Risk assessment of first time donors and the use of their blood for Intrauterine transfusion and transfusion of infants aged less than one year.

Summary

A number of changes have occurred since the original recommendation was made by the Advisory Committee on the Microbiological Safety of Blood, Tissues and Organs for Transplantation (MSBTO) (in 1997) to use only donations from donors with a previously tested negative donation in transfusions for intrauterine transfusion (IUT) and infants.

While the basis for the recommendation has not been evident, it is understood that it was based on the widely accepted fact that there is a greater infectious risk from a donation from a previously untested donor compared with one from a previously tested donor.

- In 2011, new donors comprised approximately 16.2% of all donors and contributed 8.5% of all donations.
- There have been a number of changes to the tests used for screening of blood donors for markers of infection since the 1990s.
- Changes in testing methods have included the introduction of NAT (Nucleic Acid amplification Technology) testing for hepatitis C virus (HCV), human immunodeficiency virus (HIV) and hepatitis B virus (HBV) and as a consequence a reduction in the infectious window period for all three viruses, most markedly for HBV.
- The prevalence of infections in new donors is higher than that in repeat donors, but the rates of infections are lower in new donors aged 17-20 years compared to new donors in other age groups.
- The rates of infection in repeat donors are very low for all age groups and all markers of infection; however, young male donors have higher rates of HIV infection.
- The risk of a potentially infectious donation being released into the blood supply is estimated to be higher in donations from new donors than regular donors. For HBV during 2010-2011 it was estimated that 5.5 infectious HBV donations were missed per year in donations from new donors compared with 1.6 per year in donations from repeat donors.

- The overall estimated residual risk for all blood donations, if both new and repeat donors are accepted for transfusion to neonates and children under one year old, is expected to result in missing 1.9 potentially infectious HBV window period donations per year, one HCV positive every 10 years and one HIV positive every 2.7 years.
- Compliance with the donor selection guidelines is one of the most important risk-reduction measures for window period infections.
- Any change to the guidance around first and second donations should consider whether there are any differences in behaviour between new and repeat donors.

Background

Blood transfusions are required by a number of different patient groups; these groups may have different requirements in terms of the types of components required and, in some cases, additional testing may be needed. All blood is screened for a number of markers of infection using NAT testing to look for the presence of virus, and serological methods, including the presence of antigen and antibody methods, to look for past, current and chronic infection. All screening by serology is carried out on singleton samples whereas NAT is carried out in a pool of samples; this pool size has decreased over time. All donations found to be repeat reactive on screening are referred to the reference laboratory for confirmation using additional tests.

As well as the universal screening for infection, blood donations used for transfusion to specific patient groups ie neonates and IUT, undergo additional testing for cytomegalovirus (CMV). In addition, the British Committee for Standards in Haematology (BCSH) in their guideline document of 1994 recommend that blood for IUT and infants under the age of one is only used from donors who have given at least one previous screen-negative. This was recommended as a risk-reduction measure for transfusion-transmitted infections (TTIs). The minutes from a meeting of MSBTO (1997) report that infections from routine blood donor screening are 5-10 times lower in previously tested donors than new donors. No statement about risks of missing window-period incident infection in these new donors was included as data were not available at the time. This advice regarding use of donations from previously tested donors was reiterated in the updated BCSH guidelines in 2004 in a slightly different wording referring to donors, stating that components for transfusion in utero or to children under one year of age must be prepared from blood donated by donors who have given at

least one previous donation within the past two years which was negative for all mandatory microbiological markers.

A surveillance programme run by the joint NHS Blood and Transplant (NHSBT)/Public Health England (PHE) Epidemiology Unit has been in place since 1996 to collect and analyse data on the number and types of infection detected in both new and regular donors. In addition, modelling work is used to estimate the risk of an infectious donation not being detected on screening.

