ORIGINAL ARTICLES

Surveillance report

# ESTIMATES OF THE FREQUENCY OF HBV, HCV, AND HIV INFECTIOUS DONATIONS ENTERING THE BLOOD SUPPLY IN THE UNITED KINGDOM, 1996 TO 2003

K Soldan[1], K Davison[1], B Dow[2]

Several new tests have been recently introduced by the United Kingdom Blood Services to improve safety. The frequency (or risk) of hepatitis B virus (HBV), hepatitis C virus (HCV) and HIV infectious donations entering the UK blood supply during 1996-2003 has been estimated. These years span the introduction of nucleic acid testing (NAT) for HCV, HIV combination antigen and antibody test and NAT for HIV.

The frequency of an infectious donation entering the blood supply due to i) the window period, ii) assay failures and iii) human and technical errors in testing and processing, was estimated. The window period risk was estimated using the incidence of infection in donors and the length of the window period for tests in use, with an adjustment for atypical inter-donation intervals in seroconverting donors.

The estimated frequency of infectious donations entering the blood supply during 1996-2003 was 1.66, 0.80 and 0.14 per million for HBV, HCV and HIV respectively. HCV NAT resulted in an over 95% fall in the risk of HCV. Current usage of HIV combined antibody-antigen tests and of HIV NAT reduced the estimated risk of HIV by 10%.

Since 1996, the risk of transfusion-transmitted HBV, HCV and HIV infection in the UK has been lowered by several improvements to donation testing, although the absolute reduction in risk has been small. Vigilance for errors and the affects of donor selection may be as or more important than further reductions to window periods of tests for improving blood safety with respect to HBV, HCV and HIV.

Euro Surveill 2005;10(2):17-19 Published online Feb 2005

**Key words:** blood donations, HBV, HCV, HIV, The United Kingdom, transfusion

## Introduction

Several circumstances can lead to HIV, HCV or HBV infectious donations entering the blood supply: collection of donations during the infectious 'window period' following infection when tests in use are unable to detect the infection; donations testing falsely negative due to test sensitivities less than 100%, and donations falsely issued as negative due to an error in sampling, testing, recording of test results, or removal of positive donations. Additionally for HBV, donations can be collected from individuals with fluctuating or waning levels of hepatitis B surface antigen (HBsAg) during later stages of HBV carriage, although this has not been observed in the UK in recent years, and is not considered here.

1. Health Protection Agency Centre for Infections, Colindale, London, United Kingdom

2. Scottish National Blood Transfusion Service National Microbiology Reference Unit, Glasgow, United Kingdom

## Methods

The probability of a donation being collected during the infectious window-period following infection when the tests used cannot detect evidence of infection was calculated by multiplying the incidence of infection by the length of the window-period, and then multiplying by an adjustment factor for atypical inter-donation intervals (S).

*Where, S = inter-donation interval for non-seroconverting donors / inter-donation interval for seroconverting donors*

*Incidence in repeat donors = number of seroconversions / Person years observed*

*and,*

*Incidence in new donors = incidence in repeat donors x new donor adjustment*

The adjustment (S) was 0.66 for HBV, 0.80 for HCV and 0.61 for HIV. The new donor adjustment factors for HBV, HCV and HIV incidence were 3.63, 6.15 and 2.29 respectively. These two adjustment factors were previously derived from other data [1].

The probability of a positive donation being released into the blood supply due to a false-negative test, and due to a failure, or error, in the testing system was calculated using the sensitivity of the test and the probability of a failure or error, respectively, and the prevalence of the infectious marker in the donations undergoing testing.

*Probability of false-negative test result = [(prevalence) x (1-sensitivity)] / sensitivity*

*Probability of infectious donation due to error = prevalence x frequency of process error*

Process error was defined as any error in the testing, recording, or discarding of infectious donations that would lead to release into the blood supply if it occurred during the testing of an infectious donation.

The prevalence and incidence of HIV, HBV and HCV, and the usage of the various tests over the 8 years was obtained from nationwide surveillance of donation testing. The observed frequency of seroconversion for HBsAg amongst repeat donors was multiplied by 2.68 to adjust for the expected frequency and duration of transient HBsAg as a marker of HBV infection [1]. The values used for other parameters were obtained from the literature or expert advice [Box]. The use of HCV NAT was assumed to take effect from 1 January 2000. In the presence of two tests (e.g. anti-HCV and HCV NAT), test and process errors for each test were assumed to be independent.

