FFP Support Paper - 1

Provisional estimation of the risk of HIV, HCV and HBV infection in tested blood donations from repeat donors
CONFIDENTIAL report prepared for FFP meeting: 10th September 1996

INTRODUCTION

Estimates of the risks of transfusion transmitted viral infections are needed in order to monitor the safety of the blood supply and evaluate the likely benefit and cost effectiveness of new techniques proposed to improve transfusion safety. The current very low risk of transfusion-transmitted infections makes obtaining accurate rates by prospective measurement of infection rates in transfusion recipients impractical.
Potential for infectious donations to enter the blood supply exists due to the donation of blood by seronegative donors during the infectious window period following infection, and due to test and processing errors allowing a seropositive donation to enter the blood supply.
UK guidelines require that FFP and cryoprecipitate should only be collected from previously tested donors.
This report presents prevalence rates of markers of infection, and incidence rates of seroconversion among repeat blood donors, for HIV, HCV and HBV (in part - full data pending), and **provisional** estimates of the risk of HIV, HCV and HBV infection entering the (repeat donor) blood supply due to window period donations and due to errors.

This report does not estimate the number of recipients who would have been exposed to, and infected by, components produced from the estimated numbers of infectious donations.

This report does not include estimation of the risk of seronegative infectious donations from donors with post-acute infection (i.e. tail end HBsAg carriers, anti-HCV negative HCV infectious donors). Observed post-transfusion HBV infection is most frequently due to donation during the tail end of HBsAg carriage and work to estimate the risk due to this cause is ongoing.

METHODS

Study population
Information about donation testing during 1993, 1994 and 1995 was collected from all 14 blood centres of the English National Blood Service.

Definition of repeat donor
A repeat donor was a donor who was classified by the reporting blood centre as a repeat donor. Repeat donors have not necessarily been tested for all infections previously, and, on occasions, repeat donors may donate who have been previously asked not to donate again due to a confirmed infection. Not all infections detected in repeat therefore contributed to incidence rates.

Prevalence and incidence of HIV, HCV and HBV infection among repeat donors
All HIV and HCV seropositive donations from repeat donors and the number of donations tested from repeat donors were obtained from surveillance reports. HIV seroconversions were identified from the surveillance reports. Repeat donors with serological evidence of infection with HCV between donations were ascertained by a retrospective survey of blood centre records: the results of screening and confirmatory tests were reviewed in all cases to exclude possible false positives results or indeterminate test interpretations. A seroconverting donor was defined as a donor who made a seropositive donation during the study period (1993-95) who had made a seronegative donation within the previous ten years. Incidence rates were calculated as the number of seroconverting donors divided by the total number of person years at risk. The number of person years at risk was calculated as the number of donations made by repeat donors multiplied by the average interval between donations.

Blood centres were asked to provide information about HBsAg positive donations, and the HBsAg testing of previous donations, from repeat donors. The incidence rate for HBsAg was calculated as for HIV and HCV. As infection with HBV is not always identifiable on subsequent donations by HBsAg testing, an adjustment was made to the HBsAg incidence rate to take account of the variable patterns of HBsAg after HBV infection. The adjustment assumed that i) 94% of HBV infected adults have transient HBsAg lasting an mean of 120 days, ii) 1% of HBV infected adults have no detectable HBsAg, and iii) 5% of HBV infected adults become long-term HBsAg carriers (see Figure 1). All the long term carriers, none of the donors with no antigenemia and some of the donors with transient antigenemia are identified by HBsAg testing. The percentage of donors with transient antigenemia that would be identified by HBsAg testing was calculated by dividing the estimated duration of antigenemia (120 days) by the median interval

between donations for the HBsAg seroconverting donors with their first seropositive donation during the study period. The overall probability of detecting an incident HBV infection by HBsAg testing (adjustment factor Y) was therefore 0.94 x (120/median interval) + 0.01 x 0 + 0.05 x 1. The observed incidence rate of HBsAg was multiplied by 1/Y to give an estimated HBV incidence rate.
Blood centres were also asked to provide information about the number of repeat donors bled during acute HBV infection. The average pattern of infection markers during acute HBV infection was assumed to be as in Figure 2, and a second method based on the relative lengths of time when different markers of HBV infection are detectable was used to estimate the probability of a donor donating during an infectious, HBsAg negative, stage of acute HBV infection.