Introduction

SaBTO agreed on the 10th December 2012 that the UK blood services should undertake a review of the recommendation that all products for in utero transfusion or for infants under one year of age must be manufactured from a donation given by a donor who has donated within the last two years and was negative for all mandatory microbiological markers. This review was requested in part due to the recruitment of 17 year olds who are thought to be at a significantly reduced risk of variant Creutzfeldt Jakob disease (vCJD) having not been exposed to bovine spongiform encephalopathy (BSE) in the UK food chain (Club 96).

As part of this risk assessment the following were reviewed:-

- Changes in the testing of markers of infectious disease over time
- Changes in the estimated infectious window period, related to changes in testing
- Prevalence and incidence of infections in new and repeat donations, stratified by age
- The estimated risk that a donation entering the blood supply is a potentially infectious window period donation, for both new and repeat donors
- Any available information on compliance with donor selection guidelines
- Advice from the Standing Advisory Committee on Transfusion Transmitted Infections regarding any additional factors that should be considered in this risk assessment.

Operational implications

The original request was for a risk assessment of first versus second donation for those individuals being considered as part of club 96 ie donors aged 17 years and upwards; however any change in regulations around taking first donations would be applied to the

whole donor population. Therefore this paper considers infectious risk across all ages, but with an emphasis on the younger age groups.

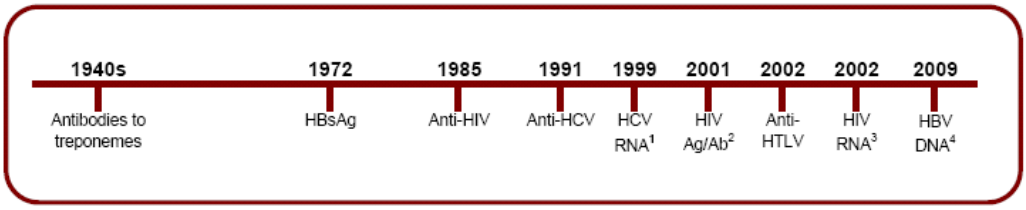
Change to blood donation testing

Window period

The infectious window period is defined as the time taken between an infection being acquired and potentially transmissible and it being detectable by routine screening tests. The window period for NAT is usually shorter than that for a serology test as virus is generally detected first, followed by antigen and then antibody. The window period of an infection may also include a short time when the infection can not be detected but nor can it be transmitted by transfusion (non-infectious window period).

Window periods for mandatory tests used in blood donation screening are estimated for both the NAT and serology test in use at the time. In the case of NAT, the pool size is of importance as a smaller pool size will result in an increase in sensitivity and a possible decrease in window period related to multiplication time of the virus.

Figure 1 Timeline of the introduction of microbiological tests for blood donations, UK [1]



1. HCV RNA testing was introduced on a pilot basis in 1999 and became a mandatory test carried out on all blood donations from 2002.
2. Northern Ireland and Republic of Ireland Blood Transfusion Services use anti-HIV.
3. HIV RNA testing was introduced in Scotland and Northern Ireland in 2002 and some parts of England and Wales from November 2003, but did not become universal until 2007.
4. HBV DNA testing began on 1 April 2009 in Filton as a by-product of the introduction of triplex NAT testing. HBV DNA testing was subsequently introduced at Manchester on 10 August 2009 and Colindale on 3 December 2009, when all donations in England were HBV DNA tested. HBV DNA testing began on 27 April 2009 in the Republic of Ireland and 1 June 2009 in Wales. Scotland and Northern Ireland began HBV DNA testing on 22 March 2010.

Testing using NAT began in 1999 with the introduction of HCV RNA testing as a pilot, and became a routine screening test by 2002. Currently, hepatitis C RNA (HCV RNA) is the only mandated NAT. The HIV window period was decreased by the introduction of fourth generation HIV Ag/Ab testing in England, Scotland and Wales in 2001. HIV RNA was added to

HCV RNA NAT from 2002 although not fully implemented for all donations until 2007. The most recent molecular test, a triplex NAT, to test for HIV, HCV and hepatitis B (HBV) DNA was introduced in April 2009 in NHSBT and across the rest of the UK blood services by 2010. The introduction of this test kit also resulted in a reduction in the sample pool size from 48 to 24 samples per pool, resulting in increased sensitivity for all three tests.

