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DONOR INFECTIOUS DISEASE TESTING

TRANSFUSION

Human T-lymphotropic virus in Irish blood donors: Impact on future testing strategy

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Abstract

Aim: A risk-based approach to the testing of blood donations for Human T-Lymphotropic Virus (HTLV) should include an assessment of blood donation seroepidemiology. The objectives of the present study were to determine the proportion of HTLV positive units in Irish blood donations, and subsequently, to estimate the current risk of transfusion transmitted HTLV (TT-HTLV).

Methods: Over 3 million donations screened between 1996 and 2020, were included in the study (n = 3,666,253). Factors considered in the assessment of TT-HTLV risk included: (I) HTLV seropositivity, (ii) probability of a leucodepletion failure, and (iii) the HTLV testing strategy.

Results: Six HTLV positive donations were detected throughout the study period, all of them in previously unscreened blood donors (0.000164%; n = 6/3,666,253), 3 of whom had donated prior to the introduction of HLTV antibody testing. On average 0.11% of manufactured blood components assessed, failed to satisfy the leucodepletion quality assurance criteria of less than 1×10^6 cells/unit. In using these values to model the risk of TT-HTLV, it was shown that the combination of leucodepletion with either universal screening of all = donors, or selective testing of first-time donors, a possible HTLV transfusion transmitted infection would be prevented every 468–3776 years.

Conclusions: This is the first report on the proportion of HTLV positive in Irish blood donations (1996–2020) and will be used to inform blood donation screening policy in Ireland. Evidence is provided for recommending a selective HTLV donor screening algorithm in Ireland that is accompanied by a robust framework for continued surveillance of leucodepletion failure rate.

KEYWORDS

blood, donation, epidemiology, HTLV, human T-Lymphotropic virus, Ireland, risk, seropositivity

Abbreviations: ATL, Adult T-cell leukemia/lymphoma; CMV, Cytomegalovirus; HAM, HTLV-associated myelopathy; HTLV, Human T-Lymphotropic Virus; IVDU, Intravenous drug use; RCC, Red cell concentrate; TT-HTLV, Transfusion-Transmitted HTLV; TSP, Tropical spastic parparesis.

1 | INTRODUCTION

Human T-Lymphotropic virus type 1 and 2 (HTLV-1/−2) are retroviruses that infect an estimated 10–20 million people worldwide. Infection is life-long and asymptomatic in the majority.[1] There are two main clinical disease manifestations directly associated with HTLV-1 infection; adult T cell leukemia/lymphoma (ATL) and HTLV-1 associated myelopathy/tropical spastic parparesis (HAM/TSP), each with a lifetime risk of approximately 1%–4%, and a long latency period of approximately 30–50 years in immunocompetent individuals.[2,3] Although the association of HLTV-2 infection with neurological disease is not as clearly defined as HTLV-1, both viruses are associated with an array of other neurological features such as leg weakness, hyperreflexia, and urinary tract dysfunction, even in the absence of overt HAM. Furthermore, a higher likelihood of urinary tract infection, bronchitis, and pneumonia was observed in the follow-up of asymptomatic HTLV-1 and -2 infected blood donors.[4–6] HTLV-1 is endemic in Japan, parts of the Caribbean, sub-Saharan Africa, Iran, Melanesia, and Romania, as well as some indigenous peoples in the Americas.[7] HTLV-2 has a broad geographic range of distribution and is most often seen in indigenous peoples of the Americas, intravenous drug users, and their sexual partners.[7,8]

The collection of blood from donors with a low risk for transfusion-transmitted infections is a critical factor for transfusion safety. HTLV transmission is cell-mediated and therefore transfusion of cellular blood components is of particular importance as a potential route of transmission.[9] The estimated mean infectious window period for HTLV reported in a 1992 study using early generation assays was approximately 51 days.[10–12] HTLV antibody seroconversion rates of 12.8%–63.4% have been reported in those exposed to HTLV-antibody positive components. The onset of HAM/TSP can occur as early as 3 months after a blood transfusion contaminated with HTLV-1 and clinical manifestations of HTLV disease are more likely to present in immunocompromised individuals.[13] Molecular techniques for HTLV proviral DNA detection, are not usually part of blood donor screening algorithms, but are used in reference laboratories for the investigation of donors with reactive HTLV antibody results for example.[14–16]

