Options for Human T-Lymphotropic Virus (HTLV) screening within the UK Blood Services

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Prepared by the
UK BTS Joint Professional Advisory Committee's (JPAC)
HTLV Working Group

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Update information – 6 October 2015

Subsequent to the SaBTO meeting of 1st September 2015, the cost-effectiveness analysis reported in Section 10 of the "Options for Human T-Lymphotropic Virus (HTLV) screening within the UK Blood Services" paper (item 5) has been updated to incorporate members' requests:

1. A new column have been added to table 10.2 giving the chance of a TTI in terms of the number of issues, e.g. 1 TTI per x issues, and similarly a new column has been added to table 10.5 for the chance of associated disease (requested by Dr Lorna Williamson).

2. An additional section covering the rates of vertical and sexual transmission of HTLV from TTI infected individuals has been added to the results section (requested by Professor Richard Tedder).

In addition to these requested updates, better estimates have been implemented for the number of infected and tested issues, and a minor error in the QALY calculation corrected. While this has impacted some of the more extreme values reported, the relative relationships and conclusions of the original report remain the same.

1. Executive Summary

1.1 HTLV screening has been performed on all donations in the UK since 2002 following an instruction from MSBT to perform it using pooled screening, deemed to be cost-effective at that time as pools were being produced for NAT screening. Since then the UK Blood Services have moved to Managed Service Contracts for testing which incorporates individual (ID) testing in two of the services, with the other two due to move to this in 2016 and 2017.

1.2 Transmission of HTLV by blood transfusion requires cell-cell interaction of white cells; the transmission risk is therefore significantly reduced by universal leucodepletion of blood components (LD). The low risk has been demonstrated by a clinical lookback study which found only one infected recipient out of 81 who received leucodepleted components originating from donors later found positive for HTLV infection – the one infected recipient had other risk factors for HTLV infection.

1.3 There is an HTLV prevalence of 5.2 per 100,000 new donors in the UK. Donors confirmed HTLV positive are resigned and referred for clinical follow-up. Seroconversion has been noted but rarely – in 10 years of testing 7 donors were found to have seroconverted.

1.4 HTLV is more prevalent in certain areas of the world, such as the Americas, Africa, the Caribbean and native populations of Australia and the South West Pacific. Most infected people have asymptomatic carriage and do not develop any associated disease. About 5%, however, will develop adult T-cell leukaemia/lymphoma (ATLL) and 3% HTLV-I-associated myelopathy (HAM), both after many years of being infected (average of 25 years for ATLL and 10 years for HAM).

1.5 Options considered for future HTLV testing strategy were to continue screening as currently, to stop screening altogether, or to selectively screen non-LD components +/- new donors. No consistent pattern of testing is seen internationally - in Europe a survey in 2012 found that out of 28 countries responding, 19 do no testing, 5 test all donations, 3 test first time donors only, and 1 tests 30% of donations: different policies in different regions within the country.

1.6 The risk of HTLV transmission for each option under consideration, calculated from HTLV donor prevalence and risk of LD failure and assuming 100% effectiveness from successful leucodepletion, is 1 per year for no screening, 1 in 8 years for screening non-LD components only, 1 in 98 years for screening new donors and non-LD donations only, and 1 in 725 years for screening all donations. It is to be noted that there are approximately 2 million components issued each year and the chance of developing a disease associated with the infection are, at most, 1 in 10. When the worst case scenario is considered, in which LD is not assumed to be 100% effective and the upper limit of possible prevalence is used, one transmission might be

expected in less than one year for no screening and non-LD components only, 1 per year for new donors and non-LD only, and 1 in 22 years for 100% screening.

1.7 Cost-effectiveness analysis shows that the most cost-effective option, compared with no screening, would be to screen non-leucodepleted components only (cost per QALY £36,000), followed by screening new donors and non-leucodepleted (£194,000). The corresponding figure for screening all donations as currently is £629,000. Limiting testing to new donors and non-LD donations only would give a saving to the UK Blood Services of £774,000 p.a; limiting to non-LD components only would save £1,056,000 p.a.

2. Recommendations

2.1 A change from universal HTLV screening of all donations to HTLV screening of new donors and non-LD donations only be permitted on the basis that:

- universal screening is not cost-effective
- all donors will be screened at least once at the time of first donation and the seroconversion rate has been shown to be very low
- additional safety in the rare event that seroconversion has occurred in an established donor will be provided by:
  - leucodepletion, which has been shown to be very effective in preventing transmission
  - screening of non-LD components, which remain high risk products.

It is recognised that change from the current strategy of universal to selective screening may incur additional expense for blood services – this may be one-off such as performing changes to IT systems, or recurrent such as increased staffing to manage the selection process. Costs provided are estimates and cost benefits may vary according to the detail of the Managed Service Contract. Each Blood Service, therefore, should perform their own cost-benefit analysis of this recommendation taking into account operational and financial considerations.

2.2 This recommendation be reviewed after 3 years to consider whether screening new donors can be removed, retaining screening for non-LD components only. Additional considerations at that time will include:

- whether there is any change to efficacy of the LD process
- any further evidence that LD is a sufficiently effective safety measure
- continuing surveillance on HTLV prevalence in new donors and seroconversion rates.

3. Background and Remit

The Joint Executive Liaison Committee (JELC, the predecessor of JPAC) first presented a report to the Department of Health Advisory Committee on the Microbiological Safety of Blood and Tissues (MSBT) on options for testing blood donations for HTLV in 1996. Following a cost-effectiveness review, testing was not recommended at that time. A further recommendation

from SACTTI / JPAC in 2000 was, however, supported. The UK blood services began screening of all blood donations for anti-HTLV 1 & 2 during the summer of 2002. The rationale for testing was based on:

- evidence of transmission via transfusion in the UK[1]
- the serious nature of HTLV I associated morbidity[2] and
- evidence of infection in UK blood donors[3-5]

The decision to commence screening was not endorsed, however, until a cost-efficient method became available. That method was to use the pools of samples prepared for pooled NAT, and to perform anti-HTLV screening on the residual pooled material after NAT had been performed. As the pools had already been produced for NAT there was no additional cost for the preparation of the pools, and the cost of screening was minimised by a reduction in the number of tests used. The risks of such pooled screening were considered minimal, and validation of the methodology identified a single assay deemed to be suitable for pooled screening, that assay demonstrating high efficiency for the detection of HTLV 1 positive samples, although a lower efficiency for HTLV 2 positive samples.

The recommendation from SACTTI in 2000 (JELC Enc. 01/21) to screen all donations for evidence of HTLV infection included a recommendation that the situation should be reviewed after a period of time (suggested 2 to 3 years) so that information about seroconversions/ new infections in previously screened donors could be accumulated. That information would be relevant to any decision to continue with HTLV screening of all donations, to change to screening only previously unscreened donors, or to some other modification of the screening regime. That review was submitted to JPAC in 2008 (JPAC 08-42), when it was noted that only one HTLV seroconversion had been observed during the period of HTLV screening within the UK blood services.

At the time of the last report to JPAC in 2008, SNBTS, which also performed NAT and HTLV screening for the NIBTS, performed NAT screening on pools of 96 samples but prepared a separate pool of 48 for HTLV screening whereas NHSBT and WBS used the same 48 sample pools for both NAT and HTLV screening.

The 2008 paper also noted that a change in the HTLV screening procedure might become necessary for reasons other than consideration of documented seroconversions. For instance, a change to the NAT screening procedure, so that pools are no longer prepared or are prepared from smaller numbers of samples, would change the cost-effectiveness of HTLV screening. SACTTI therefore recommended in 2008 that the UK blood services should continue with Option 1 (pooled screening of all donations), and consider Option 2 (single sample screening of all previously unscreened donations) as the fall-back position if pool preparation ceased in the

future. At that point, further investigation of costs would be necessary, to ascertain whether Option 2 would constitute a cost-effective method for the HTLV screening of blood donations.

In 2009 one UK Blood Service (NHSBT) changed its molecular screening to the Roche MPX assay run on the Roche s201 automated system; the other UK Blood Services subsequently also moved to the Roche MPX system. Not only was the pool size reduced to 24 samples, but the system produced pools of just 1.2ml of which 1ml was used by the s201 system for the molecular screen, the pooling tube then being automatically discarded by the system. The Blood Services therefore had to prepare a separate second pool of the same 24 samples for the HTLV screening. Thus the cost efficiency of using the same pool for both molecular and HTLV screening was lost, although pooled screening could still be performed.

Since then, the move to Managed Service Contracts for serological screening within NHSBT, SNBTS and WBS has changed the decision-making process at the operational level; NIBTS are due to move to Managed Service Contracts in 2016. As part of the response to the NHSBT serological screening tender the successful bidder proposed moving the anti-HTLV screening from pooled testing using a microplate assay to individual testing on their fully automated platform. Although such an approach increases the number of individual tests performed, it becomes a cost effective solution as such Managed Service Agreements ensure competitive and attractive pricing for an inclusive package. At the beginning of 2013 NHSBT therefore ceased pooled anti-HTLV screening and moved to ID screening, with SNBTS following suit in March 2015. The WBS and NIBTS continue to perform anti-HTLV screening in pools, but NIBTS will cease pooling in 2016 and WBS in 2017.

Analysis of the outcomes of HTLV screening within the UK Blood Services, taking into account documented seroconversions and newer information about the low risk of HTLV transmission through the transfusion of HTLV positive leucodepleted blood components, has allowed questions to be raised as to the continued need for the HTLV screening of blood donations within the UK. There is no evidence of viraemia during HTLV infection in the absence of specific antibody, nor of a free viraemia at any time, the virus being totally cell associated. This paper has been prepared to identify and review the currently available anti-HTLV screening options for the UK Blood Services.

4. HTLV Natural History / Pathogenesis (Adapted from [6])

HTLV-I is a very old virus, which appears to have infected and moved with mankind for hundreds, perhaps thousands, of years. It is thought to have migrated during ancient times with Native American Indians in North and South America, with Australian aborigines and the Melanesian people of the South West Pacific, and to Japan. During the last few centuries it has migrated from Africa to the Caribbean and again to North and South America. In some areas

more than 1% of the population carry the virus. The same rates of infection are seen in populations wherever they migrate. In Europe, HTLV-I is mainly found among people who have originated from these endemic areas.

Most people infected with HTLV-I have asymptomatic carriage: they are completely unaware of the infection and have no signs or symptoms. It is estimated that in the UK 22,000 people are infected with HTLV-I, but less than 1000 are aware of the infection.

The vast majority of persons infected with HTLV-I do not develop any associated disease. A small minority, about 1 person in 20, will develop disease but usually only after several decades of infection. There are two main diseases caused by HTLV-I:

4.1 **Adult T-cell Leukaemia/Lymphoma (ATLL)**: quoted as up to 5% (2 to 4%) life-time risk in those infected with HTLV, but this data is mainly derived from outside the UK, and ATLL is currently seen in less than 20 patients per year in the UK. It is most likely in those infected in very early life, and is unlikely to develop following infection acquired in adult-life. It is usually treated with chemotherapy, but anti-viral therapy has also been tried. Bone marrow transplantation is considered for patients in remission with ATLL. However, prognosis is poor, and the median survival is 13 months[7].

4.2 **HTLV-I-associated myelopathy (HAM)**: a slightly lower life-time risk (up to 3%) than ATLL; about 10 persons/ year are diagnosed with HAM in the UK. Evidence is emerging that the immune system is important in controlling HTLV infection. HAM is associated with higher viral loads. Typically, HAM causes spasticity of the legs, backache, a 'weak' bladder and constipation, due to inflammation of nerves in the spinal cord with cellular damage leading to demyelination. Not all of these symptoms may be present, especially at the beginning. The disease often starts slowly and symptoms may be attributed to arthritis or “getting old”. Treatment is symptomatic. The use of anti-inflammatory medications is under investigation. It has been observed that patients who acquire HTLV-I by transfusion are more likely to develop HAM than ATLL, whereas the converse is true for those acquiring the virus during breast-feeding [8].