Probability of bleeding an infectious (window period) donation
The probability of a seronegative donation being made during the window period was equal to the incidence of infection amongst repeat donors, multiplied by the most recent estimate of the window period from infection to detectable anti-HIV/anti-HCV/HBsAg. The upper and lower 95% confidence intervals on the incidence rate, and the upper and lower values of the possible range of the window period were used to produce a likely range of probabilities. As viral replication for up to one week after infection may be necessary before a donation would be infectious, the estimated window period minus 7 days was used as the most probably infectious window period.

Probability of error
Test error was defined as 1 minus the sensitivity of current tests.
Process error was defined as any technical or human error in the testing, recording, or discarding of infectious donations. No published rates of technical or human errors in the testing, recording, or discarding of donations in the UK were found. A rate of error of 0.5% (Linden JV, Kaplan HS. Transfusion errors: causes and effects. Transfusion Med Rev 1994;8:169-83. and Linden JV. Error contributes to the risk of transmissible disease. Transfusion 1994;34:1016.) was used for the most probably estimate. The probability that a process error involving an infectious donation was equal to the estimated probability of a process error (0.5%) multiplied by the probability of a donation being infected.

RESULTS

Prevalence and incidence of infection
The reported number of HIV and HCV seropositive donations from repeat donors, post-seroconversion donations from repeat donors and the number of donations tested from repeat donors for English blood centres during the study period (1993-1995) are show in Table 1.

Table 1:

Year	Donor type	Number of donations tested	HIV seropositive	HIV post-seroconversion	HIV incidence rate per 100,000 person-yr	HCV seropositive	HCV post-seroconversion	HCV incidence rate per 100,000 person-yr
1993	Repeat	2,132,673	5	3	0.16	193	5	0.27
1994	Repeat	2,109,244	4	4	0.22	119	3	0.16
1995	Repeat	2,097,991	11	8	0.44	100	5	0.28
1993-95	Repeat	6,339,908	20	15	0.27	412	13	0.24

41 HBsAg positive donations from repeat donors had been detected by English blood centres during 1993-1995.
Note: At the time of this report, accurate data about donors seroconverting for HBsAg and about acute HBV infections are not available.

Based on data from one blood centre (Trent) about the number of donors tested during 1993-1995, the average interdonation interval for repeat donors over the three year study period was estimated to be 45 weeks (average number of donations per year per repeat donor = 1.16).

Probability of an infectious donation from a repeat donor entering the blood supply
The estimated risks of infectious donations from repeat donors entering the blood supply due to donation during the window period of infection and due to test and process errors are shown in Table 3.
The risks of a donation infectious for HIV or HCV entering the repeat donor blood supply (based on 1993-1995 infection rates) are of the order of 0.2 per million donations and 1.9 per million donations respectively. (Work is ongoing to estimate the risk of a donation infectious for HBV entering the blood supply due to donation during acute infection and due to errors: the risk is likely to be similar to, or higher than, the risk for HCV.)

Table 3: Estimated risks of HIV, HCV and HBV infectious donations from repeat donors 1993-1995

A range of estimates are shown: the most probable estimate is shown in a bold box.

HIV

a) HIV due to window period donations from repeat donors

		Incidence per 100,000 person-yrs (1993-1995)					
		lower 95% CI		Estimate		upper 95% CI	
Length of window period		0.135		0.273		0.412	
		Rate/100,000 donations	Number per year	Rate/100,000 donations	Number per year	Rate/100,000 donations	Number per year
range:low[1]	6 days	0.002	0.05	0.005	0.09	0.007	0.14
estimate - 1wk	15 days	0.006	0.12	**0.011**	**0.24**	0.017	0.36
estimate[1]	22 days	0.008	0.17	0.017	0.35	0.025	0.52
range:high[1]	38 days	0.014	0.30	0.028	0.60	0.043	0.91

b) HIV due to test and process error

	Test sensitivity					
Process error rate	100%		99%		98%	
	Rate/100,000 donations	Number per year	Rate/100,000 donations	Number per year	Rate/100,000 donations	Number per year
0.00%	0	0	0.003	0.07	0.006	0.14
0.10%	0.0003	0.01	0.004	0.07	0.007	0.14
0.50%	0.002	0.03	0.005	0.10	**0.008**	**0.17**