In accordance with the European Directive (Directive 2004/33/EC Annex III) individuals who have a history of HTLV infection are permanently excluded from blood donation. In addition, the Irish Blood Transfusion Service (IBTS) introduced universal HTLV antibody testing in November 1996, followed by universal leucodepletion of blood components in 1999. Leucodepletion is a process by which leucocytes are removed by filtration from donated blood, thereby reducing the risk of febrile post-transfusion reactions, and the cell-mediated transmission of HTLV and other cell-associated viruses such as CMV.[17,18] A survey of HTLV blood donor testing in European countries reported several different HTLV screening strategies. These included universal HTLV antibody screening, selective HTLV testing of first-time donors, and for some, there was no specific requirement for HTLV blood donor screening.[19]

The World Health Organization (WHO) guidelines for transfusion-transmitted infection screening and the Good Practice Guidelines on Blood Transfusion (EDQM 20th Edition) advise that the need for HTLV blood donor screening, on either a universal or 'first-time only' basis, be assessed with reference to the regional 'epidemiological situation'.[20,21] In Ireland, limited data is available on the prevalence of HTLV infection, and the only data published to date found a high rate of HTLV-2 infections (13.5%) among persons who inject drugs.[8] The objectives of the present study were first, to determine the proportion of HTLV positive units in Irish blood donations and secondly, to propose the most appropriate TT-HTLV risk mitigation strategy based on these data and the effectiveness of leucodepletion. This is the first report of baseline epidemiological HTLV data in Irish blood donations and will directly inform local HTLV risk mitigation policies, as well as providing information on HTLV infection in Ireland.

2 | METHODS

2.1 | Blood donation population

All blood donations received by the Irish Blood Transfusion Service (IBTS) between 1996 and 2020 were included in the study ($n = 3{,}666{,}253$ blood donations). Blood donations were subsequently categorized as either (a) a first-time donation or (b) a repeat donation. Basic demographic details including age, sex, and possible route of HTLV acquisition were compiled for all HTLV positive donors. Donor selection criteria that are linked to reducing the risk of a possible TT-HTLV includes permanent exclusion of those with a history of HTLV infection or non-prescribed intravenous drug-use (IVDU), including individuals with a current sexual partner who has HTLV or injects non-prescribed drugs. In addition, a 12-month deferral applies to donors after the last sexual contact with a person who has a known HTLV infection or a history of IVDU. This study was carried out as part of a service development risk assessment, and a full research ethics committee review was not required.

2.2 | HTLV serological testing of blood donations

HTLV antibody testing was carried out between 1996 and 1997 using the Abbott commander system; from June 1997 to 2015 using the Abbott Prism HTLV-I/HTLV-II chemiluminescent immunoassay (ChLIA); and from 2016 to 2020 using the Abbott Alinity HTLV-I/HTLV-II Chemiflex immunoassay. All testing was carried out as per manufacturer's instructions. Repeat reactive results were referred to the UCD National Virus Reference Laboratory, Ireland, for confirmation and proviral load testing, as per Waters et al.[15]

2.3 | Leucodepletion filter failure rate

Pre-storage leucodepletion was carried out on all red cells and platelets to a component specification of less than 1×10^6 leucocytes per blood component using in line blood pack filtration for whole blood (Macopharma, REF LQT614B and FQE614B) and platelet pools (Terumo BCT, TACSI PL Kit, REF 93000) and at point of collection for platelet apheresis (Trima Accel LRS Platelet and Auto Pas, Plasma Set, REF 82321). Leucodepletion performance was monitored by counting residual leucocytes in approximately 2% of red cell concentrates (RCC), 30% of pooled platelets, and 100% of apheresis platelets as part of IBTS quality control procedures.