4.3 **Other HTLV-I-associated diseases**. HTLV-I has also been associated with uveitis, arthritis, myositis, alveolitis and dermatitis. These conditions are even less common than ATLL and HAM and the skin condition is usually only seen in tropical climates.

4.4 **HTLV-I and other infections Strongyloidiasis**: An infection acquired in the tropics can, after lying dormant for years, cause a serious illness in HTLV-I carriers. Although rare in the UK, all HTLV-I carriers who have lived in the tropics should be screened for Strongyloidiasis.

4.5 Prognosis. At present there is no cure for HTLV infection. Since 95% of all infected persons go through life without developing any HTLV-I-associated disease, any intervention aimed at treating the infection before symptomatic disease develops would have to be not only effective but also very safe.

4.6 Effect of immunosuppression. Reports have suggested that there may be more rapid progression of HTLV-I associated disease following organ transplantation – one multi-organ donor transmitted to 3 recipients, 2 of which developed ATLL within 3 years [9]; HAM has also been described within 2 years of transplantation [10,11]. It is not clear, however, whether immunosuppression in circumstances other than organ transplantation increases the risk of development of disease.

4.7 HTLV-II: The distribution of HTLV-II infection is quite distinct from HTLV-I. It is endemic in American Indian populations in North, Central and South America as well as being highly prevalent among injection drug users in North America and Europe. HTLV-II is less pathogenic than HTLV-I and disease associations with HTLV-II infection are less clear, but increasing evidence supports an association with HAM and other neurological abnormalities[12].

5. Epidemiology

5.1 Estimating the risk

The method used in 2008 to estimate the risk (or frequency) that a donation entering the UK blood supply is an HTLV I potentially infectious donation was adapted from that used to estimate the risk for HIV, HCV and HBV originally published by Soldan *et al* [13]. This determines the likelihood that current donation testing strategies do NOT identify an infectious donation under the following circumstances: i) a blood donation is made during the infectious window period (WP) early in the course of infection when the tests in use will not detect the marker of infection, ii) a blood donation tests falsely negative as test sensitivities are less than 100%, or iii) a blood donation is erroneously issued as negative due to a processing error (e.g. a sampling or labelling error, or fault in a reagent or piece of equipment).

The risk estimate for HTLV in 2008 was based upon pooled screening in pools of 48 donations but took no account of any risk-reduction effect of leucodepletion, which was introduced for all UK blood donations in 1998/9.

Since 2008 SACTTI has recommended to JPAC that risk estimates should not be calculated for HTLV as there were serious questions about their validity. Firstly, there is no evidence of a 'conventional' window period for HTLV infection, where a viraemia might exist in the absence of detectable HTLV antibodies with the consequent risk of an infectious, but screen negative, donation. Secondly, there is considerable evidence that leucodepletion of blood components

significantly reduces the risk of HTLV transmission (see section 6.3). HTLV transmission requires cell-to-cell contact, which in this case would be between an infected white cell from the blood component coming into contact with a white cell from the recipient [14]. Leucodepletion is known to significantly reduce the risk of HTLV transmission, although not necessarily abolishing the risk completely [15]. The HTLV lookback results have demonstrated the efficacy of leucodepletion in reducing the risk of HTLV transmission [16].

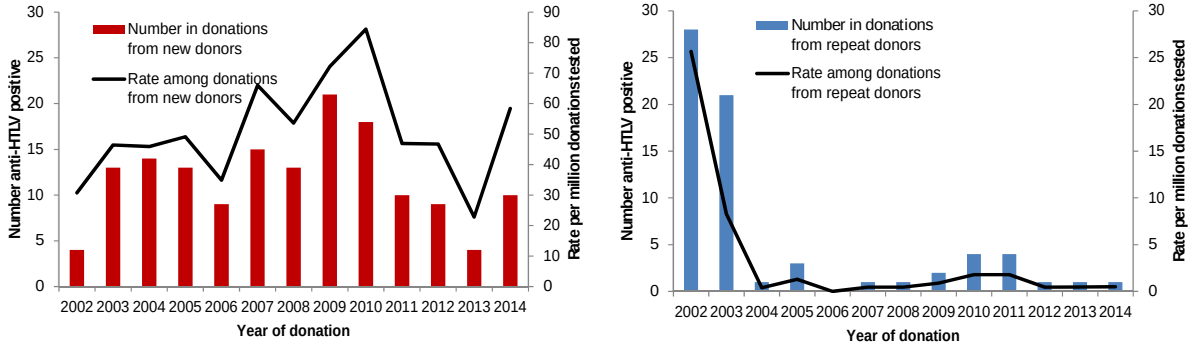
5.2 Frequency of infection in UK donors - Results from NHSBT/PHE Epidemiology surveillance

Between August 2002 and December 2014, the UK blood services screened approximately 31 million blood donations for anti-HTLV and confirmed 220 to be positive (200 HTLV-1 and 20 HTLV-2), i.e. approximately 7.1 per million donations overall. Of the confirmed positives, 211 were among donations tested by NHSBT, five by WBS and four by SNBTS.

The number and prevalence of positives among donations from first time and repeat donors each year since testing began is shown in Figure 1. Among donations from new donors, these had been fluctuating each year around an average of 16 positives and a prevalence of 52 per million donations. The number and prevalence in donations from repeat donors peaked in 2002 and 2003 but fell rapidly in subsequent years as positive donors were excluded from the donor pool and the number previously untested declined. Since 2004, among donations from repeat donors, an average of two positives has been confirmed each year, i.e. 0.8 per million donations tested.

Clinical follow up of infection in repeat donors identified three failures of screening. These were low level anti-HTLV positive donations, where earlier donations had screened negative, probably because of the dilution effect of pooling (see 6.2).

Figure 5.1: The number and rate (per million) of anti-HTLV positive blood donations in the UK made by new and repeat donors, August 2002 to December 2014



The characteristics of the HTLV infected donors identified through routine screening of UK blood donations to the end of 2014 are shown in Table 1. Where known, most were female (74%), of non-white ethnicity (55%) and born in the UK (59%). Generally, infections were

associated with HTLV-1 endemic countries, acquired either through a heterosexual partner or their country of birth, the most significant of which were in the Caribbean region but also included some in West Africa, also Iran, India and Japan. For donors with complete clinical follow up, 58% (118/204) probably acquired their infection through heterosexual sex, 45% (53/118) of whom reported a partner from an endemic country, although just less than half (53/118) of these donors were born in an endemic country and vertical transmission could not be ruled out. A further 24% (49/204) were born in/to a parent from an endemic country and did not report any other risk: moreover, some of these donors were known to have an HTLV infected mother or sibling.

Almost all (206/220) of the positive donations were made by donors previously untested for anti-HTLV by a UK blood centre; 14, however,had previously donated and been tested. Since there is clinical follow up of all infected blood donors and lookback to any of their previous donations, it is generally possible to confirm whether seroconversion has taken place. This was confirmed for seven of the 14 donors; two tested as negative more than 3 years previously and are thus not considered recent seroconverters. Further investigation of the clinical history of four of the donors suggested the screen negative result of the previous donation(s) was most likely explained by a low antibody level not detected because of the dilution effect of pooling. For the remaining donor, despite a confirmed positive anti-HTLV result with the serological findings similar in two separate laboratories, there was no other evidence of HTLV infection in the donor (proviral DNA negative) and the opinion at the specialist clinic was that HTLV infection was unlikely.

Table 5.1: Characteristics and probable exposure history of HTLV infected blood donors in the UK, August 2002 to December 2014

	Newly tested				Previously tested				All: Aug 2002-2014	
Characteristics of infected donors	Male	Female	**Total**	%	Male	Female	**Total**	%	**Total**	**%**
Number	54	152	**206**	*100*	3	11	**14**	*100*	**220**	*100*
Seroconverters (Interdonation interval < 3 years)					1	6	**7**		**7**	
Ethnic group										
White	14	66	**80**	*39*	1	7	**8**	*57*	**88**	*40*
Black-African	5	6	**11**	*5*	1	0	**1**	*7*	**12**	*5*
Black-Caribbean	16	56	**72**	*35*	1	3	**4**	*29*	**76**	*35*
Black other	1	2	**3**	*1*	0	0	**0**	*0*	**3**	*1*
Indian/Pakistani/Bangladeshi	9	3	**12**	*6*	0	1	**1**	*7*	**13**	*6*
Asian other	7	3	**10**	*5*	0	0	**0**	*0*	**10**	*5*
Mixed and other	2	11	**13**	*6*	0	0	**0**	*0*	**13**	*6*
Not known	0	5	**5**	*2*	0	0	**0**	*0*	**5**	*2*
Area of birth										
UK	18	88	**106**	*51*	1	8	**9**	*64*	**115**	*52*
Europe excl UK	0	7	**7**	*3*	0	1	**1**	*7*	**8**	*4*
Africa	5	2	**7**	*3*	1	0	**1**	*7*	**8**	*4*
Asia	16	8	**24**	*12*	0	0	**0**	*0*	**24**	*11*
Latin America and Caribbean	12	33	**45**	*22*	1	2	**3**	*21*	**48**	*22*
North America	0	1	**1**	*0*	0	0	**0**	*0*	**1**	*0*
Australasia	0	1	**1**	*0*	0	0	**0**	*0*	**1**	*0*
Not known	3	12	**15**	*7*	0	0	**0**	*0*	**15**	*7*
Probable exposure category										
Person who injects drugs (PWID)	2	1	**3**	*1*	0	0	**0**	*0*	**3**	*1*
Sex between men (MSM)	1	0	**1**	*0*	0	0	**0**	*0*	**1**	*0*
Sex between men and women	7	49	**56**	*27*	2	7	**9**	*64*	**65**	*30*
Blood/tissue transfer, blood product treatment	2	9	**11**	*5*	0	0	**0**	*0*	**11**	*5*
Blood contact possible (inc piercing)	1	0	**1**	*0*	0	2	**2**	*14*	**3**	*1*
Associated with endemic country and SBMW, partner from endemic country	9	43	**52**	*25*	0	1	**1**	*7*	**53**	*24*
Infection associated with an endemic country	21	28	**49**	*24*	1	0	**1**	*7*	**50**	*23*
No identified exposure despite interview	4	13	**17**	*8*	0	1	**1**	*7*	**18**	*8*
Incomplete follow up	7	9	**16**	*8*	0	0	**0**	*0*	**16**	*7*

Therefore, during the 13 years of testing, seven donors were confirmed to have seroconverted within three years of a negative donation, suggesting a low ongoing transmission rate amongst blood donors; a further two donors had evidence of seroconversion but their previous negative donation was over three years earlier. All seroconverters were infected with HTLV-1 and identified among donations tested by NHSBT. The donors were predominately female (7/9), aged between 23 and 57 years and of white (5), black Caribbean (3) and Indian (1) ethnicity. Their source of infection was probably their heterosexual partner; all but one of whom originated from an endemic country. The average interdonation interval between the anti-HTLV negative and positive donation was 1.35 years and ranged between 0.31 and 4.79 years.

6. Transfusion-transmission of HTLV - possible mitigation steps

No documented transfusion transmission of HTLV has been reported by SHOT since leucodepletion was implemented.

