Human T-lymphotropic virus lookback in NHS Blood and Transplant (England) reveals the efficacy of leukoreduction

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BACKGROUND: Leukoreduction of blood components was introduced in the United Kingdom during 1998. Human T-lymphotropic virus (HTLV) screening of blood donations was introduced in 2002. NHS Blood and Transplant conducted an HTLV lookback on blood components issued before 2002. A proportion of included components were nonleukoreduced, although the majority were subject to white blood cell reduction measures.

STUDY DESIGN AND METHODS: A standard lookback was conducted on untested cellular blood components from donors later confirmed to be HTLV positive, for the 4 to 5 years before 2002, and on the last tested negative donation from donors who had seroconverted.

RESULTS: A total of 437 red blood cell and platelet components were included and an outcome was reported for 84% of these. Just over half of identified recipients were dead at the time of lookback; blood samples for testing were obtained from 77% of identified living recipients. HTLV infection was confirmed in seven recipients, but one was discounted as not transfusion transmitted.

CONCLUSION: Although numbers are small, our results provide evidence of the efficacy of leukoreduction in reducing the likelihood of HTLV transmission through transfusion of cellular blood components. The HTLV-positive rate in recipients of leukoreduced components was 3.7%, a reduction of 93% compared with nonleukoreduced components. Importantly, the one infected recipient of a leukoreduced component had existing risk factors for HTLV infection. HTLV lookback was much less efficient in identifying infected recipients than was hepatitis virus C lookback.

The UK blood services began testing all blood donations for human T-lymphotropic virus (HTLV) antibodies during the summer of 2002, the rationale for which has been discussed elsewhere.[1] Between August 2002 and December 2011, a total of 194 anti-HTLV–positive donations (175 anti-HTLV-I, 18 anti-HTLV-II, and one type not confirmed) were identified in almost 24 million donations tested by the UK blood services—that is, approximately 8 per million donations. Approximately one-third (64) of these donations were collected from repeat donors who had also donated blood before the introduction of testing for anti-HTLV. Epidemiologic information suggested that many of these donors had been infected with HTLV for many years.[2] It was therefore decided that a lookback should be performed to identify recipients transfused with blood from these donors before the introduction of screening, so that the recipients could be notified and offered HTLV testing and further care, if necessary. As the available evidence suggested that the majority of HTLV-infected donors had been infected for at least 3 years, no time limit was set on the lookback, except as determined by yield. The vast majority (181/194) of HTLV-positive blood donations made in the UK were identified by NHS Blood and Transplant (NHSBT), which collects blood in England and north Wales.

ABBREVIATIONS: BCR = buffy coat reduced; GP = general practitioner; HAM = HTLV-associated myelopathy; NHSBT = NHS Blood and Transplant.

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Experience from the UK HCV lookback[3] indicated that the efficiency of lookback declined with the time since the date of the blood donation. It was not possible to identify a fate for 31% of components entering the HCV lookback since hospital records were generally not available more than 10 years before the date of the blood donation. In addition, 41% of traced blood components had been transfused to recipients who were known to be dead when the lookback was carried out. It was therefore expected that the maximum yield from the HTLV lookback, in terms of identified living recipients, would be from the most recent blood donations, with a diminishing yield for earlier years.

The HTLV lookback carried out within NHSBT commenced in 2004. Further blood donations continue to be added, as newly identified HTLV-infected donors are detected who had made untested donations before the introduction of routine screening in 2002 or who have seroconverted since last tested. This article describes the findings from the lookback on donations included up to the end of 2011.

Routine leukoreduction of all blood components was introduced in the United Kingdom during 1998 as a variant Creutzfeldt-Jakob disease risk reduction initiative.[4] HTLV is a white blood cell (WBC)-associated virus, and leukoreduction was expected to reduce, but not necessarily eliminate, the risk of HTLV transmission by cellular blood components.[5] Although the majority (65%) of the blood donations included within this lookback report were collected after 1998, some were made before leukoreduction, which allowed us to investigate the effect of leukoreduction on the transmission of HTLV infection associated with blood components collected and issued by NHSBT.