Quality control leucodepletion data from the three-year period of 2018–2020 were used to calculate the average leucodepletion filter failure rate (n = 36,814 tested / 428,497 units issued). A filter failure was defined as a filtered RCC or platelet unit with a residual white cell count (WCC) of greater than either (a) 1×10^6 cells per pack (p[filter-failure1e^6])[22] or (b) 3.6×10^5 cells per pack, respectively (p[filter-failure3.6e^5]).[10,23]

2.4 | Risk assessment of HTLV blood donation testing algorithm

The factors impacting the risk of TT-HTLV were defined as:

1. The percentage of HTLV positive units in the blood donation population, p[HTLV].
2. The leucodepletion failure rate p[filter-failure].

The probability of preventing a possible TT-HTLV (p[TT-HTLV]) was adapted from Seed et al,[10] and was calculated as a function of the filter failure rate (p[filter-failure]), the probability that the unit was contaminated with HTLV-infected lymphocytes using either universal or selective HTLV antibody testing (i.e., all donors versus first-time donors only, p[HTLV]).

$$\mathrm{p[TT-HTLV]} = \mathrm{p[filter-failure]} \times \mathrm{p[HTLV]}.$$

If HTLV antibody screening was discontinued, the risk of issuing a HTLV positive blood product, outside of the leucodepletion quality control specification, was estimated using the 2018–2020 leucodepletion data and the following equation, as outlined by the UK BTS Joint Professional Advisory Committee HTLV Working.[24]

$$\begin{aligned}\text{Corrected Residual Risk} = {} & (\#\text{products Issued}) / \\ & \Big[(\#\text{products issued Untested by QC}/ \\ & \#\text{Tested}) \times (\#\text{products tested} \\ & > \text{Filter failure specification}^{10e6 \text{ or } 3.6e5})\Big].\end{aligned}$$

2.5 | Statistical analysis

All results were collated and analyzed using Microsoft excel. Confidence intervals were calculated for the proportion of HTLV positive units using Medcalc statistical software.

2.6 | Results

2.7 | Proportion of HTLV positive units in Irish blood donations

A total of 3,666,253 blood donations, received by the IBTS between November 1996 to December 2020, were screened for HTLV-1/2 antibodies. Overall, only 6 donors had a serologically confirmed HTLV infection during this time, p[HTLV] = 0.000164%, which is approximately 1 in 611,042 donations. In addition, HTLV seropositivity declined from 0.29 to 0.05 per 100,000 donations, between the time-periods of 1996–2007 and 2008–2020, respectively (Table 1).

The 6 HTLV seropositive donors were all detected following 'first-time' HTLV antibody screening. Three donors had donated prior to the introduction of HTLV testing and 3 were first-time donors. HTLV was detected in 5 females and 1 male donor. Four of the donors were positive for HTLV-1 and two were positive for HTLV-2. All donors were followed up by a medical doctor and/or nurse at the time of detection. They were asked questions

TABLE 1 HTLV seropositive donations received between 1996 and 2020

Time-frame	HTLV-1/2 antibody screening	No of donations	# years	# donations per year	HTLV positives
1996–2020	First time donors only	359,767	25	14,391	6
1996–2007	All donors	1,735,131	12	144,594	5
2008–2020	All donors	1,957,428	13	150,571	1

TABLE 2 Demographics and risk factors of HTLV positive donors detected between 1996 and 2020

Date	HTLV genotype	Nationality	Age	Gender	First-time donor	First-time tested for HTLV
30/01/2007	HTLV-1	Irish	25	F	Yes	Yes
19/06/1997	HTLV-1	Irish	42	F	No	Yes
26/01/2011	HTLV-1	Irish	36	F	No	Yes
22/03/2001	HTLV-1	Irish	43	F	Yes	Yes
21/07/1998	HTLV-2	Irish	33	F	No	Yes
21/01/2000	HTLV-2	Irish	41	M	Yes	Yes

TABLE 3 Leucodepletion filter failure rate of red cell concentrates and platelets issued between 2018 and 2020