Possible steps to mitigate transfusion transmission are as follows:

6.1 Donor selection

Deferral of potential donors known to have an increased risk of an infectious disease is common practice, for example donors who travel to areas where malaria or Chikungunya virus is endemic. However, studies have shown that it is not easy to identify carriers of HTLV (see 5.2) – although the virus is recognised to be prevalent in some areas of the world (e.g. Caribbean, Japan) it can also be transmitted through sexual contact and five of the six anti-HTLV positive donors identified in one study were white British females [3,4]. Donor deferral, for example by excluding donors born in high prevalence areas, would result in deferral of large numbers of non-infected individuals, and lead to other consequences such as shortage of appropriate phenotype-matched donations for recipients with, for example, sickle cell disease, while not totally removing the risk of HTLV transmission through transfusion. It is therefore not an appropriate option for decreasing HTLV transfusion transmission risk.

6.2 Screening

Options for screening are addressed in this paper.

6.3 Leucodepletion

HTLV transmission requires cell-to-cell contact, which in this case would be between an infected white cell from the blood component coming into contact with a white cell from the recipient [8,14]. Leucodepletion is known to significantly reduce the risk of HTLV transmission, although it has not been clearly established whether it abolishes the risk completely. One study

calculated the minimum infectious proviral load to be 9 x 10^4 copies which is considerably in excess of the load found following leucodepletion[7]; another study identified incomplete removal of provirus by leucodepletion when donor loads were greater than 10^8 copies per litre[15].

The clinical effect of leucodepletion on HTLV transmission through blood components was investigated in the NHSBT lookback study [16]. This work is unlikely to be replicated elsewhere, as blood services in most developed countries commenced HTLV screening before the introduction of leucodepletion. UK blood services introduced leucodepletion earlier, as a vCJD risk reduction measure, and were thus in a unique position to study the effect of leucodepletion on HTLV transmission.

The NHSBT lookback study detected a small number of HTLV infections in recipients of blood components from donors who later tested HTLV positive, and the risk for non-leucodepleted components was significantly greater than for leucodepleted components. Infection was demonstrated in 1/81 who had received leucodepleted components, 1/96 who had received either leucodepleted or buffy coat reduced components and 5/17 who received components that had not undergone any white cell reduction. The one HTLV infected recipient of a leucodepleted component was transfused in 1997 and had an independent risk for HTLV infection, having being born in Jamaica. No further investigation was carried out to try and determine the origin of the virus in the recipient.

There was a statistically significant lower odds ratio (OR = 0.027, 95% CI 0.001-0.267, $p<0.001$) of being infected through transfusion if the recipient received a white cell reduced component (leucodepleted or BCR) compared to a component with no white cell reduction.

The results of the lookback provide evidence of the efficacy of leucodepletion in reducing the likelihood of HTLV transmission through transfusion of cellular blood components, to an estimated maximum overall transmission rate of 3.7%, a 93% reduction compared with non-leucodepleted components.

Leucodepletion is performed on all blood components, other than those which are specifically designed to provide leucocytes i.e. pooled granulocytes and buffy coats. Blood is leucodepleted either by the use of leucodepletion filters or by machine technology for apheresis platelets. The residual white cell count is measured on a proportion of components by flow cytometry, and monitored by statistical methods. The residual risk that an issued component, which was not one of those counted, has not been leucodepleted to specification can be calculated and this calculation is described in Appendix 4. The data indicate that apheresis platelets have a proportional calculated residual risk (PCRR) of 1:2651, pooled platelets of 1:700, and red cells 1:1750. For all processes the gross failure rate (> 100 x 10^6 per unit) is better than 1:10,000

which is equivalent to 99.99% compliance. Units with > 5 but < 100 x 10^6 leucocytes tend to be just above the 5 x 10^6 per unit level. See Appendix 4 for further details.

6.4 Pathogen inactivation

HTLV-I and –II are both inactivated by blood component pathogen inactivation techniques, currently available for plasma and platelet but not red cell components. Log kill has been reported as 4.7 for HTLV-I and 5.1 for HTLV-II [17].

7. Donation testing

7.1 Non specific reactivity and anti-HTLV screening

All 204 anti-HTLV positive donations identified in the UK up to the end of 2012 were initially picked up by minipool screening. The 16 anti-HTLV positive donations identified during 2013/14 were picked up on single donation screening. Excluding the first year of testing, around 0.1% of minipools were repeat reactive each year. The proportion of screen reactives that were subsequently confirmed positive was initially high, but decreased in 2009 when the size of the pool decreased from 48 to 24 donations: the non-specific reactivity rate of anti-HTLV testing in the UK was higher when a smaller pool size was used (Table 7.1).

Since February 2013, NHSBT has performed anti-HTLV screening on individual donations. Of almost 3.5 million blood donations tested to December 2014, 1707 (0.049%) were repeat reactive and 16 (0.00046%) were confirmed positive (Table 7.1). This compares with a figure of 25 repeat reactive donations referred and 10 confirmed positive in the whole of 2012. The additional 1691 donations (99.1%) referred between February 2013 and December 2014 were lost donations, and a not insignificant number of donors may be permanently lost to donation because of persistent low level non-specific reactivity not previously seen when the donations were screened in pools, this despite the implementation of the very effective approach of alternate assay testing of unconfirmed screen reactive donors.

Table 7.1: UK blood donations screened for anti-HTLV from 2002 to December 2014

Year of donation	No. of donations tested	No. of minipools (MP) tested	No. MP initially reactive (%)	No. MP repeat reactive (%)	No. donations sent for confirmation	No. donations positive (%)	Rate per 100,000 donations	No. non-specific reactives	Non-specific reactivity per 100000 donations
2002	1110618	22147	58 (0.26)	42 (0.19)	42	32 (76)	2.88	10	0.9
2003	2886700	62215	72 (0.12)	46 (0.07)	46	34 (74)	1.18	12	0.42
2004	2695958	58281	60 (0.1)	21 (0.04)	21	15 (71)	0.56	6	0.22
2005	2400545	52768	48 (0.09)	19 (0.04)	19	16 (84)	0.67	3	0.12
2006	2308192	51884	20 (0.04)	11 (0.02)	10	9 (90)	0.39	1	0.04
2007	2190464	49110	32 (0.07)	19 (0.04)	18	16 (89)	0.73	2	0.09
2008	1753040	37437	25 (0.07)	15 (0.04)	15	14 (93)	0.8	1	0.06
2009	2216909	60236	73 (0.12)	39 (0.06)	38	23 (61)	1.04	15	0.68
2010	2486351	97369	123 (0.13)	73 (0.07)	72	22 (31)	0.88	50	2.01
2011	2448587	95918	70 (0.07)	35 (0.04)	36	13 (36)	0.53	23	0.94
2012	2364871	97673	65 (0.07)	28 (0.03)	25	10 (40)	0.42	15	0.63
2013	635096[1]	26825	18	1	1	0	0	1	0.16
	1761846[2]	N/A	1000[3]	496[3]	496	5	0.28	491	27.9
2014	343701[1]	14453	25	1	1	0	0	1	0.3
	1977054[2]	N/A	1653	539	539	10	0.51	529	26.8

[1] Tested in minipools
[2] Tested as individual donations
[3] Individual donations

7.2 Documented Failures of HTLV screening

There have been 3 documented cases of the failure of the HTLV screening to detect an anti-HTLV positive donation.

The first case (NTMRL No. 008264) was identified in May 2010; a previously anti-HTLV screen negative donor was found to be anti-HTLV positive, screened in a pool of 24 donations. The donor had not donated since 2004, but before then had donated a number of times, including 3 donations between 2002 and 2004, after the introduction of HTLV screening. Work-up of the case confirmed that the donor was indeed infected, but the donor's risk history was inconsistent with the previous negative screening results. Further review of the donor's risk history, together with subsequent laboratory investigations, determined that it was highly probable that the donor had been infected pre 2002 and through the only risk route identified. Because the donor's

antibody was relatively low titre, reactivity was quickly lost on dilution. At a dilution of 1/48 the antibody was undetectable, but at 1/24 it was detected. The 3 donations collected between 2002 and 2004 were presumed to have been antibody positive, but undetectable at the screening dilution of 1/48 then used. The donation screened in 2010 was screened at the lower dilution of 1/24 and was detected.

The second case (NTMRL No. 204277) was identified in March 2012. A previously anti-HTLV screen negative donor was found to be anti-HTLV reactive, screened in a pool of 24 donations. The donor had just one previous donation in September 2011. Work-up of the case confirmed that the donor was indeed infected, and included the retrieval of the archive sample of the September 2011 sample. This sample was also found to be anti-HTLV positive with a similar serological picture to the March 2013 pick-up donation. When diluted 1/24 and tested on the then current screening assay this sample was still clearly reactive, indeed the sample was still reactive at a dilution of 1/48. No specific reason for the initial screening miss could be identified and a subsequent audit of the pooling process failed to identify any issues. In the absence of any identifiable reason a failure within the pooling process was assumed.

The third case (NTMRL 309368) was identified in July 2013. A previously screen negative donor was found to be HTLV repeat reactive on the first donation after the introduction of ID screening. Reactivity, and the presence of proviral DNA, was confirmed on a second blood sample, but antibody reactivity was very low and blots showed only the presence of gp21 at 1+. It was recognised that this donor was picked up in the original HTLV prevalence study conducted in the early 1990s at North London and performed on individual sample screening. The reactivity seen at that time was low level and, in the then absence of molecular testing and limited additional serology, was considered to be non-specific. No reactivity was detected over many years following the introduction of HTLV screening in pools in 2002 but there was clear reactivity detected after the switch to individual sample testing, confirming the low level of the antibody.

Lookback on the previous donations from the first two of these donors did not demonstrate any transfusion transmission of HTLV.

7.3 International comparison

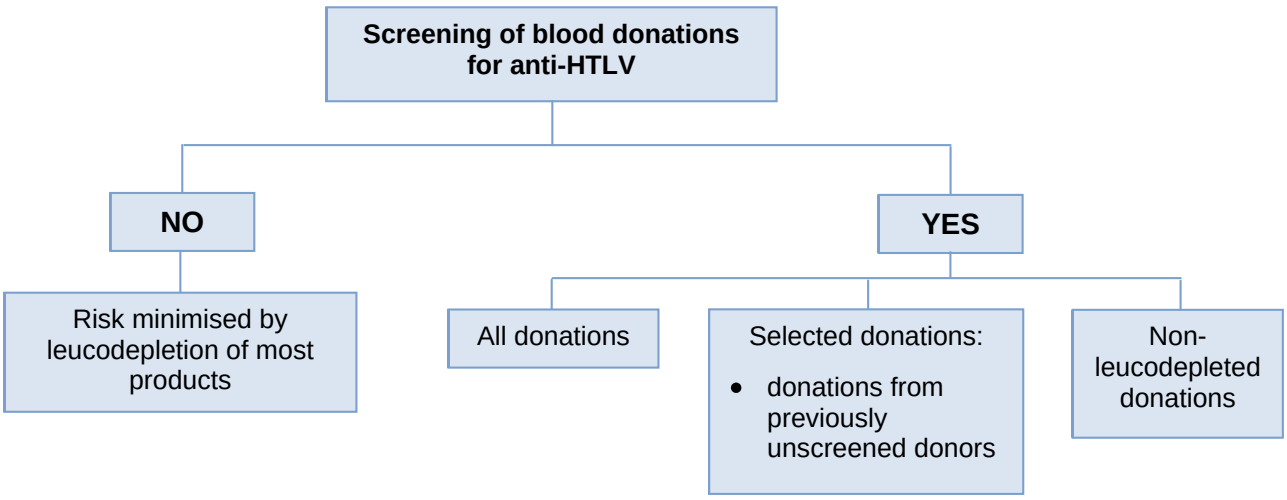
Screening began in Japan in 1986, followed by the USA in 1988, Canada in 1989, France in 1991, Australia in 1993, Denmark in 1994 and Portugal and Greece shortly afterwards[18]. Sweden commenced screening on first time donors only in 1995. Denmark subsequently changed to screen first time donors only and then ceased screening in 2011. Portugal has also changed to screen first time donors, as did the Netherlands in 2013.