Each year virologists with expertise in the field advise the NHSBT/PHE Epidemiology Unit as to the appropriate estimated infectious window periods to be used in the calculations to estimate the risk that a donation entering the blood supply is a potentially infectious window period donation. The changes in estimated window periods over time are shown in Table 1 for HIV, HBV and HCV.

Table 1. Estimated infectious window periods used to calculate risk estimates by year [personal communication]

	Estimated window period in days		
Test	2004 Pool of 48 donations	2006-2008 Pool of 48 donations	2010-2011 Pool of 24 donations
HIV	Anti-HIV 15 Ag/Ab 11 HIV RNA 9	Anti-HIV 15 Ag/Ab 11 HIV RNA 9	Anti-HIV 15 Ag/Ab 11 HIV RNA 9
HBV	80.5	66.8	38.3
HCV	4	4	4

Tests for HIV and HCV are close to the limit of their sensitivity, however, changing pool sizes and the increased sensitivity of NAT has had some impact on the suggested HBV infectious window period.

There are two potential window periods in an acute hepatitis B infection; in early infection before the appearance of HBsAg and later in infection when HBsAg declines. The introduction of NAT allows the detection of virus, which may be present prior to the detection of HBsAg in some cases, hence decreasing the window period. The addition of NAT for HBV DNA has also resulted in the detection of occult hepatitis B cases, where HBsAg is below the level of detection in routine HBsAg assays but HBV DNA is detected. Although it is

thought that the virus in these cases is likely to be scarred and dysfunctional there is still a small possibility of transmission to a recipient.

The decrease in window periods consequent on introduction of NAT assays is expected to result in incident infections in donors being picked up earlier.

Donors with any marker of infection are withdrawn from future donation, however, in the case of acute HBV, they may return to donate if they clear the virus and acquire sufficient immunity within a set time of first detection of the acute infection.

Prevalence and incidence of blood-borne infections in the general population

Prevalence and incidence of blood-borne infections vary throughout the world. The local epidemiology of blood-borne infections is important in deciding both donor selection and donation screening policy.

In the UK the prevalence of both hepatitis B and C is low, with a prevalence of <2 % and 0.4 % respectively [2,3]. The majority of HBV infection in the UK is chronic infection, usually related to the country of birth of the donor or their mother. Hepatitis B infection is defined as acute or chronic on the basis of HBV markers, liver function tests (where available) and exposure history. Acute hepatitis B is usually acquired through sex, contact with blood of an infected individual or injecting drug use. It is generally not possible to ascertain whether HCV infections are recently acquired unless there is a very good exposure history provided by the donor. The most common risk factors associated with HCV infection are injecting-drug use, being born in a country where hepatitis C is prevalent eg Eastern Europe and parts of SE Asia, or in a small number of cases due to sexual contact. The most common risk for HIV is sexual contact. Data on the incidence and prevalence of blood-borne viruses is collected by PHE (previously the Health Protection Agency).

Acute hepatitis B in England

Health Protection Unit (HPU) notifications for the calendar year 2011 were matched with the laboratory notification dataset to assign acute hepatitis B infections [4]. Cases were assigned as acute if reported by the HPU as acute and anti-HBc IgM positive or anti-HBc IgM not reported. A total of 589 infections were identified as acute or probable acute infections; an

annual incidence of 1.13/100,000 in England with the highest incidence being reported in London. A risk exposure was reported for 50% of these infections with the most likely risk exposure assigned for 42%. A heterosexual risk exposure was reported for 58% of matched cases and 20% were thought to have been acquired through men having sex with men (MSM). Men aged 25-34 years had the highest incidence of acute HBV infection with a rate 3.11/100,000. It is proposed that some of the undisclosed risk may be due to MSM activity [4]. The rates of acute hepatitis B infection stratified by age are shown below.