[1] Busch M.P., Lee L.L., Satten G.A., et al. 1995

HCV

a) HCV due to window period donations from repeat donors

		Incidence per 100,000 person-yrs (1993-1995)					
		lower 95% CI		Estimate		upper 95% CI	
Length of window period		0.108		0.237		0.366	
		Rate/100,000 donations	Number per year	Rate/100,000 donations	Number per year	Rate/100,000 donations	Number per year
range:low[2,3]	54 days	0.016	0.34	0.035	0.74	0.054	1.14
estimate - 1wk	59 days	0.017	0.37	**0.038**	**0.81**	0.059	1.25
estimate[4]	66 days	0.020	0.41	0.043	0.90	0.066	1.40
range:high[2,3]	192 days	0.057	1.20	0.125	2.63	0.192	4.07

b) HCV due to test and process error

	Test sensitivity					
Process error rate	100%		99%		98%	
	Rate/100,000 donations	Number per year	Rate/100,000 donations	Number per year	Rate/100,000 donations	Number per year
0.00%	0	0	0.066	1.39	0.133	2.80
0.10%	0.007	0.14	0.072	1.52	0.138	2.92
0.50%	0.033	0.69	0.096	2.03	**0.161**	**3.40**

[2] Lelie P.N., Cuypers H.T., Reesink H.W. et al. 1992

[3] Busch M.P., Korelitz J.J., Kleinman S.H., et al. 1995

[4] Barrera J.M., Francis B., Ercilla G., et al. 1994

Table 3: continued

HBV

a) HBV due to window period donations from repeat donors

Pending data.

b) HBV due to test and process error

Process error rate	Test sensitivity 100%		99%		98%	
	Rate/100,000 donations	Number per year	Rate/100,000 donations	Number per year	Rate/100,000 donations	Number per year
0.00%	0	0	0.007	0.16	0.014	0.32
0.10%	0.001	0.02	0.008	0.17	0.015	0.33
0.50%	0.034	0.08	0.010	0.23	**0.017**	**0.39**

FIGURES.

Figure 1: Development of HBsAg in HBV infected adults

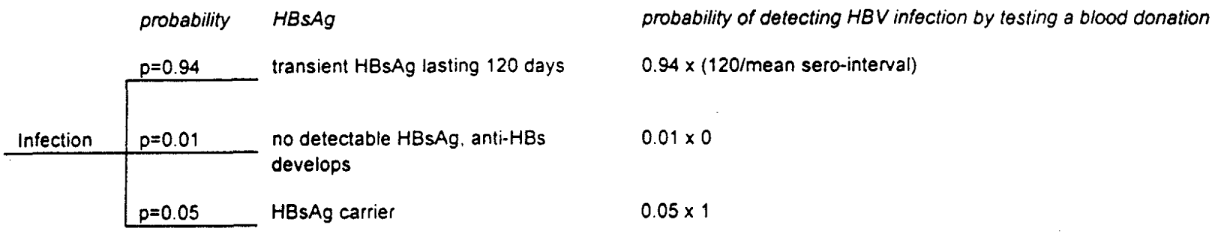
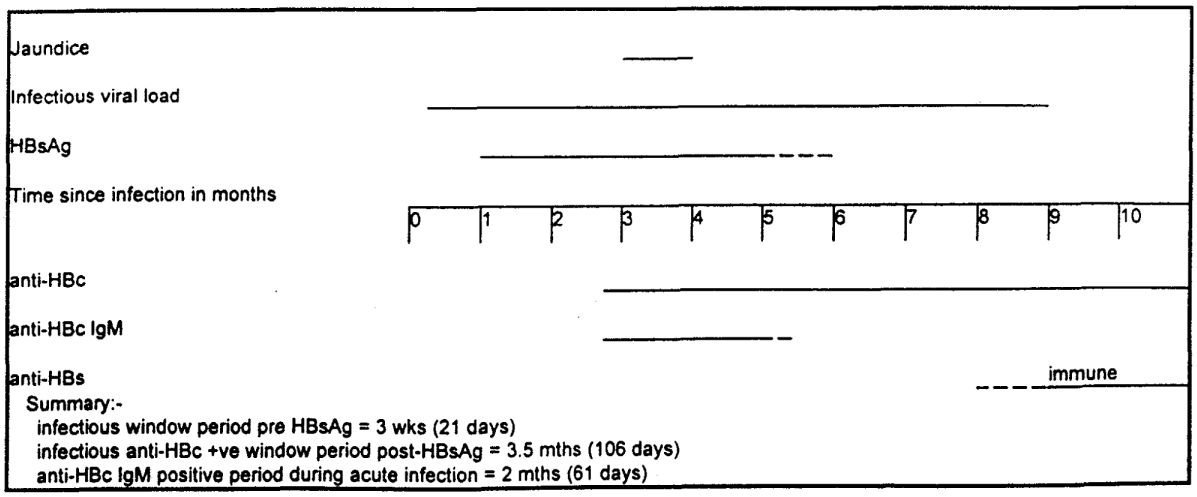