Year	Component type	# issued	# QC samples tested	Filter failure >1e6 cells			Filter failure >3.6e5 cells		
				N	Rate (%)	±[95% CI]	N	Rate (%)	±[95% CI]
2018	RCC	122,778	2610	2	0.07663	[±0.134]	101	3.86973	[±0.775]
	Platelets	20,901	11,603	8	0.06895	[±0.053]	56	0.48263	[±0.131]
2019	RCC	123,646	2479	10	0.40339	[±0.274]	64	2.58169	[±0.655]
	Platelets	22,461	8799	6	0.06819	[±0.062]	42	0.47733	[±0.151]
2020	RCC	116,591	2163	3	0.13870	[±0.188]	35	1.61812	[±0.562]
	Platelets	22,120	9160	10	0.10917	[±0.074]	54	0.58952	[±0.163]
Combined (2018–2020)	RCC	363,015	7252	15	0.20684	[±0.051]	200	2.75786	[±0.390]
	Platelets	65,482	29,562	24	0.08119	[±0.025]	152	0.51417	[±0.084]
Total	RCC + Platelets	428,497	36,814	39	0.10594	[±0.037]	352	0.95616	[±0.101]

relating to possible risk factors and mode of acquisition of HTLV. Heterosexual contact ($n = 2$) and intravenous drug use ($n = 1$) were identified as the likely modes of HTLV acquisition for 3 of the positive donors. Three of the donors had no known high-risk sexual contact or a reported history of intravenous drug use, they had an unremarkable travel history and were born in Ireland to Irish-borne parents. Therefore, despite a thorough investigation, no mode of HTLV acquisition could be identified. However, it is noted that one donor was co-infected with Hepatitis C virus, potentially indicating an undisclosed or unknown high-risk activity. Look-back investigation of recipients was performed where possible and no HTLV transmissions were identified (Table 2).

2.8 | Prestorage leucodepletion filter failure

Prestorage leucodepletion targets were derived from the European guideline quality standard of less than 1×10^6 white blood cells per unit.[22] A total of 0.21% of RCC ($n = 15/7252$) and 0.08% of Platelets ($n = 24/29562$) failed to meet the criteria of less than 1×10^6 white blood cells per unit, giving an average combined filter failure rate of 0.11% (p[Filter failure$_{1e6}$]; Table 3).

A second leucodepletion filter failure threshold, based on the published estimated infectious dose for TT-HTLV of 90,000 leucocytes with integrated provirus,[23] was used to retrospectively analyze the collated quality control data. A total of 2.76% and 0.51% of RCC and platelet,

TABLE 4 Probability of a producing a HTLV-infected blood pack

Time-frame	Testing strategy	p(HTLV-provirus)	p (filter failure$_{1e6}$) filter failure rate of 1×10^6 cells/pack	p (filter failure$_{3.6e5}$) filter failure rate of 3.6×10^5 cells/pack	p (TT-HTLV) filter failure rate of 1×10^6 cells/pack	p (TT-HTLV) filter failure rate of 3.6×10^5 cells/pack
1996–2020	First time testing	1.67E-05	1.06E-03	9.56E-03	1.77E-08	1.59E-07
1996–2020	Universal	1.64E-06	1.06E-03	9.56E-03	1.73E-09	1.56E-08
1996–2007		*2.88E-06*	*1.06E-03*	*9.56E-03*	*3.05E-09*	*2.76E-08*
2008–2020		*8.80E-07*	*1.06E-03*	*9.56E-03*	*9.32E-10*	*8.42E-09*

Note: The probability of producing a blood component containing HTLV-infected lymphocytes is dependent on donor HTLV seropositivity and the leucodepletion acceptance criteria.

TABLE 5 Prevented HTLV transfusion transmitted infections depending on the testing algorithm and leucodepletion criteria