The most recent data available from the Council of Europe Survey (2012) on donation testing is provided in Appendix 1. In summary, out of 28 countries providing data, 19 do not test, 5 test 100% of donations and 3 test first time donors only. Spain reports doing 'selective testing' on 30% of donations (testing strategy differs between blood centres).

8. HTLV Screening Options

There are a number of options now available to the UK Blood Services and these can be stratified according to level of intervention (Figure 2). Because whole blood donations, except those used to prepare buffy coats for clinical use and granulocyte products, are leucodepleted prior to processing, this provides the baseline intervention to minimise risk of HTLV transmission.

Figure 8.1: Options for HTLV antibody screening by UK blood services



Screening options considered:

- No screening
- Screen all donations
- Screen non-leucodepleted products only
- Screen donations from previously untested donors only
- Screen donations from previously untested donors/non-LD donations

The option of pooled testing has not been considered further, as all four UK Blood Services have now either implemented, or are planning to implement, individual donation testing, as a result of moving to Managed Service Contracts for all donation testing.

Table 8.1 attempts to identify the key issues and overall risk associated with each option. However, at present there is no agreed and nationally accepted safety level for transmission of HTLV (or any other infectious agent) through UK blood donations.

Table 8.1: HTLV screening options

Option	No anti-HTLV screening	Screen all donations individually	ID Screen non-leucodepleted donations only	ID screen donations from previously untested donors/non-LD donations
Description	No screening performed	ID screening of all donations	ID screening non-LD donations	ID screening of donations from previously untested donors and non LD donations
Sensitivity of strategy	Risk reduction dependent upon LD of the majority of blood donations/ components. LD estimated to provide a 93% risk reduction compared to non-LD products	Approx 98-100% dependent on assay selected	Approx 98-100% dependant on assay selected Selection process has est. 0.1% potential error rate Requires specific selection of samples for screening	Approx 98-100% dependent on assay selected and seroconversion rate in previously screened donors. Selection process has est. 0.1% potential error rate. Requires electronic flagging of donors to be screened with specific selection of samples for screening
Specificity	N/A	Est. of 3 non-specific reactives per 10,000 donations	Est. of 3 non-specific reactives per 10,000 donations	Est. of 3 non-specific reactives per 10,000 donations
Detection of early infection	Will not be selected for	Best option for most sensitive screening	Will not be selected for	Will not be selected for
Seroconversion in previously tested donor	Will not be detected	Will be detected	May be detected by chance	Will not be detected
Number of test systems available	N/A	A range of suitable assays/systems available, but determined by existing contracts	A range of suitable assays/systems available, but determined by existing contract	A range of suitable assays/systems available, but determined by existing contract

Abbreviations: ID = individual screening; LD = leucodepletion

9. Operational Considerations

Reports on operational considerations from each Blood Service are detailed in Appendix 2. Issues identified are summarised below.

9.1 Selection of first time donors for HTLV screening

All Services currently select out first time donors for additional testing, therefore the selection process for HTLV screening would not be a significant increase in workload. There may be the potential for error and missing samples in such a manual process, although if selection of first

time donors is implemented there would need to be additional IT safeguards to ensure that all required donations are tested (see below).

Selection of programmes on testing equipment to run some testing including HTLV and some not might be problematical.

9.2 Ensuring screening of non-LD components

These are pooled granulocytes (NHSBT only) and clinical buffy coats. Most granulocyte components are pre-ordered, but there are occasions when urgent requests are made and when clinical buffy coats are issued, these may be selected randomly from the available supply, so this option is more problematical and would require additional testing to have these components available at short notice. Systems would be needed to identify sufficient donations for this purpose. In urgent cases there may be a need to issue components not tested for HTLV – in such circumstances retaining testing of new donors so that all donors have been tested at least once would provide an increased safety margin.

SNBTS supply fewer buffy coats than NHSBT and consider that if testing of these donations were the only testing being performed there may be an issue of being able to maintain in-date, validated kits for this limited use. WBS and NIBTS, the latter supplying only 100 buffy coats per annum, would have similar issues.

9.3 Higher repeat reactive rate for ID and potential donor loss

As detailed above, individual donor testing increases the repeat reactive rate from 0.0042% (0.1% of pools) to 0.049%, of which 99.1% are non-specific, consequently increasing further testing and potential donor loss. As previously noted, however, it is considered unlikely that Services will move back to pooled screening.

9.4 Impact of non-identification of positive donor on health of donor

A donor confirmed positive for HTLV is referred to a specialist HTLV clinic for further follow-up. An initial evaluation is made, and if agreeable the patient will be included on the national HTLV register. He / she is subsequently followed up at intervals. There is currently no treatment for HTLV infection, but onward transmission to others, for example through breast feeding, may be avoided.

As testing of blood donors may be the only way that infection in some individuals will be identified, there may be public health concerns if this testing ceases.

9.5 IT requirements

To enable selective testing, various new IT requirements will be necessary, such as identification of new donors, identification of donors with no previous HTLV test result, ability to

do a final check at the point of validation that an HTLV test has been done and found negative, ability to identify HTLV testing as mandatory for product type (i.e. non-leucodepleted donations).

10. Cost-Effectiveness Analysis

Cost implication of HTLV blood screening options

Prepared by Matthew Katz, HPAT, Department of Health July 2015

10.1 Background

The UK blood services began screening all blood donations for anti-HTLV I+II during the summer of 2002. Currently, each UK blood service has its own screening procedure: NHSBT and SNBTS perform serological screening as part of a managed service contract in which each blood donation is screened individually using a fully automated platform; WBS perform pooled screening as part of a managed service contract and will be moving to individual screening in 2017; NIBTS currently screen in pools but will be moving to individual screening under a managed service contract in 2016. All of the UK blood services perform individual anti-HTLV I+II screening for non-blood donations.

Recently, NHSBT completed an 11 year look-back study that demonstrates the efficacy of leucodepletion in reducing the risk of HTLV transmission through blood components. This, combined with greater knowledge of how HTLV is transmitted, has raised questions regarding the applicability of previous models used in selecting the current blood screening procedure. The Health Protection Analytical Team has been commissioned to develop a new model and consider the cost-effectiveness of various HTLV screening options.

10.2 Methodology

This work models anti-HTLV I+II blood screening options that differ according to the types of donations screened. There are currently four options being considered:

- No screening
- Screening only non-leucodepleted donations[1].
- Screening of non-leucodepleted donations (non-ld) and “new” donors[2].
- Screening of all donors.

[1] Non-leucodepleted donations are used to manufacture granulocytes and buffy coats for clinical use. Approximately 18k are screened each year (0.8% of all donations) and the model assumes they will be individually screened.

[2] Here “new” is used to denote donors who have either not previously donated or those who do not have a previous HTLV screening result (these lapsed donors will be very few in number).

To compare the different screening options a model has been developed using data from the UK on the prevalence of HTLV in different donors and our current understanding of the effect of leucodepletion on HTLV infectivity. This model combines both HTLV I and HTLV II infections and measures the possible numbers of transfusion transmitted infections (TTIs) and associated QALY loss against the total cost of each screening option to perform a cost-effectiveness analysis.

10.3 Model

In the model non-leucodepleted, red blood cell, and platelet components are considered separately to account for differences in HTLV prevalence, transmission probability, and QALY loss. Donors are also separated by gender as there is a marked difference in the prevalence of HTLV in the male and female population.

To calculate the occurrence and prevalence of HTLV in the different donor types, data from the PHE Epidemiology Unit covering 2002 to 2014 were used. These include details on the proportion of infected individuals who are male and seroconversions in the repeat donor population. In this period, there were 3 million new donors of which 153 were identified as HTLV positive[3]. This gives a HTLV prevalence of 5.2 (range 1.8 – 9.2) per 100,000 new donors and an occurrence of 11.8 (range 4 - 21) HTLV positive new donors per year. Between 2004 and 2014[4], there were 7 recorded seroconversions within the repeat donor panel giving an occurrence of 0.6 (95% CI 0.3 to 1.3) HTLV positive repeat donors per year.

Without screening all infected new donors would enter the repeat donor panel. This leads to a steady state in which the prevalence of HTLV in repeat donors due to the influx of infected new donors would be the same as that of the new donor population (as this represents the occurrence in the population as a whole). The number of infected donors[5] can then be calculated by multiplying the number of repeat donors by the prevalence giving 5.2 x 1.1m / 100,000 = 58.0. To account for the accumulation of seroconversions in the repeat donor panel, it is assumed that seroconversion occurs 1.35 years (range 0.31 – 4.79) through a donor career and that an average career is 6.7 years[6]. In the steady state this gives 0.6 x (6.7 – 1.35) = 3.4 infected donors. Combining these two sources gives a total of 61.4 HTLV infected donors in the repeat donor panel under the steady state without screening. This is equivalent to a prevalence of 5.5 per 100,000 repeat donors.

[3] Note this number differs from that previously stated as it is the number of HTLV positive cases in new donors and not newly tested donors.
[4] Prior to 2004 seroconversions could not be identified due to the presence of previously unscreened donors.
[5] Throughout this report, a factor of 2.0 has been used to convert from donations to donors calculated using donor and donation numbers from “Safe Supplies: Reflecting on the Population 2013”.
[6] Donor career is based on donor data from NHSBT for donors whose last donation occurred between 1st Jan 2011 and 31st Aug 2013.

To account for the effect of screening, the sensitivity of individual screening was obtained from the "SACTTI HTLV Discussion Paper: Options for HTLV Screening within the UK Blood Services"[7] with the lower bound being used to give the most conservative estimate of TTIs. This gives 98% sensitivity for individual screening with a further 0.1% additional error rate used to account for the extra complexity in screening options that involve selective testing. By applying this sensitivity the donor prevalence for the different screening options can be calculated in a similar manner to that of no screening given above. It should be noted that the model does not take into account the affect due to screening non-leucodepleted donations, false negative screening of seroconverted donors nor multiple false negative screening of the same donor as these are negligible. The calculated prevalence under each screening option is given in Table 10.1.

Table 10.1: Steady-state HTLV prevalence in different donor groups under each screening option.

Screening option	New donor prevalence (per 100,000)	Repeat donor prevalence (per 100,000)
No Screening	5.2	5.5
- range	(1.8 - 9.2)	(1.8 - 10.0)
Non-leucodepleted	5.2	5.5
- range	(1.8 - 9.2)	(1.8 - 10.0)
New and non-ld	0.11	0.41
- range	(0.04 - 0.19)	(0.08 - 0.93)
All	0.10	0.006
- range	(0.04 - 0.18)	(0.001 - 0.015)

The number of blood components issued annually was provided by the different blood services and split into red blood cell, platelet, and non-leucodepleted[8] components. With reference to the specifications[9], the number of infected issues was then calculated for each component separately by combining the number of component issues with the annual donations and HTLV prevalence among donors under the different screening options.