The overall frequency of infectious donations entering the blood supply was the sum of the frequencies for each risk component, minus the product of any mutually exclusive risks. A sensitivity analysis was conducted on the estimates for HIV risk during 2003 in England and Wales to determine the relative importance of the parameters used.

**Box**

**Values of parameters used in estimates, United Kingdom**

| Test | Infectious WP in days* [ref.] | Test sensitivity (%) [ref.] | Error frequency (%) |
|---|---|---|---|
| Single tests: Anti-HIV | 15 [2] | 0.999 (99.9%) [3] | 0.001 (0.1%) |
| HIV NAT (pools of 95 donations) | 8 | 0.995 (99.5%) | 0.001 (0.1%) |
| HIV ag/ab | 11 | 0.999 (99.9%) | 0.001 (0.1%) |
| Anti-HCV | 59 [4] | 0.990 (99.0%) [5] | 0.001 (0.1%) |
| HCV NAT (pools of 48 donations) | 4 | 0.995 (99.5%) | 0.001 (0.1%) |
| HBsAg | 80.5 ** | 0.999 (99.9%) | 0.001 (0.1%) |
| Combined tests: | | | |
| Anti-HCV & NAT | 4 | 1-((1-0.990)x(1-0.995)) =0.99995 (99.995%) | 0.0012=0.000001 (0.0001%) |
| Anti-HIV & NAT | 8 | 1-((1-0.999)x(1-0.995)) =0.999995 (99.9995%) | 0.0012=0.000001 (0.0001%) |

* 7 days were subtracted from Published window periods to give the infectious window periods.

** (=52 days [6] early acute window + 30 days late acute window in 95% of infections)

## Results

The frequency (both prevalence and incidence) of detected infections amongst UK blood donors was generally low and stable over the period analysed [Figure 1]. The prevalence of HCV fell over this period. During the last 2-year period there was, in contrast to the previous long-term decreasing trend, a slight increase in HIV infection amongst blood donors.

**Figure 1**

**Prevalence and incidence of HBV, HCV and HIV in UK blood donors, 1996-2003**

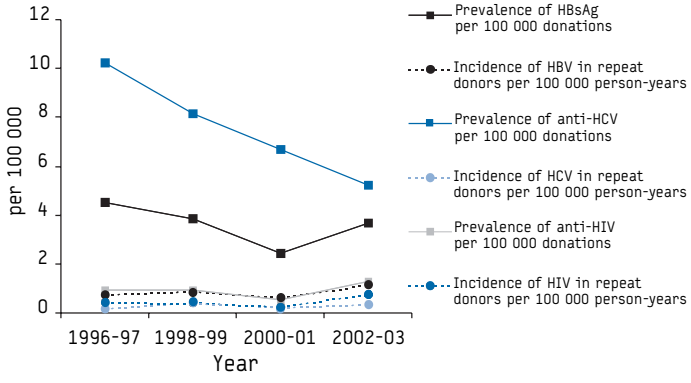



Table 1 and Figure 2 show the overall estimated frequency of infectious donations entering the blood supply in the UK, and the breakdown of this risk by cause (i.e. window period and infection incidence, or errors and infection prevalence) and by donor type (i.e. new donors and repeat donors).

**Table 1**

**Frequency of infections in donors and estimated frequency of HBV, HCV and HIV infectious donations entering the blood supply in UK, 1996-2003**