MATERIALS AND METHODS

Identification of components for lookback

The current computer system (Pulse) was introduced into NHSBT blood centers in a staged fashion during the late 1990s. The earliest date was 1997, but most blood centers changed to Pulse in 1998 or 1999. Previously, there was no national NHSBT computer system and all information relating to donors and their blood donations was held in individual blood centers on computer systems generally introduced during the late 1980s or early 1990s. Before that date all information was contained in paper records. Although the earlier records are in theory available, it was decided to start the HTLV lookback by dealing with only those donations held on Pulse. These were the most likely to be traceable through hospital records to living recipients. The lookback was therefore planned in two phases: Phase 1, identifying donations recorded within the national Pulse database, and Phase 2, using archived historic databases in individual blood centers. It was agreed not to address the question of earlier donations until the results of Phase 1 were available.

As part of the routine lookback procedure, the earliest available archive sample was tested for all 64 repeat donors, to establish whether the reactivity was new. Archive samples of all donations are kept for a minimum of 3 years, but are then discarded at a point usually dictated by storage space, so for most long-standing repeat donors the earliest available archive sample was just over 3 years old. Seroconversion in previously tested donors was consistent with exposure history.

Lookback was initiated once the bulk of donors had been screened (i.e., screening had been in place for at least 12 months), since it was judged preferable for operational purposes to carry out the bulk of the lookback on a "one-off" basis. Lookback has continued until the present day, adding cases when infected donors are newly identified.

The Pulse records for each donor found to be anti-HTLV positive were reviewed and all components made from previous, untested, donations were identified. The issue fate of each component was established and all issued red blood cell (RBC) and platelet (PLT) components, but not plasma, were included in the lookback. Because leukoreduction of blood components was introduced from 1998, the majority of lookback blood components were leukoreduced. Figure 1 gives a timeline for the introduction of the Pulse computer system, the implementation of leukoreduction, and the introduction of HTLV screening of blood donations.

Identification and testing of recipients

The procedure for identification of recipients has been previously described in the HCV lookback.[3] Briefly, a form was prepared for each lookback component and forwarded to the relevant hospital blood transfusion laboratory with a request to identify the fate of the blood component. If recorded as issued for transfusion, the hospital staff identified the intended recipient from laboratory records and checked the medical notes for documentation of transfusion. When the fate of the component had been established, the form was returned to the blood center. For living recipients, blood center staff contacted the clinician currently caring for the recipient (either hospital clinician if still under hospital care, or the general practitioner [GP] if not) to ascertain whether notification was appropriate. The clinician was asked to indicate whether he or she preferred to notify the patient or whether the task was to be delegated to blood center staff. If the notification was carried out by the treating clinician, the relevant information and forms were provided by the blood center and blood samples from the recipient sent to the blood center for HTLV testing. If notified by the blood center, the recipient was contacted by letter, provided with

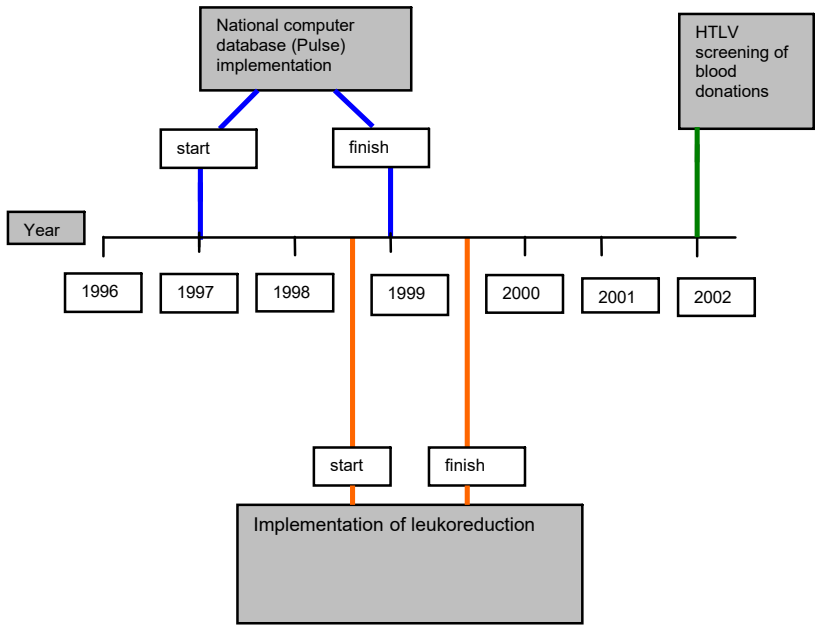

Fig. 1. Timeline for the introduction of the Pulse computer system, the implementation of leukoreduction, and the introduction of HTLV screening of blood donations.

information about the lookback, and invited to contact blood center medical staff for a discussion.