Table 2. Rates of acute hepatitis B infection in general population in England during 2010

years	Incidence of reported acute hepatitis B/100,000[1]	
Age	Number	Rate
Under 15	2	0.02
15-24	94	1.37
25-34	156	2.26
35-44	145	1.94
45-54	99	1.39
55-64	59	0.97
65 years and over	34	0.40
Total	589	1.13

[1]Mid-2010 population, ONS

Hepatitis C epidemiology in England

Data on laboratory testing for anti-HCV is available from the hepatitis sentinel surveillance system. This contains data on both newly tested and chronically infected individuals - it is not possible to separate acute and chronic infections. A total of 160,590 individuals were tested during 2011 at the laboratories which report to the surveillance system with >98% completeness for gender and age [5]. A total of 41,111 individuals aged 15-19 were tested and 29,237 aged 20-34 years; 0.4% of the 15-19 year olds tested positive and 1.1% of 20-24 year olds. Of young adults tested aged 15-24, 0.9% tested positive compared with 2.6% of all individuals.

HIV epidemiology in the UK

By the end of 2011, an estimated 96,000 people were living with HIV in the UK (6). There were 6280 new HIV diagnoses, 52% of these in MSM. The Recent Infection Testing Algorithm

(RITA) was used to try and estimate whether infections were recently acquired ie within the last 4-6 months. Approximately 50% of all newly diagnosed HIV cases had RITA applied (3070), and of these 16% were assessed as being recent. The proportion of recently acquired infections varied by age. For individuals defined as heterosexual, the age group with the highest proportion of a likely recently acquired infection was those aged 15-24. Although numbers were small in this age group, 20/80 (21%) of women and 3/20 (14%) had a recently acquired infection. Of course older individuals will potentially have been at risk for a longer period of time and may have acquired their infection at an early age but not been tested.

Prevalence and incidence of infections in new and repeat donors

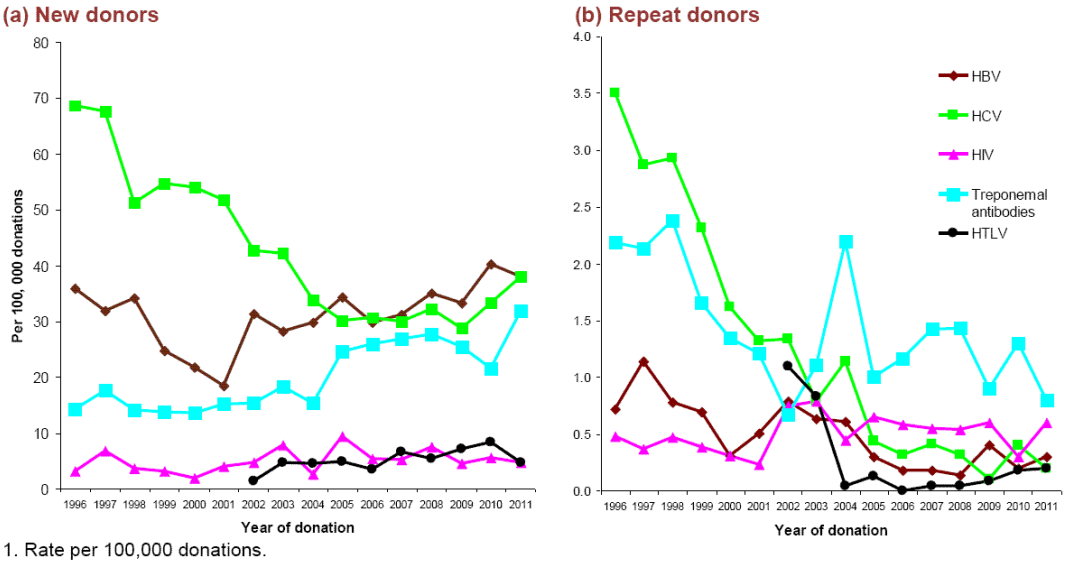
The number and rates of infection in new and repeat donors have been routinely collected since 1996 [7]. The numbers of infections in both new and repeat donors have decreased over time; however, the rate of infections in new donors continue to be greater than those in repeat donors (Figure 2). The majority of infections in new donors are prevalent infections ie infections that have been present for some time but for which the donor has never been tested. Occasionally a new, acute infection will be detected but this is uncommon. However, in regular donors all infections represent recently acquired infections in the inter-donation period and therefore will usually be a recently-acquired acute infection. Newly acquired infections are of great concern to the blood services as these are the infections that may be in the infectious window period and hence missed by donation screening. A combination of test infectious markers, avidity testing (where available) and donor history aids in the classification of these infections as either chronic or acute/recently acquired.