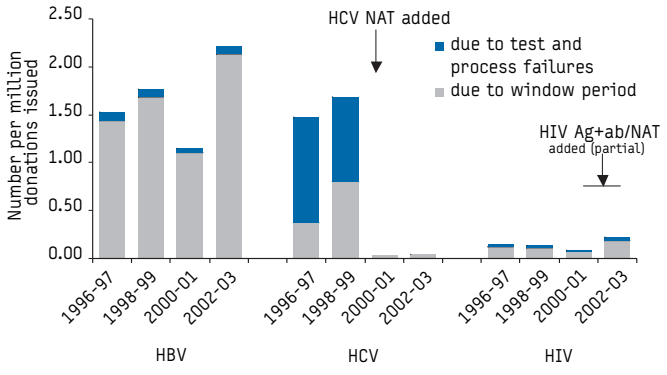
| HBV | 1996-97 | 1998-99 | 2000-01 | 2002-03 | 1996-2003 |
|---|---|---|---|---|---|
| Prevalence of HBsAg per 100 000 donations | | | | | |
| donations from new donors | 33.89 | 29.14 | 20.23 | 29.84 | 28.41 |
| donations from repeat donors | 0.93 | 0.74 | 0.41 | 0.73 | 0.70 |
| Incidence of HBV in repeat donors | | | | | |
| per 100 000 person-years | 0.77 | 0.90 | 0.60 | 1.16 | 0.85 |
| ***Test in use*** | ***HBsAg*** | | | | |
| **Overall risk per million donations** | **1.52** | **1.76** | **1.15** | **2.20** | **1.66** |
| risk due to window period donations | 1.43 | 1.68 | 1.10 | 2.13 | 1.59 |
| risk due to test and process errors | 0.09 | 0.08 | 0.05 | 0.07 | 0.07 |
| risk for donations from new donors | 4.72 | 5.33 | 3.56 | 6.70 | 5.07 |
| risk for donations from repeat donors | 1.13 | 1.32 | 0.88 | 1.70 | 1.26 |
| **HCV** | 1996-97 | 1998-99 | 2000-01 | 2002-03 | 1996-2003 |
| Prevalence of anti-HCV per 100 000 donations | | | | | |
| donations from new donors | 51.06 | 41.08 | 39.86 | 31.15 | 41.07 |
| donations from repeat donors | 2.39 | 1.84 | 1.09 | 0.86 | 1.55 |
| Incidence of HCV in repeat donors | | | | | |
| per 100 000 person-years | 0.20 | 0.43 | 0.22 | 0.34 | 0.30 |
| ***Test in use*** | ***antiHCV*** | | ***anti-HCV+NAT*** | | |
| **Overall risk per million donations** | **1.48** | **1.69** | **0.03** | **0.05** | **0.80** |
| risk due to window period donations | 0.37 | 0.80 | 0.03 | 0.04 | 0.31 |
| risk due to test and process errors | 1.10 | 0.88 | 0.00 | 0.00 | 0.49 |
| risk for donations from new donors | 8.51 | 8.88 | 0.14 | 0.19 | 4.51 |
| risk for donations from repeat donors | 0.58 | 0.78 | 0.02 | 0.03 | 0.35 |
| **HIV** | 1996-97 | 1998-99 | 2000-01 | 2002-03 | 1996-2003 |
| Prevalence of anti-HIV per 100 000 donations | | | | | |
| donations from new donors | 3.44 | 3.32 | 2.81 | 6.23 | 3.91 |
| donations from repeat donors | 0.61 | 0.65 | 0.26 | 0.74 | 0.56 |
| Incidence of HIV in repeat donors | | | | | |
| per 100 000 person-years | 0.44 | 0.41 | 0.28 | 0.77 | 0.47 |
| ***Test in use*** | ***anti-HIV*** | | ***Test A[1]*** | ***Test B[2]*** | |
| **Overall risk per million donations** | **0.14** | **0.14** | **0.09** | **0.22** | **0.14** |
| risk due to window period donations | 0.13 | 0.12 | 0.08 | 0.19 | 0.12 |
| risk due to test and process errors | 0.02 | 0.02 | 0.01 | 0.02 | 0.02 |
| risk for donations from new donors | 0.32 | 0.30 | 0.21 | 0.51 | 0.32 |
| risk for donations from repeat donors | 0.12 | 0.12 | 0.07 | 0.19 | 0.12 |

1 Test A: 86% anti-HIV. 14% anti-HIV+ag

2 Test B: 50% anti-HIV, 45% anti-HIV+ag and 5% anti-HIV+NAT

**Figure 2**

**Estimated frequency of HBV, HCV and HIV infectious donations entering the blood supply in the UK, 1996-2003**



The estimated probability of HCV infectious donations entering the blood supply fell by over 95% between 1998-99 and 2000-01, from 1 in 0.6 million to 1 in 32 million donations – less than 1 in 11 years. This was largely attributable to the introduction of NAT for HCV, due to both improved detection of incident infections, and the effect of double-testing for prevalent infections. Without the introduction of NAT, the risk would have fallen by approximately 34% due only to the reduction in the frequency of HCV infections in blood donors.

The use of HIV antigen tests on 45% of donations and HIV NAT on 5% of donations during 2002-2003 reduced the probability of HIV infection by approximately 10%, from 1 in 4.1 million (estimate with 100% donations only anti-HIV tested) to 1 in 4.6 million donations (0.22 per million), or once every 1.6 years. The higher frequency of HIV infection amongst blood donors during 2002-3 resulted in an over two-fold higher risk of infectious donations entering the blood supply than during the previous 2-years.

