person who knew the donor well, for deceased donors;

(c) an interview with the treating physician;

(d) an interview with the general practitioner;

(e) the autopsy report.

1.2.3. In addition, in the case of a deceased donor, and in the case of a living donor when justified, a physical examination of the body must be performed to detect any signs that may be sufficient in themselves to exclude the donor or which must be assessed in the light of the donor's medical and personal history.

1.2.4. The complete donor records must be reviewed and assessed for suitability and signed by a qualified health professional

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1.4. Donor documentation

1.4.1. For each donor, there must be a record containing:

(a) the donor identification (first name, family name and date of birth — if a mother and child are involved in the donation, both the name and date of birth of the mother and the name, if known, and date of birth of the child);

(b) age, sex, medical and behavioural history (the information collected must be sufficient to allow application of the exclusion criteria, where required);

(c) outcome of body examination, where applicable;

(d) haemodilution formula, where applicable;

(e) the consent/authorisation form, where applicable;

(f) clinical data, laboratory test results, and the results of other tests carried out;

(g) if an autopsy was performed, the results must be included in the record (for tissues and cells that cannot be stored for extended periods, a preliminary verbal report of the autopsy must be recorded);

(h) for haematopoietic progenitor cell donors, the donor's suitability for the chosen recipient must be documented. For unrelated donations, when the organisation responsible for procurement has limited access to recipient data, the transplanting organisation must be provided with donor data relevant for confirming suitability.