After this discussion, if the recipient elected for testing, a blood sample was obtained and tested for the presence of anti-HTLV. Results were sent to the patient and copied to the GP and any other relevant clinician. For HTLV-infected recipients, direct referral to a specialist HTLV clinic was offered.

Collation of data

The lookback was managed through the NHSBT Transfusion Microbiology Office and all data were collected and entered onto a computer database (Microsoft Access Version 7, Microsoft Corp., Redmond, WA). The database linked information about donors, donations, components, and recipients.

Statistical analysis

Statistical analyses were performed using computer software (R [CRAN] on a Windows platform, http://www.r-project.org/). Using the t test, the mean age of recipients tested for anti-HTLV at transfusion and testing were compared for positive and negative groups. Due to the small number of cases, two-sided Fisher's exact tests were used to determine the odds ratio (OR) for the number of anti-HTLV–positive versus anti-HTLV–negative recipients among those receiving WBC-reduced components (leukoreduced or "buffy coat reduced" [BCR]) and those receiving non–WBC-reduced components.

RESULTS

For 64 anti-HTLV confirmed-positive donors there were associated records on Pulse of a total of 617 earlier donations (Fig. 2). These donations had 837 associated components; records for 437 RBC and PLT components from these donations were available. RBCs accounted for 77% (335) of these components, and PLT components for 23% (102). A total of 65% (284) of these components were leukofiltered, 14% (60) were BCR (a process for WBC reduction, which was used before the universal introduction of WBC filtration), and the remaining 21% (93) had undergone no WBC reduction measures (Table 1). Lookback forms for these 437 blood components were forwarded to the relevant hospital laboratories, which were repeatedly encouraged to complete the identification and record tracing. By the date of analysis (March 2012), 368 (84%) forms had been returned from hospitals, and 354 forms (96% of those returned) confirmed that a recipient had been identified. No details of the recipient or intended fate of the component were reported for three cases. It has been assumed that the remaining forms have not been returned because the fate of the blood component could not be established. Almost half the blood components (202, 58% of those linked to identified recipients) had been transfused to recipients known to be dead at the time the form was completed.

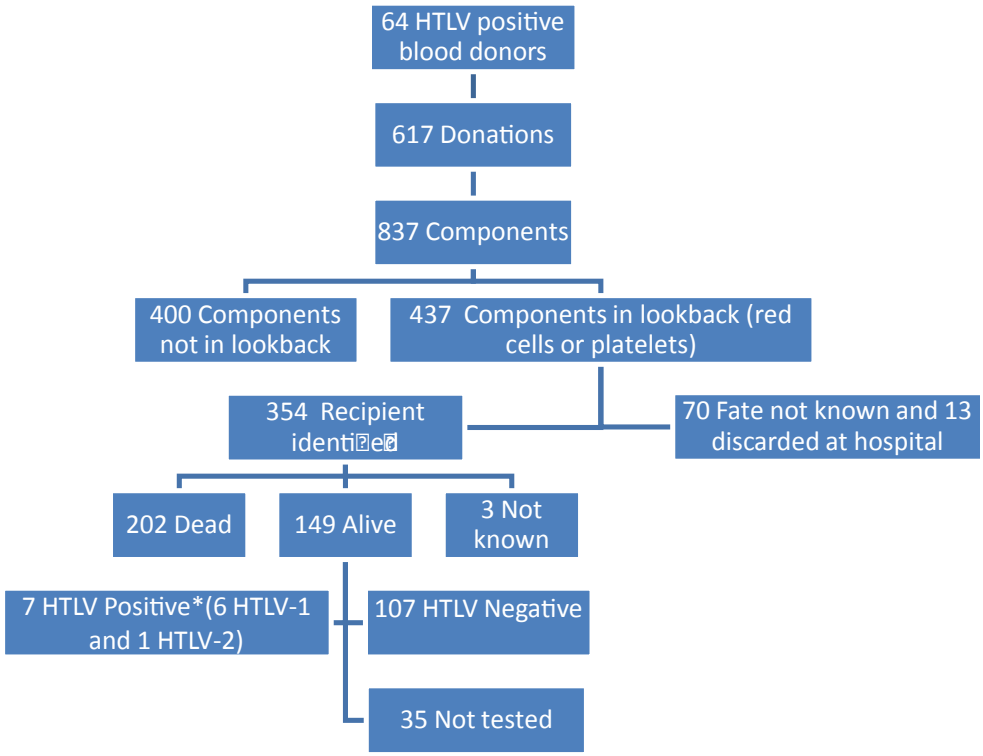

Fig. 2. The results of the HTLV lookback in England.