		HTLV testing without leucodepletion		HTLV testing with leucodepletion (filter failure rate of 1×10^6 cells/pack)		HTLV testing with leucodepletion (filter failure rate of 3.6×10^5 cells/pack)	
Time-frame	Virus	No. donations	Years [±95% CI]	No. donations	Years [±95% CI]	No. donations	Years [±95% CI]
FIRST-TIME TESTNG							
1996–2020	HLTV-1&2	59,961	4 [±4.6]	56,600,266	3933 [±123.5]	6,271,052	436 [±41.5]
	HTLV-1	*89,942*	*6* [±5.4]	*84,900,400*	*5899* [±151.5]	*9,406,578*	*653* [±50.5]
	HTLV -2	*179,884*	*12.5* [±7.7]	*169,800,799*	*11,799* [±213.5]	*18,813,157*	*1307* [±71.5]
UNIVERSAL SCREENING							
1996–2020	HTLV-1&2	611,042	4 [±4.6]	576,792,470	3933 [±123.5]	63,905,984	436 [±41.5]
	HTLV-1	*916,653*	*6* [±5.4]	*865,188,705*	*5899* [±151.5]	*95,858,976*	*653* [±50.5]
	HTLV-2	*1,833,127*	*12.5* [±7.7]	*1,730,377,410*	*11,799* [±213.5]	*191,717,952*	*1307* [±71.5]
1996–2007		*347,026*	*2* [±3.5]	*327,574,937*	*2265* [±93.5]	*36,293,814*	*251* [±31.5]
2008–2020		*1,957,428*	*13* [±7.7]	*1,847,711,494*	*12,271* [±217.5]	*204,718,035*	*1360* [±73.0]

Note: The HTLV infection prevented per *X* number of donations or per *Y* number of years are listed.

were outside of this range, respectively, giving an average combined filter-failure rate of 0.96% (p[Filter failure$_{3.6e5}$]; Table 3).

2.9 | HTLV transfusion transmitted infection risk assessment

The probability of issuing a blood component containing HTLV-infected lymphocytes was calculated based on the number of HTLV seropositive donations, p[HTLV], and the leucodepletion filter failure criteria, p[filter-failure$_{1e6}$] or p[filter-failure$_{3.6e5}$]. As all HTLV positive donations over the last 25 years were detected in donors tested for the first time, the risk of issuing a blood component with HTLV-infected lymphocytes was approximately 10-fold higher if the donation was obtained from a first-time donor (Table 4). Leucodepletion alone significantly reduced the risk of transmission to approximately 1 possible TT-HTLV in every 56 million to more than 1 billion donations (Table 5). When the average number of donations each year is considered, it is estimated that screening of first-time donors or universal screening will prevent a possible TT-HTLV every 436–3933 years depending on the filter-failure criteria (Figure 1). Specifically, for HTLV-1, the more clinically significant virus, first-time donor screening should prevent a possible transmission every 653–5899 years. If HTLV testing is withdrawn completely it is estimated that there would be a risk of issuing a HTLV positive blood product in excess of the leucodepletion criteria of 3.6×10^5 or 1×10^6 every 476–4303 years (Table 6).