Figure 2: HBV serology during acute HBV infection



Discussion

These estimates are provisional, and may be revised following further discussion of the methods and additional collection of data.

The interdonation interval for seroconverting donors is longer than for the average donor. (The average interdonation interval for the 13 HCV seroconversions was 63 weeks) This will tend to make all the estimates overestimates. (The sensitivity of the estimates to the interdonation interval is such that increasing the average inter-donation interval by 20% (to 54 wks), decreases the window period risk estimates by 15% to 0.009 and 0.032 per 100,000 donations for HIV and HCV respectively, and decreasing the window period by 20% (to 36 wks) increases the estimates by 25% to 0.014 for HIV and 0.046 for HCV.)

The estimates are highly dependent on accurate and complete identification of seroconverting blood donors. Our definition of a seroconverting repeat donor required detailed information about the first seropositive donation and the last seronegative donation. If this information was absent, a true seroconversion may have been excluded from this study, and so our seroconversion estimates, and therefore risk estimates, may be conservative.

Several additional factors need to be considered in order to estimate the number of recipients infected e.g. number of components made, wastage of components, number of components transfused per recipient, recipient immunity, transmission rate. Detection of transfusion transmitted HIV, HCV and HBV is limited by sub-clinical infections, long lag periods between infection and disease and death from other causes. Furthermore, transfusion may not be suspected as the cause of clinically apparent post-transfusion infections, and such infections may not be reported to the blood transfusion service. Since HIV antibody testing of blood donations began, one HIV infectious donation to the Scottish National Blood Service has been detected by observed infection in a recipient (Crawford RJ, Mitchell R, Burnett AK, Follett EAC. Who may give blood? BMJ 1987;294:572.). No cases of transfusion transmitted HCV infection by HCV antibody tested blood donations have been reported.

Since reporting of suspected post-transfusion infections to the NBA began in October 1995, 1 transfusion transmitted HBV infection has been reported: a donation from an anti-HBc only donor, who had given a previous donation, i.e. was a repeat donor, was concluded to have probably transmitted HBV infection (look-back found the recipient of the previous donation to have died). At the NBS-North London Centre, between 1985-1993, 3/13 (23%) of observed transfusion transmitted HBV infections were due to acute infection in the donor, the remainder, and majority, were due to donors with anti-HBc only. A recent survey of post-transfusion HBV infections probably due to an anti-HBc only donor found approximately 6-7 such cases per year in England. The risk of HBV transmission by transfusion due to donors at the tail end of HBsAg carriage are therefore expected to be much greater than the risks due to acute infection or errors.

Report prepared by: Kate Soldan
Advisors to the study: Dr J Barbara and Professor R Tedder

Some of the methods used in this study have been used previously and are presented in:-
Lackritz E.M., Satten G.A., Aberle-Grasse J. et al. Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. N Eng J Med 1995;333:1721-5. and,
Schreiber G.B., Busch M.P., Kleinman S.H. The risk of transfusion transmitted viral infections. N Engl J Med 1996:334:1685-90.

References:

[1] Busch M.P., Lee L.L., Satten G.A., et al. Time course of detection of viral and serological markers preceding human immunodeficiency virus type 1 seroconversion: implications for screeing of blood and tissues donors. Transfusion 1995;35:91-7.
[2] Lelie P.N., Cuypers H.T., Reesink H.W. et al. Patterns of serological markers in transfusion-transmitted HCV virus infection using second generation assays J Med Virol 1992;37:203-9.
[3] Busch M.P., Korelitz J.J., Kleinman S.H., et al. Declining value of alanine aminotransferase in screeing of blood donors to prevent posttransfusion hepatitis B and C virus infection. Transfusion 1995;35:903-10.
[4] Barrera J.M., Francis B., Ercilla G., Nelles M, Achord D, Darner J, Lee SR, Improved detection of anti-HCV in post-transfusion hepatitis by a third-generation ELISA. - *Vox Sang* 1995;68:15-18.