The combined risk of any of these three infections during 1996-2003 was 2.59 per million donations, or 1 in 385 000 donations. Seventy-eight per cent of this risk was due to window period infections and 22% was due to test failures and errors. Donations from new donors constituted 11% of the blood supply and contributed 34% of the HBV risk, 64% of the HCV risk and 24% of the HIV risk.

Variation of the parameters for the HIV estimates for the year 2003 showed the estimates to be most sensitive to changes in incidence and length of window period. A doubling of anti-HIV prevalence amongst donors would have increased the risk estimate by 13%; a doubling of the anti-HIV incidence would have increased the risk estimate by 83%.

## Discussion

The frequency of HBV, HCV and HIV infectious donations entering the blood supply in the UK during 1996-2003 was estimated to be low, and to have been decreased by the introduction of better tests for HCV and HIV infection. Transfusion recipients during these years were most at risk of exposure to HBV. The risk of exposure to HCV through blood transfusion is now extremely low.

For comparison with estimates from other countries, it is important to note that the estimates for HCV in the UK are based upon an infectious window period for HCV NAT of 4 days. It was the opinion of experts in the UK that HCV NAT was highly sensitive and the window period was shorter period than Published in the literature. Had we used a longer window period of 10 days, the overall risk of HCV per million donations in the presence of NAT testing would have more than doubled; from 0.03 to 0.07 per million donations in 2001-02 and 0.05 to 0.11 per million donations in 2002-03. Also, the overall risks include an effect for errors in the testing of prevalent infections, and for the higher risk associated with donations from new donors. Both these factors had important effects on the overall estimates for the UK. Leaving them out would lower the estimates. Including them leans towards caution, or overestimation, but we believe gives a better picture of the risk to transfusion recipients, and of the options to control and further reduce this risk.

When two testing systems were used in parallel we assumed independence of errors and so multiplied the probability of human or technical errors, making this component of risk negligible. This assumption is unlikely for some errors (e.g. specimen collection/labeling) and so may have resulted in conservative estimates of risk due to all human and technical errors when 2 tests were in use.

The estimates of risk associated with window period donations were sensitive to the incidence of infection, and therefore dependent on accurate and complete identification of seroconversions in repeat blood donors. The definition used for a seroconversion amongst UK donors during these years required proof of negativity for the "pre-seroconversion" donation. This is an important guard against falsely high incidence rates, but may in fact result in underestimation of incidence, as cases with no available archive sample may fail to meet the definition. In Scotland and Northern Ireland, archives are generally available for up to 20 years. In England and Wales they may be unavailable after 3 to 4 years. Repeat donors who seroconvert tend to have longer than average inter-donation intervals around the time of seroconversion. This observation was incorporated into our calculation of the probability of a window period donation, and lowered the estimated risk of infectious donations. The effect of this adjustment also showed that the risk contributed by serocoverters who are undetected due to inter-donation intervals longer than the archive-life of their last donation, would be relatively small.

These estimates should be used with caution. The probable range around each estimate is wide (not shown), and there are few data available to verify the results. The frequency of observed transfusion-transmitted HBV, HCV and HIV is broadly consistent with (i.e. lower than) the estimated frequency of infectious donations released. NAT detects infectious donations that are missed by serological tests and is therefore providing some data that can be used to validate components of these estimates. However, with the current low level of estimated risk, many years of data collection from NAT may be needed to test the accuracy of the estimates. So far, the rate of detection of infectious donations by NAT and by HIV combination antibody and antigen tests in the UK is not inconsistent with expectations based on these estimates. HCV NAT in the UK has detected approximately 1 infectious window period donation per 1.4 million issued as anti-HCV negative. This detection rate is a very close match to the expected rate, based on the risk of window period donations. The component of risk attributable to test and human errors in anti-HCV testing has not been evident, and this is starting to suggest that this risk may have been overestimated. HIV NAT has been applied to only 0.5 million donations so far (to mid-2004), and has yielded one infectious donation that was not detected by anti-HIV testing.

## Acknowledgments

We gratefully acknowledge all the staff who provided the data used in this study, particularly all reporters of data to the Infected Donors Surveillance system and Antoaneta Bukasa for extracting and preparing these data.

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