Between 1996 and 2011 the total number and rate of donors with any mandatory marker of infection have fallen by 40% from 19.9 to 12.1 per 100,000 tested [7]. The numbers and rates of infected donors are affected by rates in the general population, donor selection criteria and the compliance of donors with these donor selection criteria. Year-on-year the number and rate of infections has been greater in new donors, however this has fallen from 122.1 to 117.3 over this time period, a decrease in rate of 4%. In contrast, a greater decrease in markers has been observed in repeat donors from 6.9 to 2.1 per 100,000 donors but this decrease in repeat donors reflects a decrease in newly acquired infections as any prevalent infections would be detected on the first donation.

The numbers and rates of infections for HIV, HCV and HBV stratified by age and all markers of infection during 2010 and 2011 are shown in Table 3. In new donors it may not always be possible to identify an infection as acute for example hepatitis C. The rates of infections for new and repeat donors per 100,000 donations over a two year period is reported below. These data include both new and established infections in new donors.

Small numbers of infected donors are observed in the 17-20 year old donors. No cases of HBV were observed, one HCV infection in a repeat donor with an unidentified risk and two new cases of HIV in two young male donors. Given the small numbers of positive donations, statistical analysis has not been carried out. It is assumed that prevalent ie long established infections with positive serology would be detected on first donation; the greater risk is posed by recently acquired infections that may be in the window period.

Figure 2 The rate of markers of HBC, HCV, HIV, HTLV and treponemal antibodies in blood donations from new and repeat donors made at blood centres in the UK, 1996-2011 [7]



1. Rate per 100,000 donations.

Table 3 Number and rate (per 100,000 donations) of HBV, HCV and HIV in donations from new and repeat donors in England by age group, donor type and gender, 2010-2011.

Total number of donations tested: new and repeat donors during 2010/2011

Age group	New donors	Repeat donors
17-20	91,082	156,967
21-24	45,613	223,525
25-34	79,749	540,144
35-44	63,014	801,450
>44	67,008	2,002,682

Hepatitis B virus (HBsAg/ HBV DNA)

	New male		New female		Repeat male		Repeat female	
	No.	Rate	No.	Rate	No.	Rate	No.	Rate
TOTAL	**109**	**71.61**	**35**	**18.02**	**4**	**0.23**	**2**	**0.10**

Hepatitis C virus (HCV Ab/HCV RNA)

	New male		New female		Repeat male		Repeat female	
	No.	Rate	No.	Rate	No.	Rate	No.	Rate
TOTAL	**86**	**56.5**	**39**	**20.08**	**5**	**0.28**	**8**	**0.41**

HIV (HIV Ab/Ag; HIVRNA)

	New male		New female		Repeat male		Repeat female	
	No.	Rate	No.	Rate	No.	Rate	No.	Rate
TOTAL	**12**	**7.88**	**2**	**1.03**	**15**	**0.85**	**4**	**0.20**

All mandatory markers of infection (HBV, HCV, HIV, HTLV and treponema)

	New male		New female		Repeat male		Repeat female	
	No.	Rate	No.	Rate	No.	Rate	No.	Rate
TOTAL	**276**	**181.34**	**122**	**62.80**	**48**	**2.73**	**30**	**1.53**

Note
Summary data only are given in these tables.