TABLE 1. WBC status and fate of pooled PLT and RBC components entering the HTLV lookback*

Status/fate of component	Pooled PLTs	RBCs	Total
Number	102 (100)	335 (100)	437 (100)
WBC status of component			
Leukoreduced	72 (71)	212 (63)	284 (65)
BCR	NA	60 (18)	60 (14)
No WBC reduction	30 (29)	63 (19)	93 (21)
Fate of component			
Transfused			
Recipient infected	2 (2)	5 (1)	7 (2)
Recipient not infected	17 (17)	90 (27)	107 (24)
Recipient not tested	55 (54)	183 (55)	238 (54)
Discarded by hospital	6 (6)	7 (2)	13 (3)
Fate not known: no response from Lookback Form 1	22 (22)	50 (15)	72 (16)

* Data are reported as n (%).

Blood samples for anti-HTLV testing were obtained from 114 individuals, accounting for 77% of the total number of presumed living recipients; all but two were tested within NHSBT. The tested recipients comprised 82 who had received leukoreduced blood components, 15 who had received BCR components, and 17 who had received components that were not subject to any WBC reduction measures. HTLV infection was confirmed in seven (6.1%) tested recipients: six were anti-HTLV-I positive and one was HTLV-II positive. The anti-HTLV-II–positive recipient had received a transfusion of leukoreduced RBCs from an HTLV-I–infected donor. A total of 10 components from this donor entered lookback: five recipients had already died, two were not notified, and three tested HTLV negative (two received leukoreduced components, one nonleukoreduced). It is considered that the HTLV-II infection did not originate from the donor.

The age and sex of the remaining 113 recipients tested for anti-HTLV are shown by HTLV status in Table 2. Approximately half of both groups were female. HTLV-positive recipients were marginally older than negative recipients at transfusion and at testing but the difference was not found to be significant. Of the six HTLV-I–infected

TABLE 2. Age and sex of the HTLV-positive and -negative recipients identified in the lookback and a comparison of the WBC status of the components received

Characteristic	HTLV positive*	HTLV negative	Total	Statistical comparison
Number	6	107	113	
Number (%) female	3 (50%)	52 (49%)	55 (49%)	
Mean age (years) at transfusion	55.2	48.7	48.9	t = 0.87; p = 0.415
Mean age (years) at testing	62.2	53.1	53.4	t = 1.26; p = 0.251
Received leukoreduced or BCR component				
Yes	1	95	96	
No	5	12	17	OR, 0.027; p < 0.001
Received leukoreduced component				
Yes	1	80	81	
No	5	27	32	OR, 0.069; p = 0.007

* One additional HTLV-positive recipient was identified. This was an HTLV-II infection in a recipient of leukoreduced RBCs. It was concluded *not* to be due to transfusion and is excluded here.

recipients, two had received nonleukoreduced pooled PLTs, three nonleukoreduced RBCs, and one leukoreduced RBCs. Thus, infection was demonstrated in one of 81 who had received leukoreduced components, one of 96 who had received either leukoreduced or BCR components, and five of 17 who received components that had not undergone any WBC reduction (Table 2). The analysis presented in Table 2 shows a significant lower odds (OR, 0.027; 95% confidence interval [CI], 0.001-0.267; $p < 0.001$) of testing HTLV positive after transfusion if the recipient received a WBC-reduced component (leukoreduced or BCR) compared to a component with no WBC reduction. If the component was leukoreduced then the odds of a recipient being infected were still lower than if they had received a nonleukoreduced component (OR, 0.069; 95% CI, 0.001-0.658; p = 0.007) but the overall effect was less.

Two of the infected recipients (including the sole infected recipient who received a leukoreduced component) had other risk for HTLV infection as they were of Caribbean origin. Neither had been tested previously for HTLV infection, so existing infection could not be excluded. In the first case, where nonleukoreduced RBCs had been transfused on Day 14 of shelf life, after molecular typing of the donor and recipient viruses it was concluded that the infection was more likely than not to have been acquired from the donor. Five other recipients of this donor tested HTLV negative: one had received nonleukoreduced components, and the other four had received leukoreduced RBCs.