To calculate the transmission probability it has been assumed that successful leucodepletion (< $5x10^6$ white cells per unit) is enough to provide complete protection against the transmission of HTLV. Patients receiving components with a greater white cell count (leucodepletion failures)

[7] JPAC 14-32
[8] Plasma has been excluded from the analysis as it does not transmit HTLV.
[9] Given by the "NHSBT Portfolio of Blood Components and Guidance for their clinical use" (SPN223/6.2) and including such factors as whether new donors can be used, if the component is pooled, and the required gender mix of donors in each component.

are conservatively assumed to have a 100% probability of becoming infected after receiving a HTLV positive component. Leucodepletion data[10] was used from all blood services (except WBS) for Q1 2010 to Q1 2015. The failure rate was then calculated for each component type using the following formula:

$$\frac{\Sigma \left({}^{No.\ units > 5 \times 10^6}/_{No.\ units\ tested} \right) * No.untested\ units}{Total\ units\ issued\ all\ services}$$

with the summation being across the different blood services. This gives a transmission probability of 0.10% (95% CI 0.08 to 0.14%) or a rate of 1 in 979 (95% CI 1 in 736 to 1276) for leucodepleted components. For non-leucodepleted components a conservative transmission probability of 100% was used.

While it has been assumed, on the advice of an expert panel, that successful leucodepletion is 100% effective at preventing HTLV infectivity there is some research that suggests that this may not be the case. To account for this uncertainty, a worst case scenario has also been modelled. Under this scenario HTLV transmission from infected components occurs in 15% of platelet transfusions and 6% of red blood cell transfusions[11] and the upper limit of possible prevalence is used. The results from this scenario are presented alongside the best estimate throughout this report for comparison.

By combining these transmission rates with the number of infected components transfused the total annual TTIs under a steady-state can be calculated for each screening option, see Table 10.2.

[10] Provided by Simon Procter, Lead Specialist, Blood Supply (Manufacturing Development Team), NHSBT

[11] "Cost-effectiveness of additional blood screening tests in the Netherlands". Transfusion, Volume 52 (2012)

Table 10.2: Annual number of donations screened and HTLV TTIs for each screening option.

Screening option	Tests	TTIs	Rate of TTIs	
			1 in x years	1 in x issues
No Screening	0	1.04	1	2.2m
- range		(0.34 - 1.90)	(<1 - 3)	(1.2m - 6.8m)
- worst case		*20*	*<1*	*120k*
Non-leucodepleted	18k	0.13	8	19m
- range		(0.04 - 0.23)	(4 - 24)	(10m - 57m)
- worst case		*18*	*<1*	*130k*
New and non-Id	190k	0.01	95	220m
- range		(0.00 - 0.02)	(41 - 500)	(96m - 1.2bn)
- worst case		*2*	*<1*	*1.3m*
All	2,200k	0.001	720	1,700m
- range		(0.000 - 0.003)	(300 – 4.3k)	(710m - 10bn)
- worst case		*0.05*	*22*	*51m*

To calculate the QALY cost of an HTLV infection a state space model was used as presented by Borkent-Raven et al[11]. Each infected group is split into one of three states (latency, disease, death) with each state being assigned a QALY value. At each time step, individuals move between the states according to predetermined transmission probabilities[12] and the total QALY loss is calculated.

Transfusion distributions and survival rates for red blood cells and platelets were derived from data from the EASTR study. For non-leucodepleted components a worse case estimate was used by assuming that all transfusions go to neonates and assuming a 100% survival rate. The model assumes that if transfusion recipients live past 10 years then their mortality and health state return to that of the general population. Standard mortality rates from the Office for National Statistics (ONS) were used to calculate death due to other causes and QALE values used to calculate QALY loss due to premature death.

The standard model assumes that in 5% of cases an HTLV infection results in adult T-cell leukaemia/lymphoma (ATLL) after 25 years, the diseased state has a health value of 0.98 QALYs and causes death in 1 year. In 3% of cases, infection results in HTLV associated myelopathy (HAM) 10 years after infection. Patients with HAM survive for 20 years with an associated health value of 0.98 throughout this period before dying.

[12] An additional state is included to represent death due to other causes.

To account for the more rapid progression of HTLV associated disease following organ transplantation, a further QALY model was created in which the latency of ATLL and HAM were reduced from 25 and 10 years to 1 and 2 years respectively. This represents the earliest onset of these diseases recorded in the literature and so is a conservative estimate. The output was then combined with that from the standard model by weighting the effects according to the number of transfusions that go to organ transplant recipients each year (150k out of 2,300k ~ 7%). The characteristics of HTLV associated diseases used in the model are given in Table 10.3.

Table 10.3: Characteristics of HTLV associated diseases used in the model (numbers in brackets represent different parameters used to represent early onset in transplant recipients).

Disease	Life-time risk	Latency (years)	Duration (years)	Health value
ATLL	5%	25 (*1*)	1	0.98
HAM	3%	10 (*2*)	20	0.98

Only primary TTI infections were considered by the model and all QALY values are discounted at the DH standard rate of 1.5%. The effect of a single infection caused by transfusion of different blood components can be seen in Table 10.4.

Table 10.4: Annual effect of a single HTLV infection due to transfusion of different blood components.

Component	QALYs lost	QALYs lost over 60s)	Disease	Deaths	Life years
Platelets	0.30	0.01	0.03	0.02	0.44
Red Blood Cells	0.24	0.02	0.05	0.02	0.34
Non-Leucodepleted	1.92	0	0.08	0.08	2.95

Combining the QALY and transmission models allows the calculation of the effectiveness of each screening option and these can be seen in Table 10.5.

Table 10.5: Annual effectiveness for each HTLV screening option compared with no screening.

Screening option	QALYs gained	Life years gained	Rate of associated disease	
			1 in x years	1 in x issues
No Screening	0	0	13	30m
- range	-	-	(7 - 38)	(16m - 90m)
- worst case	*0*	*0*	*1*	*2.6m*
Non-leucodepleted	1.76	2.71	170	400m
- range	(0.58 - 3.20)	(0.89 - 4.94)	(93 - 530)	(220m - 1.2bn)
- worst case	*3.20*	*4.94*	*1*	*3.0m*
New and non-ld	1.79	2.75	1,900	4.5bn
- range	(0.59 - 3.26)	(0.90 - 5.01)	(830 - 10k)	(1.9bn - 24bn)
- worst case	*7.61*	*11.25*	*14*	*32m*
All	1.79	2.75	10,000	23bn
- range	(0.59 - 3.26)	(0.90 - 5.02)	(4.1k - 62k)	(9.7bn - 145bn)
- worst case	*8.05*	*11.88*	*470*	*1.1bn*

10.4 Costs

Unit costs of the different screening methods were provided by NHSBT[13] and were given as £0.4 per donation for screening all donations, using the Abbott Prism immunoassay analyser, and £1.84 per donation for screening selective donations, using ARCHITECT immunoassay analyser, with an additional wastage cost of 1% added in each case.

The specificity of screening was derived from the UK screening data given in the SACTTI HTLV discussion paper[7]. This gives a non-specific reactivity per 100,000 donations of 27.3 for individual screening and this was assumed to be the same irrespective of the type of screening.

The number of false positives was calculated by combining the total donations tested with the specificity of each screening method. For each false positive there is an incurred cost of £147 representing the combined cost of the confirmatory testing (£96)[14] and replacement cost of the donation (£50)[15]. To calculate the cost of lost donors[16], 0.025% of all donors were assumed to be lost and need replacing with a replacement cost of £75 each[17].

[13] Provided by John Spence, Finance Business Partner, Blood Supply (National Ops & MDT), NHSBT
[14] The cost of confirmatory testing within NHSBT was provided by Alan Kitchen.
[15] The replacement cost of a donation is calculated using the weighted average of the cost of red blood cells (£43) and apheresis platelet (£83) components.
[16] Donors deferred due to repeat reactivity on both the primary and secondary assay but who are confirmed HTLV negative.
[17] Rate and cost for lost donors was provided by Vaughan Sydenham.

An additional staff usage of 0.25 WTE per testing site (2x NHSBT, 1x SNBTS, and 1x NIBTS) was added to selective screening options[18] to account for the additional complexity and this was costed at £28,500 per annum. Cost savings due to prevented infections were not included due to the small number of TTIs and the long latency of the associated diseases making these negligible. Costs arising due to legal action over TTIs were also excluded from the analysis. A breakdown of the annual costs can be seen in Table 10.6.

It should be noted that these cost figures exclude WBS as, due to the small number of donations screened annually, any change in their screening process will not be cost-effective.

Table 10.6: Annual cost of the different screening options (note: cost of screening includes wastage and losses, cover false positives and lost donors).

Screening option	Screening	Losses	Additional staff	Total
No Screening	£0	£0	£0	£0
Non-leucodepleted	£34k	£1k	£29k	£63k
New and non-Id	£350k	£11k	£29k	£390k
All	£870k	£128k	£0	£1,000k

10.5 Results

A comparison of the cost-effectiveness of the different screening options compared to no screening is given in Table 10.7. Based on these figures none of the screening options meets the £15k cost per QALY threshold. If screening is to continue then screening only non-leucodepleted donations is the most cost-effective option for the UK blood services at £36k per QALY. Moving to this option would save approximately £940k per year compared to the current practice of screening all donations.

Assuming screening of non-leucodepleted donations were to be adopted, moving to screening new donors and non-leucodepleted donations costs an additional £330k for only a further 0.03 QALY gain giving an incremental cost-effectiveness ratio of £12m per QALY. The case is even worse for screening all donors with an incremental cost-effectiveness ratio of approximately £31m per QALY compared with screening non-leucodepleted donations only. Selecting either of the other options would also incur a greater opportunity cost[19] to the blood services with the number of additional QALYs that could be bought elsewhere shown in the table.

[18] Screening non-leucodepleted, and new and non-leucodepleted donors.
[19] The number of QALYs that could be gained by using the investment elsewhere given a standard cost per QALY of £15k

Table 10.7 Annual cost-effectiveness in terms of QALYs of the different screening options compared to no screening and savings compared to the current practice of screening all donations.

Screening option	Cost per QALY	Opportunity cost (QALYs)	Saving
Non-leucodepleted **- range** **- *worst case***	£36k (£20k - £110k) *£20k*	2 (1 - 4) *1*	£940k
New and non-ld **- range** **- *worst case***	£220k (£120k - £670k) *£51k*	24 (23 - 26) *18*	£620k
All **- range** **- *worst case***	£560k (£310k - £1,700k) *£130k*	65 (64 - 67) *59*	£0k

It is interesting to note that under the worst case scenario screening all donors, and new donors and non-leucodepleted donations does greatly increase the numbers of TTIs prevented (see Table 10.8). The low QALY loss associated with each infection, however, means this increase does not offset the greater cost of screening and no screening option is below the £15k threshold. If a cautionary approach is taken to minimising the number of TTIs then under the worst case scenario screening new donors and non-leucodepleted donations is the most cost-effective option at £21k per TTI prevented. Moving to this option would still save approximately £620k per year compared to the current practice of screening all donations.

Table 10.8: Annual cost-effectiveness in terms of TTIs prevented of the different screening options compared to no screening.

Screening option	Number of TTIs prevented	Cost per TTI prevented
Non-leucodepleted **- range** **- *worst case***	0.9 (0.3 - 1.7) *2*	£69k (£38k - £211k) *£38k*
New and non-ld **- range** **- *worst case***	1.0 (0.3 - 1.9) *18*	£380k (£210k - £1,100k) *£21k*
All **- range** **- *worst case***	1.0 (0.3 - 1.9) *20*	£970k (£530k - £2,900k) *£50k*

The greatest uncertainty in the model, apart from the efficacy of leucodepletion, comes from the prevalence of HTLV in new donors. To better understand the model dependence, sensitivity

analysis was performed over a range of new donor prevalence (the results can be seen in Table 10.9). This shows that the number of TTIs scales approximately linearly with the prevalence and, consequently, so does the cost-effectiveness both in terms of cost per QALY and TTIs prevented.