New and acute infections

In general, acute infections are rare in blood donors - the vast majority of detected infections are chronic infections. As described above, it is difficult to assign an HIV or HCV infection as acute or newly acquired without a previous test and a good history. However, many HBV infections can be assigned as acute on the basis of markers. During 2011 four acute HBV infections were identified in UK blood donors - one late acute infection in a new donor and three seroconversions in donors who had donated in the previous three years.

Estimated risk of HBV, HIV and HCV in new and repeat donors

Current blood donation testing strategies minimise the risk of transfusion transmitted infections in the UK, however there is always the risk that a window period donation will not be detected and hence enter the blood supply. The risk of a window period donation being missed in the UK was originally estimated using the methods developed by Soldan et al [8] and adapted over the years. The model uses both observed data and expert opinion of the current tests in use by the UK blood services.

The risk that a donation entering the blood supply is a potentially infectious window period donation in the UK during 2010 and 2011 was estimated for donations from new and repeat donors according to the previously published method [8].

Incidence among repeat donors was calculated from the number of new infections (seroconverters) with evidence of a previous negative donation within three years divided by the number of person years at risk. The incidence in new donors was estimated as that in repeats multiplied by an adjustment factor (Z) which uses observed data in repeat and new donors and person years at risk of infection including the ratio of acute or NAT only yield in new versus repeat.

Two additional adjustments were made, to account for (i) the proportion of HCV positive donors who are likely to be uninfectious (those HCV RNA negative but anti-HCV positive) and (ii) the under-estimation of HBV incidence in repeat donors due to some infections being unknown to us because the infection has cleared before it can be detected at the next donation. The risk due to window period amongst donations from new and repeat donors was combined using the number of donations collected from repeat and new donors (91% from repeat donors, 9% from new).

The estimated number of potentially infectious HBV, HCV, or HIV window period donations per million donations that entered the UK blood supply during 2010-2011 was 0.76, 0.036 and 0.15 respectively (Table 5). At current donation levels (approximately 2.5 million donations each year), testing is estimated to *NOT* identify approximately two potentially infectious HBV window period donations every year, one potentially infectious HCV window period donation every 10 years and one potentially infectious HIV window period donation every 2.7 years. Donations from new donors that enter the blood supply were estimated to be more likely to be infectious compared with donations from repeat donors that enter the blood supply. This is due to an estimated increased incidence in new donors. From the calculated risks for all donors, HBV was the virus most likely to be missed on testing due to a window period donation during 2010-2011.

The number of reported confirmed transfusion-transmitted infections is much lower than calculated by the model. This may be due to the model overestimating the risk, immunity in recipients or infectious donations not being transfused. The most recent transfusion-transmitted infections were due to acute, window-period HBV infections in 2005 and 2011.

Table 5 The estimated risk that a donation entering the UK blood supply is a potentially infectious HBV,HCV or HIV window period donation per million donations (and one million donations), 2010-2011 Source: NHSBT/PHE Epidemiology Unit

Risk due to window period	*HBV*[1]	*HCV*[2]	**HIV**[3]
All donations			
Per million	0.76	0.04	0.15
1 per X years[4]	0.5	10.0	2.7
New donations			
Per million	2.19	0.15	0.21
1 per X years	0.18	2.6	1.9
Repeat donations			
Per million	0.62	0.03	0.15
1 per X years	0.6	13.3	2.7

[1] HBV testing assumed all donations were tested for markers of HBsAg and HBV DNA using NAT, with a window period of 38.3 days. However, Scotland did not commence HBV NAT until March 2010

[2] anti-HCV testing and HCV NAT with a window period of 4 days

[3]Combined HIV Ag/Ab testing and HIV NAT with a window period of 9 days.