The second case of an HTLV-positive recipient originating from the Caribbean had been transfused with leukoreduced RBCs, also on Day 14 of shelf life. This recipient was an elderly lady, born in Jamaica, and had no pretransfusion HTLV testing. No further work was carried out on the donor and recipient viruses, so it is not possible to reach any firm conclusion on the source of the recipient's infection. Of the other donations made by the blood donor, only two other recipients were alive and tested, and both were found to be HTLV negative. Transfusion transmission appears unlikely in this case.

The PLT components associated with HTLV-infected recipients were transfused within 5 days of collection, consistent with the shelf life of such components. The nonleukoreduced RBC components were transfused on Days 6, 8, and 14 of shelf life. The leukoreduced RBC component was transfused on Day 14.

DISCUSSION

For the 368 returned forms, 96% were traced to a named recipient. A total of 57% identified recipients were established to be deceased. This figure is of the same order as other studies examining the survival of transfused patients.[6,7]

The figure of 77% living recipients going on to testing is slightly higher than that achieved in the much more extensive HCV lookback, commenced in 1995, where the figure was 62%.[3] Some recipients in the HTLV lookback were not offered testing, or declined testing, usually because they were in an older age group, or the possibility of underlying (asymptomatic) HTLV infection was felt by the GP or the recipient to be irrelevant to the recipient at that stage. In those caseswhere this decision was made by the GP, the fact that the GP was informed of the risk, and it was recorded in the medical records, was felt to be sufficient to alert medical caregivers to consider the possibility of HTLV infection if there were concerns or relevant symptoms in the future.

After intense effort, 84% of forms were returned from hospitals. Although this might appear to be a good response rate, it should be remembered that laboratories were being asked to trace blood components issued up to a maximum of 7 years previously (and much less than this for the majority of blood components at the start of the exercise in 2004). All laboratories should have had electronic records covering this time span. The Blood Safety and Quality Regulations (2005) have stipulated that there should be retention of records for 30 years, but before this regulation laboratories would have been adhering to Royal College of Pathologists guidelines and storing

records for (generally) 11 years or so. The fact that retrieval of data was so difficult for many hospital laboratories must therefore be viewed with concern.

There are a number of possible explanations for the difficulties experienced, including the inability to trace the blood component(s) at all in the laboratory records and a change in record systems, with the old system not available to current staff. Information from returned forms shows that some relate to components that could not be traced at hospital laboratory level. It is likely that the majority of nonreturned forms also belong to this category. It is also possible that the likely recipient was identified in laboratory records, but staff were unable to access medical records to confirm further details about the recipient and evidence of transfusion. Finally, there may have been resource issues; lookback exercises often depend on the hospital laboratory manager or other senior staff members who have numerous other tasks to perform and ever-decreasing resources.

Overall, the first stage of our lookback confirmed the findings of others[8] that a large amount of resource was required to identify a small number of asymptomatic infected recipients. Some recipients were not tested because the possibility of asymptomatic HTLV infection appeared irrelevant. A 2004 study in England[6] found that the mean age of recipients of transfusion was 60.9 years (median, 67 years; range, 0-103 years) and issues such as vertical transmission of HTLV through pregnancy or breast-feeding do not often arise. Furthermore, the 5-year overall survival for blood transfusion recipients aged more than 50 years is less than 50%. Nevertheless, we have knowledge of two cases of HTLV transmission due to blood component transfusion in England, before this lookback, where the transmission came to light because the recipients developed HTLV-associated myelopathy (HAM) and progressed rapidly to serious disability. A handful of such cases have been reported.[9] The resources required for lookback are not insignificant, and the further back a lookback extends, the more difficult it is to retrieve information. The resources that would be required, with diminishing returns, did not justify extending the lookback to donations which predate the current computer system, that is, Phase 2 of the lookback.