Supporting document 2 for FFP submission to MSBT 10th Meeting

NBA Octaplas Trial - Status as at 30th September 1996

The objective of the study was to examine, by a randomised comparison of standard and solvent detergent treated (SD) FFP (Octaplas), immediate side effects, efficacy in correcting coagulopathy and seroconversion of the lipid coated (HIV, HBV and HCV) and non lipid coated (HAV, B19) viruses in approximately 70 patients requiring correction of coagulopathy prior to either liver transplant (LT) or liver biopsy (LB). It was also planned to treat 6 patients requiring plasma exchange for thrombotic thrombocytopenic purpura (TTP) with SD FFP only.

In September 1996, the eligibility criteria were extended to allow the inclusion of liver transplant patients whose coagulation was initially normal but in whom FFP was required during surgery.

To date, 30 patients have been treated, and although the rate of recruitment has increased significantly over the last 2 months, and the projection for the end of the trial (mid-January 1997) is 50-55 patients. The main reason for failure to reach target was the prolonged suspension of the study by the MCA. The shelf life of the product cannot be extended beyond mid-January 1997.

1. **Side effects.** Seven severe adverse events were reported (3 FFP, 4 SDFFP). Six of these were considered unrelated to the product, while the seventh experienced nausea and pruritis during infusion of SD FFP.

2. **Correction of coagulopathy.** In stable liver biopsy patients, maximal correction of prothrombin time was seen at 3 hours with either product. Statistical analysis will be performed at trial closure, but review of data on individual clotting factors has not to date highlighted gross differences. However, the numbers treated with each product in each disease category are too small for definite conclusions to be drawn.

Virology. All patients were HBsAg, anti-HCV and anti-HCV negative prior to the study, while 11/15 tested so far were anti-HAV positive. B19 results are awaited, as are 6 month post treatment virology samples for retesting.

Production of cryoprecipitate from SD FFP

As there is no licensed fibrinogen concentrate on the UK market, fibrinogen replacement is the main indication at present for the clinical use of cryoprecipitate. A small amount is also used for treatment of von Willebrand's disease. We have prepared cryoprecipitate from SD FFP (results attached). These suggest that SD cryoprecipitate would be an acceptable source of fibrinogen, but that treatment of von Willebrand's disease would not be efficacious.

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		Plasma	Cryoprecipitate	Fold increase
Factor VIII (iu/ml)	unTx	1.08 (0.092)	6.39 (0.884	5.9
	SDTx	0.64(0.040)	3.64 (0.243)	5.7
	p	<0.01	<0.01	NS
vWF.Ag(u/ml)	unTx	1.16(0.106)	12.15(1.326)	10.5
	SDTx	1.11(0.124)	4.52(0.479)	4.1
	p	NS	<0.01	<0.01
vWF.act(u/ml)	unTx	0.99(0.138)	9.60 (1.314)	9.7
	SDTx	0.58(0.088)	3.45(0.640)	5.9
	p	<0.01	<0.01	<0.05
Fibrinogen (g/l)	unTx	2.51(0.096)	9.79 (0.819)	3.9
	SDTx	2.08 (0.046)	7.08 (0.394)	3.4
	p	<0.01	<0.05	NS

Table 1. The mean (sd) for the 12 units from each group. unTx - untreated individual plasma units. SDTx = solvent detergent treated plasma units. p = probability, NS = not significant. The right hand column shows the mean cryoprecipitate concentration divided by the mean plasma concentration.

Supporting document 3 for FFP submission to MSBT 10th Meeting

Octaplas data

1992 - 1996 > 2 million units of SD plasma from > 3,000 batches for > 600,000 patients - no case of viral transmission confirmed.

January 1992 - December 1995 1,802,406 units of Octaplas sold ≡ 600,000 patient exposures.

During this period only 5 serious adverse events reported to Octapharma.

Clinical trial data same period - overall adverse reaction rate in patients = 17% (199 patients)