[4] assume 2.5 million donations per year

All NAT was carried out in pools of 24 donations

Donor compliance

Donor selection guidelines are based on best evidence and aim to reduce the risk of accepting donations from people who may either cause harm to themselves, or may be at higher risk of infection and potentially cause harm to a recipient. However, these donor selection guidelines are only effective if people understand the questions asked of them on the donor health check and answer these as fully and truthfully as possible. The UK blood services collect information on donor compliance from donors who test positive for markers of infection, but currently we do not know the level of compliance in the general (non-infected) donor population. During 2010, 14% of donors with markers of infection were thought to be non-compliant, ie they had risk factors which if disclosed at donation would have resulted in a deferral [4,9]. Half of HIV positive donors had not complied with the donor selection guidelines, eight were MSM and one had a high-risk sexual partner. In 2011, 11% of infected donors were non-compliant with most non-compliant donors being HCV positive; these donors had not disclosed a previous history of injecting drugs.

NHSBT is working with PHE to develop a study to look at compliance in both new and regular donors who do not have any markers of infections. This study is currently at the pilot stage but it is hoped that a large study of 50,000 donors will run through 2013 and be completed in July 2014. There are some data available on compliance in MSM [10], however this may not be generalisable to all donors. The main reasons for non-compliance were reported as not understanding the questions, thinking that the question did not apply to them, and thinking risk behaviours were too long ago to be important.

Policy regarding first versus second donations in other countries

Currently some countries have different selection criteria in place for donors whose donations will be issued for use in neonates [11]. Only Italy and the UK request at least one previous negative donation; three previous donations in Italy, one in the last two years in the UK. Other risk-reduction measures across Europe include providing CMV-negative products and other measures such as providing parvovirus B19 negative donations in The Netherlands.

Although other countries may not have specific exclusions in place for neonatal collections they do sometimes qualify donors ie only take a sample at first visit. A small number of

European countries insist on potential donors giving a sample, which if negative allows donors to return to give a full donation. Currently Denmark, Lithuania, The Netherlands and parts of Germany take this approach - Italy intends to introduce qualification of donors in 2014. In addition, Australia only takes whole blood from first time donors: neither platelets nor plasma are processed at first donation. In the UK all apheresis donors are required to give a negative sample or to have been previous whole-blood donors before they can become component donors. Ireland tests all non-Irish donors by singleton NAT at first visit and only takes a full donation after a negative test (EID Monitor minutes).

Note: confidential information omitted here about transmission of infection abroad.

Problems with the qualification approach include the assumption that if a donor is negative on the first sample, they will not have had any high-risk behaviour in the intervening period before a full donation is taken; and the logistics of implementing such a scheme. The merit of a first time sample is dependent on the epidemiology within a country, the current testing in place and the sensitivity of the testing regime, but the main advantage is in detecting prevalent infections and therefore in avoiding the costs of collecting a donation which must be discarded. It is not clear what time-scale ECDC is working to.

Test seeking behaviours

The accessibility of tests for HIV and other blood-borne viruses varies across countries. In some European countries these tests are not available without payment, unlike in the UK where individuals can be tested for free at genito-urinary medicine clinics without having to give full details. In addition, greater efforts have been made to normalise HIV testing in the UK, with testing being routinely offered in some A&E centres in high-prevalence areas eg parts of London. There are few data on test-seeking among blood donors, except in those who are infected. To date, the NHSBT/PHE Epidemiology Unit surveillance data do not suggest that test seeking is a significant reason for donation, although a small number of donors report donating blood to find out their blood group for a variety of reasons.

Emerging infections

Emerging infections continue to be a cause of concern for all blood services. The greatest risk to the blood supply is posed by new and emerging infections which have long asymptomatic periods and thus it may be months or years before there are identified eg HIV. However, in recent years many of the emerging infections have been zoonoses, and related

to changes in climate and habitat of the host eg West Nile Virus. It appears unlikely that the risk of an emerging infection in a new donor is greater than in a repeat donor.

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