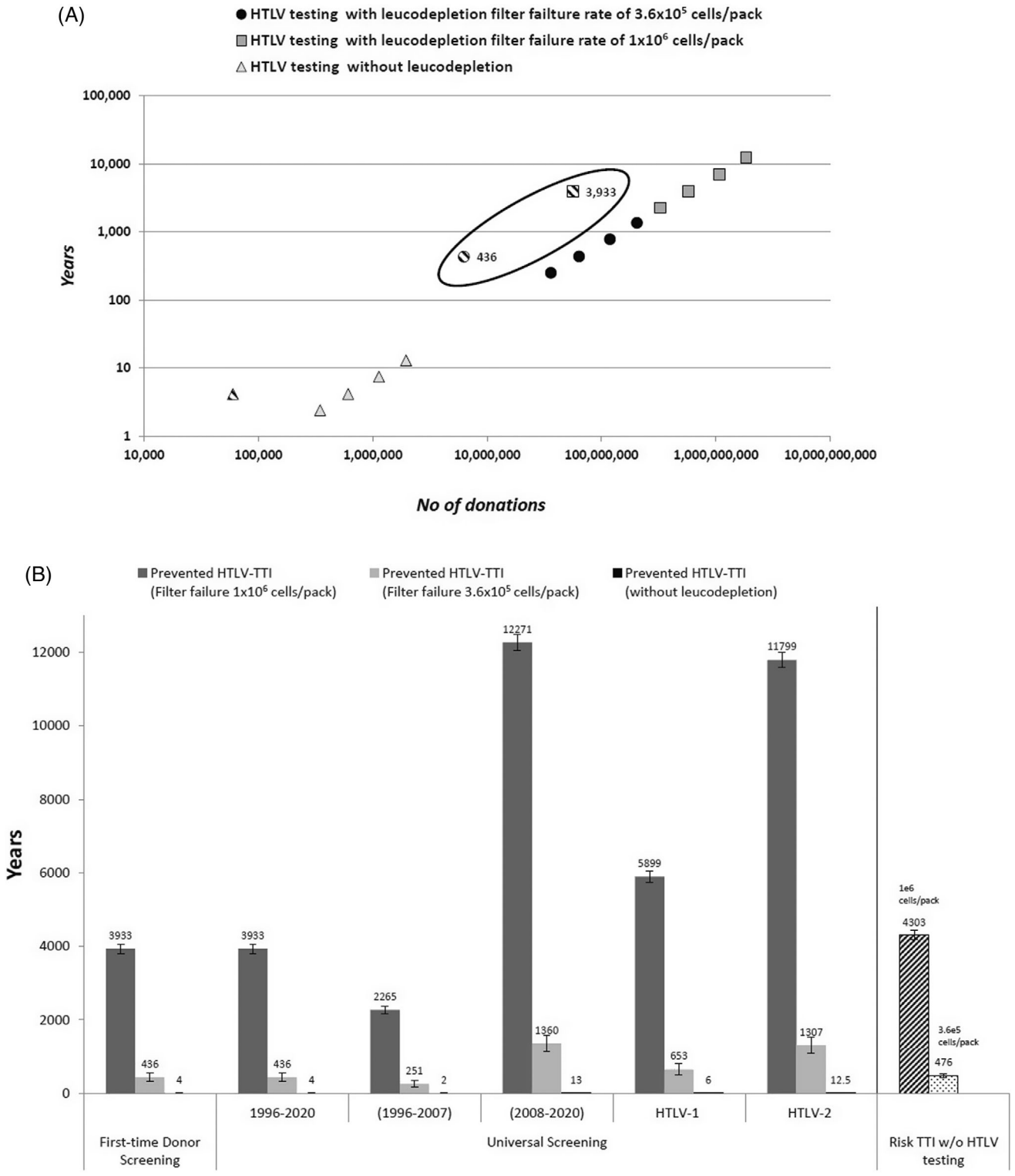

FIGURE 1 Prevented HTLV transfusion transmitted infections between 1996 and 2020 according to each testing algorithm. (A) The estimated number of prevented transfusion-transmitted HTLV infections (TT-HTLV) per number of donations screened per year is shown. A universal testing algorithm is depicted by filled shapes and varied depending on leucodepletion parameters. A selective first-time donor testing algorithm is depicted by striped shapes and varied depending on leucodepletion parameters. The circled values estimate the number of prevented TT-HLTV using selective first-time donor HTLV screening in combination with leucodepletion. (B) The estimated number of prevented transfusion-transmitted HTLV infections (TT-HTLV) compared to leucodepletion without any HTLV testing is shown. The prevented TT-HTLV for first-time testing, universal testing and per HTLV strain shown. Leucodepletion is the most significant factor at reducing TT-HTLV. Rates are based on quality control data from 2018 to 2020.

TABLE 6 Withdrawal of HTLV testing: Potential risk of a HTLV positive unit being issued

	No. donation issued without QC screening	Number of units outside of filter failure rate issued	% filter failure rate	Risk of HTLV positive donation	Risk of issuing HTLV positive units Years [±95% CI]
Filter failure rate of 1×10^6 cells/pack	391,683	379	0.097	1.6×10^{-9}	4303 [±129.5]
Filter failure rate of 3.6×10^5 cells/pack		3423	0.874%	1.6×10^{-8}	476 [±43.5]

3 | DISCUSSION

The present study determined, for the first time, the proportion of HTLV positive units in Irish blood donations, and the associated risk of a TT-HTLV in Ireland. The risk of TT-HTLV is influenced by a number of different factors, including donor assessment and donation deferral policy, disease prevalence, leucodepletion of blood components, the approach to serological testing and the assays used, blood component cellular shelf life, and pathogen reduction technologies.[25] Therefore, policy guidance from the WHO and the EU state that risk-mitigation strategies in the blood services should be informed by local prevalence data.