For the option of screening all donors to be as cost-effective (QALYs) as screening non-leucodepleted donations only, the new donor prevalence would have to be approximately 16 times larger than that assumed in the model. For the same to be true of screening new donors and non-leucodepleted donations, the new donor prevalence would have to be approximately 6 times greater. To put this into context, over the 11 years of data collection the maximum annual prevalence has been recorded at 9.2 per 100,000 slightly less than twice the value modelled.

Under the worst case scenario and concentrating on TTIs prevented, for the screening of all donors to be as cost-effective as screening new donors and non-leucodepleted donations would require the prevalence to increase by approximately a factor of 2.5. While this increase is still greater than the maximum observed it is more possible and so the prevalence of HTLV in new donors should be closely monitored if this option were to be selected.

While only primary infections were considered in this analysis, further modelling was undertaken to estimate the rate of secondary infections due to sexual and vertical transmission from TTI infected individuals[20]. To calculate the number of vertical transmissions the state space model was combined with birth rate data from the ONS and a vertical transmission probability of 0.25 found in the literature[21]. For sexual transmissions data from the National Survey of Sexual Attitudes and Lifestyles (Natsal) and a sexual transmission probability of 0.1%[22] from the literature[21] were used. The results of this modelling can be seen in Table 10.10.

In all cases the rate of vertical transmission is at least 25 times lower than that of primary TTIs. These vertical transmissions will also occur a significant amount of time after the initial TTI leading to heavy discounting with, for example, an average of 29 years between primary and secondary infection in the case of no screening. This low rate and long time horizon means that the QALY loss due to vertical transmission is negligible and so will not have a significant impact on the effectiveness analysis.

While the sexual transmission rate can be comparable to that of primary TTIs, individuals infected via sexual transmission will have an older age distribution than those transfused. Infected individuals must initially be sexually mature and, due to the low sexual transmission probability of HTLV, have prolonged exposure to an infected partner. This exposure period can be substantial

[20] Further transmissions from the secondary infected individuals have not been considered.
[21] "Human T-cell lymphotropic virus testing of blood donors in Norway: a cost-effect model", International Journal of Epidemiology, Volume 29 (2000)
[22] This is the male-to-female transmission rate as sexual transmission of HTLV appears to be far more efficient from males to females.

with, for example, 36 years between primary and secondary sexual infection in the case of no screening. The shifted age profile and extended period before infection leads to lower QALY loss due to HTLV associated diseases and heavy discounting so sexual transmissions will not have a significant impact on the effectiveness of screening.

Table 10.9: Sensitivity analysis: Annual cost-effectiveness of the different screening options compared to no screening under different new donor prevalence (worst case scenario of greater transmission probability only given in brackets).

Screening option	New donor prevalence without screening (per 100,000)	Number of TTIs prevented	Cost per QALY	Cost per TTI prevented
Non-leucodepleted	2.6	0.5 (*0.5*)	£68k (*£68k*)	£130k (*£130k*)
	5.2	0.9 (*0.9*)	£36k (*£36k*)	£69k (*£69k*)
	10.3	1.8 (*1.8*)	£19k (*£19k*)	£36k (*£36k*)
	25.8	4.4 (*4.4*)	£8k (*£8k*)	£15k (*£15k*)
	51.6	8.7 (*8.7*)	£4k (*£4k*)	£7k (*£7k*)
New and non-leucodepleted	2.6	0.5 (*5.2*)	£ 420k (*£180k*)	£720k (*£76k*)
	5.2	1.0 (*10.3*)	£220k (*£93k*)	£380k (*£38k*)
	10.3	2.0 (*20.5*)	£110k (*£47k*)	£200k (*£19k*)
	25.8	5.0 (*51.3*)	£46k (*£19k*)	£80k (*£8k*)
	51.6	9.9 (*103*)	£20k (*£9k*)	£40k (*£4k*)
All	2.6	0.6 (*5.8*)	£1,100k (*£430k*)	£1,800k (*£170k*)
	5.2	1.0 (*11.0*)	£560k (*£230k*)	£970k (*£91k*)
	10.3	2.0 (*21.5*)	£290k (*£120k*)	£500k (*£47k*)
	25.8	5.0 (*52.8*)	£120k (*£48k*)	£200k (*£19k*)
	51.6	9.9 (*105*)	£60k (*£24k*)	£100k (*£10k*)

Table 10.10: Rate of HTLV TTIs, and subsequent vertical and sexual transmissions

Screening option	Rate of TTIs (1 in x years)	Vertical transmission rate (1 in x years)	Sexual transmission rate (1 in x years)
No Screening - range - *worst case*	1 (<1 - 3) *<1*	23 (13 - 72) *5*	1 (<1 - 2) *<1*
Non-leucodepleted - range - *worst case*	8 (4 - 24) *<1*	1,300 (720 - 4.2k) *8*	21 (12 - 66) *<1*
New and non-ld - range - *worst case*	95 (41 - 500) *<1*	1,800 (4.2k - 57k) *84*	190 (79 - 1k) *1*
All - range - *worst case*	720 (300 – 4.3k) *22*	20,000 (8k - 130k) *2,600*	470 (190 - 3.1k) *46*

11. Discussion

Although pooled HTLV testing regimes are cost-effective in a number of ways, the move to Managed Service Contracts (MSA) for serological screening has effectively passed the decision on anti-HTLV screening methodology to the potential suppliers, although the minimum screening requirements are set by the Blood Service in the tender specification and have to meet any regulatory or other mandated screening requirements. As the whole-life costs of the overall contract are the only costs considered, and the contracts provide an overall combined cost for a set repertoire of tests on a donation resulted basis, the same cost issues associated with the introduction of HTLV screening no longer exist. It must be noted, however, that following the implementation of MSAs the individual UK Transfusion Services now have different procedures for HTLV screening, with both ID and pooled screening being used currently, although all will move to ID by 2017. Whilst the implementation of ID HTLV screening has significant operational advantages, there are knock-on effects in the increased number of screen reactive donations, a consequent potential increase in lost donations due to non-specific reactivity, and an increased amount of confirmatory testing and subsequent donor re-entry activity. Except for penalties for lost donations above the maximum contracted repeat reactive level, such additional costs are not directly included in the tender process.

The information gathered since the introduction of HTLV screening of blood donations in 2002, after the initial screening sweep of all donors, has indicated that the majority of confirmed infections originate from donors new to the test i.e. first-time donors, or lapsed donors. Currently the UK blood services identify on average 13 anti-HTLV positive donations each year; these are

mostly prevalent infections amongst new donors. Infections in donors have been generally associated with HTLV-1 endemic countries, either through country of birth of the donor or heterosexual partner. Nevertheless, a small number of seroconversions have now been observed in established donors. There is some evidence of ongoing heterosexual transmission of HTLV among blood donors; in the years 2004 - 2014 seven repeat donors seroconverted for anti-HTLV with an average of 1.4 years between donations.

Since transmission of HTLV is believed not to occur in the traditional window period situation where there is viraemia in the presence of a negative screening (antibody) test, but instead requires cell-to-cell interaction, leucodepletion is a significant factor in mitigating the transmission risk.

Single sample screening of all donations is undoubtedly the safest of all methods but will result in a significant number of donations (and donors) lost due to non-specific reactivity, and for minimal gain in blood safety. However, within the Managed Service Contracts, ID testing is now (or about to be) established and therefore reversion to pooled testing has not been considered as an option in this paper.

A strategy to test only previously untested donors and non-leucodepleted donations would reduce both the overall number of tests required and the absolute number of non-specific test results, while introducing a small increased risk of a missed true positive result due to seroconversion in a previously tested donor not selected for testing. Such a strategy would, however, have some operational implications in the selection of those donation samples requiring screening. In considering such an approach, blood services would need to consider the definition of ‘already screened’.

Selective screening of blood donations for HTLV has been considered in other blood services. In July 2013, Sanquin (Netherlands) changed from universal screening to HTLV screening of new blood donors only. In Australia, conversely, it has been decided that it becomes logistically impractical to screen donations from first-time donors for a different microbiology test profile than that used for existing donors. The added operational procedures required reduce the cost savings of screening fewer donations for HTLV and also introduce possible process errors, where donation samples from first-time donors might not be correctly identified for screening.

The main argument for change from universal screening in those blood services that have considered it was that HTLV transmission through blood components had not been reported since the introduction of leucodepletion, and HTLV screening on all blood donations is not cost-effective. No HTLV seroconversions were recorded in Australia from 2005 to 2009, but one was documented in 2010, indicating a low but on-going incidence. Some European blood services have discontinued HTLV screening: Finland ceased completely in 2008, and Denmark in 2012,

although until then screening in Denmark had been restricted to new donors so seroconversion rates would not be known. Austria considers leucodepletion of all blood components is sufficient protection and for that reason does not screen for HTLV, and other countries (see Appendix 1 for status in 2012) have never screened donations for HTLV. Detailed epidemiological information about HTLV prevalence, incidence, and seroconversions is not available for these countries.

It is clear that the considerations previously used in decisions about HTLV screening are not all relevant in the climate of managed service contracts. A reversal to pooled testing has not been considered here. Individual sample testing of all donations has the highest knock-on “cost” in terms of lost donations, increased reference laboratory work, and potential loss of donors from the panel if reactivity persists and/or alternative assay systems are not in place. Individual sample testing of only previously untested donors will have a low failure rate (an estimated maximum of one missed donor per year due to seroconversions and false negatives) and the impact of these failures is assessed as very low, since leucodepletion will be a significant mitigating factor in reducing the risk of onward transmission of infection to a recipient.

The risk of HTLV transmission for each option under consideration, calculated from HTLV donor prevalence and risk of leucodepletion failure and assuming 100% effectiveness from successful leucodepletion is 1 per year for no screening, 1 in 8 years for screening non-LD components only, 1 in 98 years for screening new donors and non-LD donations only, and 1 in 725 years for screening all donations. It is to be noted that there are approximately 2 million components issued each year and the chance of developing a disease associated with the infection are, at most, 1 in 10.

When the worst case scenario is considered, in which LD is not assumed to be 100% effective and the upper limit of possible prevalence is used, one transmission might be expected in less than one year for no screening and non-LD components only, 1 per year for new donors and non-LD only, and 1 in 22 years for 100% screening.

Cost-effectiveness analysis shows that the most cost-effective option, compared with no screening, would be to screen non-leucodepleted components only (cost per QALY £36,000), followed by screening new donors and non-leucodepleted (£194,000). The corresponding figure for screening all donations as currently is £629,000.

It should be noted that if Services change to screen non-LD donations only, then the prevalence of HTLV infection amongst repeat donors will gradually increase back to a similar level to that when testing was first introduced, as new donors carrying the virus will not be identified and deferred.

12 Reference List

1. Stainsby D, Jones H, Asher D, Atterbury C, Boncinelli A, Brant L, Chapman CE, Davison K, Gerrard R, Gray A, et al. Serious hazards of transfusion: a decade of hemovigilance in the UK. Transfus.Med Rev 2006 Oct;20(4):273-82.

2. Taylor GP. The epidemiology of HTLV-I in Europe. J.Acquir.Immune.Defic.Syndr.Hum.Retrovirol. 1996;13 Suppl 1:S8-14.

3. Brennan M, Runganga J, Barbara JA, Contreras M, Tedder RS, Garson JA, Tuke PW, Mortimer PP, McAlpine L, Tosswill JH, et al. Prevalence of antibodies to human T cell leukaemia/lymphoma virus in blood donors in north London. BMJ 1993 Nov 13;307(6914):1235-9.