Seven recipients were found to be anti-HTLV positive. In one case, the donor was anti-HTLV-I positive but the recipient was anti-HTLV-II positive, and this case has been discounted as a case of transfusion transmission. This means that 5.3% of tested recipients and 4.0% of all identified living recipients were found to have evidence of HTLV infection. Although a transmission rate as high as 63.4% (26/41; 95% CI, 48.7%-78.1%) has been reported for infected blood transfusions in Japan,[10] the 29.4% (5/17; 95% CI, 7.7%-51.1%) infection rate of cellular components not subjected to leukoreduction observed in our study is in keeping with most previous reports. At the time of introduction of donor screening in Jamaica, 44.4% (24/54; 95% CI, 31.1-57.6) became infected,[11] with similar rates reported from Brazil,[12] 46.1% (6/13; 95% CI, 19-73.2), and the United States,[13] 27.4% (26/95; 95% CI, 18.3-36.3). Outliers to this pattern are the data from Sweden[14] with only three of 35 donations found to have resulted in infection (8.6%; 95% CI, 0%-17.9%) and early data from the United States[15] (12.8%; 95% CI, 7.2%-18.5%), although in the latter study HTLV-I and HTLV-II were not distinguished.

The lifetime risk of HTLV-associated disease is estimated to be between 5% and 7%,[16] comprising 3% risk of HAM and 2% to 4% risk of adult T-cell leukemia/lymphoma. The risk of other HTLV-associated diseases is less well documented but these include chronic disabling polymyositis as well as uveitis, thyroiditis, and alveolitis. As a proportion of the recipients included in the lookback would have been seriously ill and immunosuppressed, there might be a higher risk of lifetime HTLV-associated disease in this cohort of transfused patients. Nevertheless, the efficiency of the lookback procedure in detecting individuals infected with HTLV, and thus at risk of disease in the long term, was much less than that of the HCV lookback program where approximately one infected recipient was identified per 12 components entering lookback and per eight recipients identified. The equivalent figures for the HTLV lookback were one infected recipient per 62 blood components entering lookback, and per 51 recipients identified, although one of the seven infected recipients was clearly not infected by the transfused component.

Although the figures are small, our data provide evidence of the efficacy of leukoreduction in reducing the likelihood of HTLV transmission through blood transfusion to an estimated maximum overall transmission rate of only 3.7%. However, transmission of HTLV is known to be related to age of the component at the time of transfusion, and it is possible that the transmission rates we have demonstrated could be related to the age of the blood component rather than the effect of leukoreduction. We have therefore looked at the rates of HTLV positivity in tested recipients of PLT components that were all transfused within the 5-day shelf life for such components. None of 13 leukoreduced PLT components were associated with infected recipients, compared with two of six nonleukoreduced PLT components. These figures, although small, support a protective effect of leukoreduction.

There have been no documented transmissions of HTLV from cellular blood components transfused after 14 days of shelf life.[13,15,17] In our study, the only infected recipient associated with a leukoreduced component received RBCs transfused 14 days after donation, but this recipient had other risk for HTLV infection. One nonleukoreduced RBC component associated with an infected recipient was also transfused on Day 14 of shelf life. Although this recipient also had other risk for HTLV

infection, further molecular studies on the donor and recipient virus led to the conclusion that the viruses were related and transfusion transmission was more likely than not. However, this case is complicated by the fact that the donor's only risk for HTLV infection was PLT transfusion in the UK some years previously, and it remains possible that the PLT donor originated from the same area of the world as the infected RBC recipient, thus accounting for the related viruses found in the RBC donor and the infected recipient.

The one infected recipient of a leukoreduced cellular component was an elderly lady born in Jamaica. UK surveillance data show that 65% of HTLV diagnoses are made in women, who have a median age at diagnosis of 55. For those cases where ethnicity was reported, 61% were black Caribbean. Rates of HTLV infection in England and Wales (based on 2007 population data estimates) continue to be much higher among black Caribbeans at 48 per 100,000 population, compared to 5.4 and 0.2 per 100,000 in persons of black-African and white ethnicity, respectively.[18] Furthermore, this recipient received a RBC component transfused on Day 14 of shelf-life, and HTLV transmission has not been reported in cellular blood components transfused after Day 14. It is therefore unlikely that this case represents transfusion transmission of HTLV-I.

In conclusion, despite the small numbers involved, our findings support the view that leukoreduction significantly reduces the likelihood of transmission of HTLV-I infection through cellular blood component transfusion[19] by demonstrating at least 93% reduction in the odds of transfusion transmitted HTLV compared with nonleukoreduced blood components. This is the first study to demonstrate a positive effect of leukoreduction in reducing HTLV transmission and therefore adds to the available information.[20] On the basis of our results, the English blood service will be reconsidering the need for HTLV lookback for leukoreduced cellular blood components in the future.

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CONFLICT OF INTEREST

The authors certify that they have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in this manuscript (e.g., employment, consultancies, board membership, stock ownership, honoraria).

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