The estimated window period for detectable HTLV antibodies is not well defined and is dependent on the mode of HTLV acquisition, the infectious proviral load, the HTLV genotype and the screening methodology.[10–13,16] The residual risk for TT-HTLV based on the incidence/window period model has been estimated by other blood establishments, and can range from five per million donations in HTLV endemic countries, such as Brazil, to one per 20 million donations in non-endemic countries, such as France.[25] The model employed in our study uses data on HTLV antibody positive blood donations and the risk of leucodepletion failure to estimate the probability of preventing a possible TT-HTLV event. Although the model has the advantage of being simple to use, it does not include additional factors considered by other studies such as the infectivity of HTLV positive blood products (rate of HTLV transmission via cellular transfusion), the probability of developing HTLV disease after infection and the probability of dying from an unrelated disease.[26,27] We believe that given the very low seropositivity of HTLV in Irish blood donors and the application of universal leucodepletion at the IBTS, that the estimation of a very low transfusion transmission risk of HTLV is valid.

This study provides evidence that first-time and HTLV untested Irish donors have the highest risk of HTLV infection compared to repeat donors. In the United Kingdom the incidence of HTLV infection in first-time donors was also reported as significantly higher than repeat donors[28] such that the NHSBT, UK blood service, now screen for HTLV antibody in previously untested donors and non-leucodepleted donations only. This same trend was observed in the Netherlands, where the incidence of infection was approximately 3-times higher in first-time donors.[27]

TT-HTLV requires cell-to-cell contact between the infected white cells in a blood component and the white cells from the recipient, and cell free products such as FFP and plasma derivatives have not been shown to transmit HTLV infection.[9,26] This infers that filter-based leucodepletion, in the absence of additional testing, is a critical TT-HTLV risk mitigation step.[29] A UK lookback study showed a 93% reduction in HTLV transfusion transmission compared with non leucodepleted components.[30] Consequently, Norway, Finland, and Denmark, countries who also report a very low HTLV prevalence, have withdrawn HTLV testing completely.[19] Although the leucodepletion process should reduce the number of HTLV infected lymphocytes below the minimum infectious dose of the HTLV virus, the minimum number of leucocytes required for transmission is not absolute, and estimates vary greatly in the literature ranging from $>10^7$ to as little as 10^4 cells. If HTLV testing is completely withdrawn, there may still be a small risk especially where the recipient is immunocompromised, and therefore the quality control of the leucodepletion process becomes paramount.[31] The residual risk of a TT-HTLV decreased from 1 in 20 million to 1 in 178 million donations in France following a change in policy from HTLV testing alone, to HTLV testing and leucodepletion.[29]

The present study indicates that the IBTS has identified a very small number of HTLV positive donors and, importantly, no HTLV positive donors have been detected since 2011. However, due to the application of strict donor eligibility criteria during donor selection, this low seropositivity cannot necessarily be extrapolated to the wider population. Over the last 10 years 0.04% of donors who attended to donate, were deferred for intravenous drug use (IVDU). HTLV is not a reportable disease in Ireland and the data in the literature with regard to HTLV in the general population is limited. Indeed, further studies in at-risk populations, such as in persons

who inject drugs, are critical to calculate a true estimate of HTLV infection in the wider population.

This is the first report describing HTLV infections in Irish blood donors and will directly inform blood donation screening policy in Ireland. Evidence is provided for a selective HTLV screening strategy that is accompanied by a robust and quality-controlled framework for continued surveillance of leucodepletion failure rate. Future developments in blood component production will include pathogen reduction, which has been demonstrated to achieve a 4.7 log reduction in viral copies and will add a greater level of safety for blood products. A combination of leucodepletion and pathogen inactivation, when available for both platelets and red cells concentrates, may obviate the need for HTLV antibody donor screening in the future.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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