4. Flanagan P, McAlpine L, Ramskill SJ, Smith AG, Eglin R, Parry JV, Mortimer PP. Evaluation of a combined HIV-1/2 and HTLV-I/II assay for screening blood donors. Vox Sang. 1995;68(4):220-4.

5. Dow BC, Munro H, Ferguson K, Buchanan I, Jarvis L, Jordan T, Franklin IM, McClelland M. HTLV antibody screening using mini-pools. Transfus.Med. 2001 Dec;11(6):419-22.

6. The National Centre for Human Retrovirology Taylor GP. 2009. (http://www.htlv1.eu/index.html

7. Sobata R, Matsumoto C, Uchida S, Suzuki Y, Satake M, Tadokoro K. Estimation of the infectious viral load required for transfusion-transmitted human T-lymphotropic virus type 1 infection (TT-HTLV-1) and of the effectiveness of leukocyte reduction in preventing TT-HTLV-1. Vox Sang. 2015 Aug;109(2):122-8.

8. Pique C, Jones KS. Pathways of cell-cell transmission of HTLV-1. Front Microbiol. 2012;3:378.

9. Glowacka I, Korn K, Potthoff SA, Lehmann U, Kreipe HH, Ivens K, Barg-Hock H, Schulz TF, Heim A. Delayed seroconversion and rapid onset of lymphoproliferative disease after transmission of human T-cell lymphotropic virus type 1 from a multiorgan donor. Clin.Infect.Dis. 2013 Nov;57(10):1417-24.

10. Toro C, Rodes B, Poveda E, Soriano V. Rapid development of subacute myelopathy in three organ transplant recipients after transmission of human T-cell lymphotropic virus type I from a single donor. Transplantation 2003 Jan 15;75(1):102-4.

11. Soyama A, Eguchi S, Takatsuki M, Ichikawa T, Moriuchi M, Moriuchi H, Nakamura T, Tajima Y, Kanematsu T. Human T-cell leukemia virus type I-associated myelopathy following living-donor liver transplantation. Liver Transpl. 2008 May;14(5):647-50.

12. Biswas HH, Engstrom JW, Kaidarova Z, Garratty G, Gibble JW, Newman BH, Smith JW, Ziman A, Fridey JL, Sacher RA, et al. Neurologic abnormalities in HTLV-I- and HTLV-II-infected individuals without overt myelopathy. Neurology 2009 Sep 8;73(10):781-9.

13. Soldan K, Barbara JA, Ramsay ME, Hall AJ. Estimation of the risk of hepatitis B virus, hepatitis C virus and human immunodeficiency virus infectious donations entering the blood supply in England, 1993-2001. Vox Sang. 2003 May;84(4):274-86.

14. Bangham CR. The immune control and cell-to-cell spread of human T-lymphotropic virus type 1. J.Gen.Virol. 2003 Dec;84(Pt 12):3177-89.

15. Pennington J, Taylor GP, Sutherland J, Davis RE, Seghatchian J, Allain JP, Williamson LM. Persistence of HTLV-I in blood components after leukocyte depletion. Blood 2002 Jul 15;100(2):677-81.

16. Hewitt PE, Davison K, Howell DR, Taylor GP. Human T-lymphotropic virus lookback in NHS Blood and Transplant (England) reveals the efficacy of leukoreduction. Transfusion 2013 Oct;53(10):2168-75.

17. Prowse CV. Component pathogen inactivation: a critical review. Vox Sang. 2013 Apr;104(3):183-99.

18. Goncalves DU, Proietti FA, Ribas JG, Araujo MG, Pinheiro SR, Guedes AC, Carneiro-Proietti AB. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. Clin.Microbiol.Rev. 2010 Jul;23(3):577-89.

19. Pennington J, Garner SF, Sutherland J, Williamson LM. Residual subset population analysis in WBC-reduced blood components using real-time PCR quantitation of specific mRNA. Transfusion. 2001 Dec;41(12):1591-600.

Appendix 1: HTLV testing in Europe 2012

(Information taken from the EDQM Questionnaire on the collection, testing and use of blood components 2012 – Table 6.1 Donation testing strategy for infectious agents)

Country	HTLV I/II	Comments
Albania		
Andorra		
Armenia	0	
Austria		
Azerbaijan		
Belgium	0	
Bosnia / Herzegovina		
Bulgaria		
Croatia	0	
Cyprus		
Czech Republic	0	
Denmark	0	Testing of first time donors in Denmark was stopped by the end of 2011
Estonia	0	
Finland	0	
France	100	
FYR Macedonia		
Georgia	0	
Germany	0	
Greece	100	
Hungary	0	
Iceland	0	
Ireland	100	
Italy	0	
Latvia		
Liechtenstein		
Lithuania		Not mandatory
Luxembourg	First	
Malta		
Moldova	0	
Montenegro	0	
Netherlands	100	(Changed to first time only in 2013)
Norway	0	
Poland		
Portugal	First	Testing also travellers returning from endemic zones
Romania		
Russian Federation	0	
San Marino		
Serbia	0	
Slovakia	0	
Slovenia		
Spain	30	Testing varies between different establishments
Sweden	First	
Switzerland	0	
Turkey		
Ukraine		
United Kingdom	100	

Appendix 2: Reports on operational considerations from UK Blood Services

NHS Blood and Transplant (NHSBT)

Introduction

A JPAC sub-committee has been formed to consider future strategy on HTLV 1/2 antibody testing in blood donors, based on surveillance and sero-conversion data both in the UK and other countries. Currently, in the UK and ROI, all donations are tested, either as a singleton test (England, Scotland, ROI) or in pools of 24 (Wales, Northern Ireland). One possible outcome is to reduce testing to include only first time (new) donors and donations which are used to produce non-leuco-reduced cellular components. In order for this choice to be a viable option, consideration must be given to the operational requirements of handling these donations to ensure that a secure and robust system is in place to block issue of products from donations that do not have a negative HTLV result in place where required.

New donors. Each testing site already has systems in place to identify donations from donors who have not previously donated. It is a simple process to identify these and select for testing. This can be controlled by worklist from the LIMS (Pulse or eProgessa). Realistically, because new donors only account for approximately 8% of the total bleed, these numbers would be very small, making a pooled testing system less cost effective with the two sites using this option producing less than 2 pools a day. As this would be the sole screening test, the more sensitive singleton testing option could be seen as a safer option.

Returning donors. These are donors who have previously donated but not within the past 2 years. Most of these would have previously donated since HTLV testing was introduced so would have a historic negative result on file. There are a number of recruitment drives targeting lapsed donors who may have not donated for several years, especially in the BAME (Black, Asian, Mixed Ethnic) minority population groups in support of sickle cell disease and thalassaemia patients. These may not have been previously tested for HTLV so secure systems need to be in place to identify them for testing.

Non-leuco-reduced products. These may be divided into granulocytes (apheresis or pooled) or single donor buffy coats for clinical use. Use of granulocytes is the preferred product for treatment of profoundly neutropaenic patients with refractory infections. Where these are not available, use of clinical buffy coats may be considered though this is not the preferred option and is only used occasionally, for example over bank holiday periods.

Granulocytes. Apheresis granulocytes are not collected by NHSBT but may be the preferred option for smaller testing sites where it is not possible to manufacture pooled buffy coat granulocytes, especially of blood groups O- and A-. However, they will be bled to order so the donation is easily identified for HTLV testing. Pooled granulocytes are a labour intense product and routine testing must be completed early enough to allow processing, irradiation and issue to the requesting hospital in time to transfuse the product. They are therefore identified and selected very early in the testing process so would not pose a problem in performing HTLV tests.

Buffy coats for clinical use. This group of products is the most problematic, as they would be by random selection from the day's work so could not easily be targeted at the start of the day. Systems would need to be in place to identify these units and allow for identification and selection of sample tubes for prioritising for HTLV antibody testing.

I.T. requirements.

1. Ability to identify new donors for HTLV antibody testing.
2. Ability to identify existing donors without historical HTLV negative results for HTLV antibody testing.
3. Final check at validation of leuco-reduced products (RBC, platelets, frozen) that a historical negative HTLV result is present.
4. Ability to allow selection of specified donations for testing and blocking release until the result is present.
5. Ability to identify HTLV test as mandatory for product type (i.e. non-leuco-reduced products).

Summary.

Systems are already in place to identify new donors because of the requirements to group them twice. Returning donors without historical negative HTLV result would be very small numbers and would be trapped by the validation check that all products have a current or historical negative HTLV result. Donations for granulocytes are already selected for priority testing due to the tight timelines in getting them manufactured and irradiated before release. It would be a simple matter to perform HTLV testing at the same time. Donations for clinical buffy coats would be the most difficult to manage due to the random nature of their selection.

In principle it would be relatively straight forward to switch to testing only new donors. Non-leuco-reduced products are less easy to manage, especially single buffy coats for clinical use. Although ultimately a clinical decision, the benefits of testing these products are questionable. The sero-conversion rate for HTLV is low in the UK. There is a low (5%) life time chance of post transfusion infection developing into symptomatic illness. The recipients of these products are gravely ill with profound neutropaenia and life threatening infections, with underlying illness with relatively low lifetime expectations.

Peter Rogan, Regional Testing Manager, NHSBT Manchester (11th June 2015)

Scottish National Blood Transfusion Service (SNBTS)

We currently screen 200 000 donations per year for HTLV of which in the region of 9% (18, 188 in 2014) are first time donors. Currently this at a cost of £0.40 per test. Therefore switching to screening of first time donors only would save in the region of £72 000 per annum. Current number of non-LD components is in the region of 80.

The challenge of selective testing of new donors for HTLV (n = approximately 2000 per month) would be how to handle these donations on the PRISM. To facilitate it may require a separate run, otherwise it would be necessary to manually **edit all other donations not to test for HTLV. This is likely to add up to an additional 2 hours to testing per day (prime, calibration and tests). SNBTS has recently commenced a new MSC with Abbott (5 years) and now screens for HTLV in individual donations on both testing sites (Glasgow and Edinburgh). Whereas Edinburgh currently has two PRISM, Glasgow only has one instrument. Both sites have an Architect which could be used to screen for HTLV but it likely that the Architect assay is more expensive (in the region of 4x the cost).**

The selection of new donors is straightforward however it is another sample group to pick out (currently selected donations are already picked out for testing for CMV, WNV and probably HEV. In addition SNBTS tissues require to be selected out as they are tested individually on the NAT assays. In addition to new donors, stem cell donors, tissues and breast milk samples will also need to be selected out for HTLV testing.

SNBTS perform contingency testing for the Irish. It could be more challenging if both organisations have adopted different testing strategies.

Kit usage may be an issue as well due to the kit size (4000 tests) for the PRISM. The ratio of controls to tests will increase etc. The number of pooled granulocytes issued Apr 14 – Mar 15 was 157 but it is difficult to predict when these will be required as they are prepared ‘on demand’.

Some IT work on the interface will be required.

Lisa Jarvis, SNBTS

Northern Ireland Blood Transfusion Service (NIBTS)

In 2014-2015 NIBTS screened 59236 donations for anti-HTLV1/2 at an approximate cost of £27,000 (current price £0.45). This includes all red blood cells and platelets (BC and apheresis) which are leucodepleted. Current usage of clinical buffy coats (granulocytes-non-leucodepleted) is approx. 100 per annum. A MSC has recently been awarded to Abbott Diagnostics for serology testing using the Architect system. The cost of a single HTLV test on the Architect will be £0.54 per result giving an approximate cost of £32,000. The proposed live date for the Architect system is January 2016.

In 2014-15 NIBTS tested 6812 first time donors (11.5%). To move to testing first time donors would reduce the cost to approx. £4000 (a saving of approx. £23,000). Operationally, this would not have a major impact and in fact would reduce the workload. Currently pools of 24 samples are prepared on a Hamilton star and transferred to a Diasorin ETI 3000 for testing. The new system will be a single platform to perform all mandatory screening assays (including anti-CMV) which will reduce staff "hands on" time.

To move to testing only clinical buffy coats would not be cost effective for NIBTS. Our annual usage is less than 100 which would mean we would have to maintain a stock of in-date, validated kits for immediate use as and when the buffy coats were required. It would not be feasible to send the samples to another testing laboratory as the BC's must be transfused within 24 hours. This would greatly increase the actual cost of each BC because reagent would time expire with subsequent wastage of unused reagents. Operationally there would be no major IT impact as previously stated for NHSBT

Mark Clarke, NIBTS

Welsh Blood Service (WBS)

WBS currently tests 85,000 donations annually (to increase to 109,000 in May 2016) for anti-HTLV I/II in all blood donations in pools of 24 samples. Bio-Rad supplies the Murex/Diasorin HTLV ELISA for this as part of managed service contract for Transfusion Microbiology. In 2017 (actual date not available) Bio-Rad will install their new Blood Screening Evolex Analyser which will perform individual HTLV 1+II test on all blood donations with no increase in cost. The operational impact of changing to individual donation testing for new donors and non leucodepleted components will be increase in cost, manual selection of samples for testing and re-configuration of eProgesa computer system and validation.

Lionel Mohabir, WBS

Appendix 3: Membership of the JPAC HTLV Working Group

Dr Sheila MacLennan	-	Professional Director of JPAC **(Chair)**
Dr Alan Kitchen	-	Chair the JPAC SAC on Transfusion Transmitted Infection
Miss Caroline Smith	-	JPAC Manager
Mr Mark Clarke	-	Northern Ireland Blood Transfusion Service
Mr Matthew Katz	-	Department of Health
Dr Joan O'Riordan	-	Irish Blood Transfusion Service
Mr Peter Rogan	-	NHS Blood and Transplant
Mr Simon Procter	-	NHS Blood and Transplant
Dr Ines Ushiro-Lumb	-	NHS Blood and Transplant
Dr Pat Hewitt	-	NHS Blood and Transplant
Dr Lisa Jarvis	-	Scottish National Blood Transfusion Service
Mr Lionel Mohabir	-	Welsh Blood Service

Appendix 4: Leucodepletion – Quality Monitoring using Statistical Process Monitoring and calculation of leucodepletion residual risk

Universal leucodepletion (LD) of components was implemented by all four UK Blood Services in 1999, primarily as a vCJD risk reduction measure. Other countries have adopted universal LD for other benefits that it may bring including reduction in the risk of viruses contained within leucocytes, such as HTLV and CMV, and reduction in febrile transfusion reactions. There is evidence to suggest that leucodepletion filters are particularly efficient at removal of monocytes [19][23].

Table A4.1 Current international specifications for LD per unit:

Component	Red Cells in AS	Platelets Apheresis	Platelets Pooled
BSQR - 2005	< 1 x 10^6	< 1 x 10^6	< 1 x 10^6
Council of Europe - 18th Ed.	< 1 x 10^6 (>90%)	< 1 x 10^6 (>90%)	< 1 x 10^6 (>90%)
GBTS (8th Ed) - 8th Ed.(a)	< 5 x 10^6 (>99%) < 1 x 10^6 (>90%)	< 5 x 10^6 (>99%) < 1 x 10^6 (>90%)	< 5 x 10^6 (>99%) < 1 x 10^6 (>90%)
AABB - 27th Ed.(a)	< 5 x 10^6 (>95%)	< 5 x 10^6 (>95%)	< 5 x 10^6 (>95%) < 8.3 x 10^5 (>95%) (b)

(a). Statistical process control /monitoring requires 95% confidence.
(b). For a single PRP unit.

The UK LD specification of 99% of components with <5x10^6 white cells per unit, with 95% confidence, equates to a 3-log reduction in the white cell count. In 2014 the UK Blood Services reviewed the specification in the Guidelines for the Blood Transfusion Services in the UK (Red Book) and confirmed that components tested with >5x10^6 white cells per unit should only be issued under concessionary release.

In part the Red Book specifications for components WBC LD reflects: the current capability of LD systems, that usually only a proportion of components are tested for residual white cells, and that the limit of sensitivity of current counting methods by flow cytometry is one white cell per µL (typically equivalent to 0.2x10^6 to 0.3×10^6 per unit).

Quality Monitoring routinely monitor component specification compliance using statistical process control. WBC filtration is a high criticality process and poor process performance requires increasing sampling frequency potentially to the point of 100% testing or cessation of the process.

As QM do not routinely tests all components the UK Blood Services additionally monitor the probability of issuing a component that has a WBC count above the specification but has not been tested.

[23] *Pennington,J., Garner,S.F., Sutherland,J., & Williamson,L.M. (2001) Residual subset population analysis in WBC-reduced blood components using real-time PCR quantitation of specific mRNA. Transfusion., **41**, 1591-1600.*

The Corrected Residual Risk (CRR) is calculated as follow:

Corrected Residual Risk =
(No. Issued) / ((No. Issued Untested/No. Tested) x (No. Tested > Specification))

The Corrected Residual Risk is dependant on: the number of components issued, the number tested and the process failure rate (the number of components found to be above the specification limit as a proportion of the number tested, expressed as 1 in nnn). The calculation corrects for the number of WBC LD failures excluded from issue by testing whilst applying the expected process failure rate to the untested population to define the remaining residual risk, expressed as 1 in nnn.

For processes where a very high proportion of components are tested the CRR is likely to be low even if specification failures occur frequently as the proportion untested is very low. Conversely, where the proportion tested is low, the specification failure rate also needs to be low in order to achieve a low residual risk.

However, the current UKBTS CRR calculation as reported to SACBC combines all the component process data. This potentially leads to a skewed figures, for example, where a BTS has implemented a high sampling frequency due to a higher WBC LD failure rate this will improve their compliance and CRR but their WBC LD failures will then be counted against the untested issues for the other services in the combined CRR.

Therefore, a proportional CRR (PCRR) has been calculated which combines the data by taking into account the relative number of WBC LD failures from each dataset in the final combined PCRR. The Proportional CRR (PCRR) is calculated as follow:

Proportional Corrected Residual Risk =
(No. Issued – No.) / ((No. Untested Failures Issued)

Where No. Untested Failures Issued =
(No. Failures / No. Tested) x (No. Issued – No. Tested)

Table A4.2 Current combined UK Blood Services WBC LD process capabilities are tabled below:

UK BTS: 2010 Q1 to 2015 Q1	Component			
Data	**Apheresis Platelets**	**Pooled Platelets**	**Red Cells**	**All Components**
No. Issued	665549	323916	11005326	11994791
No. Tested	327110	62321	369401	758832
No. >1x10e6/u	3207	2601	3266	9074
No. >5x10e6/u	264	300	313	877
No. >100x10e6/u	54	1	15	70
Failure Rate >1 (1:nnn)	102	24	113	84
Failure Rate >5 (1:nnn)	1239	208	1180	865
Failure Rate >100 (1:nnn)	6058	> 62321	24627	10840
CRR >1 (1:nnn)	201	30	117	89
CRR >5 (1:nnn)	**2437**	**257**	**1221**	**924**
CRR >100 (1:nnn)	11912	> 77168	25482	11573
PCRR >1 (1:nnn)	175	57	136	133
PCRR >5 (1:nnn)	**2651**	**700**	**1750**	**1713**
PCRR >100 (1:nnn)	10161	> 77168	38264	33968

The data indicate that the apheresis platelets have a CRR of 1:2437, pooled platelets of 1:257, and red cells 1:1221 and that apheresis platelets have a PCRR of 1:2651, pooled platelets of 1:700, and red cells 1:1750. For all processes the gross failure rate (> 100 x 10^6 per unit) is better than 1:10,000 which is equivalent to 99.99% compliance. Gross failures can be flagged by the apheresis machines as potential high WBC collections, processing issues or visual inspection. These units are treated as special cause failures and the units WBC tested. Units with > 5 but < 100 x 10^6 leucocytes tend to be just above the 5 x 10^6 per unit level, particularly for red cells and platelets.

Appendix 5: HTLV screening options framework

	Key Measure	Assumptions			Effect of Hazard on Patient		Impact of initiative		
							Mitigating Hazard	Patient	Component Supply
		Transmission probability	Disease progression	HTLV prevalence in new donors (per 100,000)	Estimated annual HTLV TTIs without screening	Estimated annual discounted QALYs lost due to HTLV TTIs without screening	Estimated annual discounted QALYs gained per intervention	Annual HTLV TTIs prevented	% change in supply
Best estimate	Screening of non-leucodepleted donations only	non-leucodepleted: 100%; platelets: 0.04%; red blood cells: 0.11%	ATL: latency 25 years (1 year in transplant recipients); duration 1 year	5.2 (1.8 - 9.2)	1.04 (0.34 - 1.89)	1.79 (0.59 - 3.26)	1.76 (0.58 - 3.20)	0.9 (0.3 - 1.7)	negligible*
	Screening of new donors and non-leucodepleted donations						1.79 (0.59 - 3.26)	1.0 (0.3 - 1.9)	negligible*
	Screening all donors (current)						1.79 (0.59 - 3.26)	1.0 (0.3 - 1.9)	negligible
Worst case scenario	Screening of non-leucodepleted donations only	non-leucodepleted: 100%; platelets: 15%; red blood cells: 6%	HAM: latency 10 years (2 years in transplant recipients); duration 20 years	9.2	20.14	6.21	3.20	1.7	negligible*
	Screening of new donors and non-leucodepleted donations						7.61	18.4	negligible*
	Screening all donors (current)						8.05	20.1	negligible

Notes: Impact of initiative - Component Supply:
*May be issues of delayed release of buffy coats for clinical use (c.f. HEV screening)

Appendix 5: HTLV screening options framework

	Key Measure	Value for Money			Linkages	External Considerations		Operational Considerations
		Net recurring costs (£/annum), excluding compensation costs	Cost-effectiveness compared to no screening (discounted cost per QALY saved)	Cost-effectiveness compared to no screening (discounted cost per TTI prevented)	Linked Decisions	Legal	Reputational	Selective screening
Best estimate	Screening of non-leucodepleted donations only	£0.1m	£36k (£20k - £110k)	£69k (£38k - £211k)	Public health Testing of blood donors may be the only way to identify HTLV infection in some individuals. There may be public health concerns if the number of donors tested is reduced leading to a potential increase in onward transmissions	Legal and compensation costs may be incurred with reduced screeening options.	None From the Council of Europe Survey (2012), out of 28 countries providing data: 19 do not test; 5 test 100% of donations; and 4 test first time or selected donors only. Three countries have moved from screening all to first time donors only and Denmark changed to first time donors only before ceasing screening in 2011.	Limited Selective screening will require IT changes, has the potential for errors and missing samples, and requires procedures for handling urgent non-leucodepleted product requests. There may also be issues with maintaining in-date, validated HTLV testing kits for the smaller services.
	Screening of new donors and non-leucodepleted donations	£0.4m	£220k (£120k - £670k)	£380k (£210k - £1,100k)				
	Screening all donors (current)	£1.0m	£560k (£310k - £1,700k)	£970k (£530k - £2,900k)				
Worst case scenario	Screening of non-leucodepleted donations only	£0.1m	£20k	£38k				
	Screening of new donors and non-leucodepleted donations	£0.4m	£51k	£21k				
	Screening all donors (current)	£1.0m	£130k	£50k				

Notes: Impact of initiative - Component Supply:
*May be issues of delayed release of buffy coats for clinical use (c.f. HEV screening)