Papers

Incidence of seroconversion to positivity for hepatitis C antibody in repeat blood donors in England, 1993-5

K Soldan, J A J Barbara, J Heptonstall

Abstract

Objective: To estimate the rate of seroconversion to positivity for hepatitis C antibody in repeat blood donors in England and to describe the probable routes of infection in these donors.
Design: Retrospective survey of blood donors becoming positive for hepatitis C antibody and of the results of donation testing.
Setting: The 14 blood centres in England.
Subjects: All repeat donors giving blood between January 1993 and December 1995.
Main outcome measures: Number of donors developing hepatitis C between donations during the three years of testing for hepatitis C antibody at English blood centres and the rate of seroconversion among repeat blood donors. Probable routes of infection.
Results: 14 donors during 1993-5 fulfilled the case definition for seroconversion to positivity for hepatitis C antibody. The estimated seroconversion rate for infection with hepatitis C in repeat donors was 0.26 per 100 000 person years (95% confidence interval 0.15 to 0.43). Counselling after diagnosis found that four of these donors had risk factors specified in the criteria excluding people from giving blood but these factors had not come to light before donation. Another of the donors who seroconverted had a risk factor that has since been included in the exclusion criteria. Heterosexual intercourse was considered to be the most likely route of infection for five of the 14 donors.
Conclusions: The rate of seroconversion for positivity to hepatitis C antibody in repeat blood donors in England was extremely low. During 1993-5 fewer than 1 in 450 000 donations were estimated to have come from repeat donors who had become positive for hepatitis C antibody since the previous donation.

Introduction

In September 1991 blood transfusion services in the United Kingdom began routinely testing all blood donations for antibody to hepatitis C virus. Since then around 2 million healthy adults have been tested for the antibody each year by the English national blood service. National collation of test results and of characteristics of donors positive for hepatitis C antibody provides valuable information about donors and about a selected sample of the adult population of England.

Most acute infections with hepatitis C are asymptomatic, and most probably pass undetected. Recent infection is implied when a donation that is positive for hepatitis C antibody was preceded by a donation that was negative for the antibody. The testing of donations from repeat donors therefore provides a rare opportunity to identify incident infections with hepatitis C virus. Information about incident infections is of interest to blood transfusion services and to public health workers as it relates to current rather than past transmission of the virus. The selection process for blood donors aims to exclude donors who have recognised risks of contracting bloodborne infections. Incident infection in blood donors usually indicates one of three things: a failure in the definition or application of selection criteria; an unrecognised exposure to bloodborne infection; or infection through an exposure that is not included in the selection criteria because it is common in blood donors and thought to be associated with a comparatively small risk of infection. There remains a small risk of transmission of hepatitis C virus by transfusion from the infectious donations of donors who are negative for hepatitis C antibody and from failures in the testing and exclusion of donations that are positive for the antibody. The number of donors who seroconvert between donations is needed to estimate the risk of collecting a donation from a recently infected donor who has not yet developed detectable hepatitis C antibodies and hence the risk of transmitting hepatitis C by transfusion.

During 1994-5 we surveyed seroconversions to hepatitis C antibody detected by English blood centres from September 1991 to December 1995. We used these results with data from the infection surveillance system of the National Blood Authority and Public Health Laboratory Service Communicable Disease Surveillance Centre to estimate the rate of seroconversion to positivity for hepatitis C antibody in repeat donors in England during 1993-5.

Subjects and methods

Sample

Blood donations in England are obtained from voluntary unpaid donors. The selection procedure excludes people who are outside the age range 18-65 years, those who have been at known high risk of contracting

Public Health Laboratory Service Communicable Disease Surveillance Centre, London NW9 5EQ
K Soldan, *clinical scientist, National Blood Authority-PHLS CDSC*
J Heptonstall, *consultant microbiologist*
National Blood Service, London and South East Zone, London NW9 5BG
J A J Barbara, *lead scientist in microbiology*
Correspondence to: Dr Barbara john.barbara@nbs.nhs.uk

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bloodborne infections, and those who have any medical condition which contraindicates either the loss of 450 ml of blood or the giving of their blood to patients. The number of repeat donors in 1994 constituted around 4% of the population aged 18-65 in England in the middle of 1994.

During the study all donations were tested for hepatitis C antibody using enzyme linked immunosorbant assays (ELISAs). Initially reactive donations were retested by ELISA. Donations that were reactive on repeat testing were not used, and supplementary tests (additional ELISAs and recombinant immunoblot assay and, in some cases, the polymerase chain reaction for hepatitis C DNA) were performed on them to clarify the infection status of donors.

Donors with evidence of infection with hepatitis C virus were contacted by the blood centres and offered additional testing and counselling by the blood centre, with referral to a relevant medical specialist, or they were referred to their general practitioner for further management.[1] Risk factors for hepatitis C were discussed with donors during their follow up and any acknowledged by the donor were recorded.

Case definition

A standardised algorithm for confirmatory testing of blood donations had not been used, and we had to accommodate variation in the tests used. We used a comprehensive case definition that was designed to include all true biological seroconversions and exclude false positive results and any spurious results caused by changes in test format and performance over time.

The three case definitions were:

- Negative results in third generation recombinant immunosorbent assay in pre-seroconversion donation and positive results in third generation recombinant immunosorbent assay in post-seroconversion donation, without negative results in polymerase chain reaction for hepatitis C DNA for the post-seroconversion donation if given <12 months after the pre-seroconversion donation
- Negative results in ELISA and second generation recombinant immunosorbent assay in pre-seroconversion donation and positive results in ELISA (of same manufacturer and generation as pre-seroconversion test) and second generation recombinant immunosorbent assay in post-seroconversion donation, without negative results in polymerase chain reaction for hepatitis C DNA for the post-seroconversion donation if given <12 months after the pre-seroconversion donation
- Negative results in third generation ELISA in pre-seroconversion donation and positive results in third generation ELISA and recombinant immunosorbent assay in post-seroconversion donation, without negative results in polymerase chain reaction for hepatitis C DNA for the post-seroconversion donation if given <12 months after the pre-seroconversion donation.

Methods

In July 1994 all English blood centres were asked to return information about the tests performed and results obtained on the first donation positive for hepatitis C antibody (post-seroconversion donation) and the last donation negative for hepatitis C antibody (pre-seroconversion donation) for each donor who was considered to have seroconverted between donations since testing began in 1991. Seroconversions identified after July 1994 were also reported and included in the survey. Information was also requested about possible exposures to hepatitis C virus. In October 1995 the national system for the surveillance of donation testing was revised and seroconversions were then identified from routine surveillance reports.

Test results were examined to see whether they met the case definition. If they did not the reporting blood centre was contacted and asked for any additional test results or to perform additional tests on archived samples. Most commonly they were asked to perform parallel recombinant immunoblot assays on samples of pre-seroconversion and post-seroconversion donations. Follow up of missing returns and requests for additional information continued during 1995.

During 1991 (September-December) and 1992 most repeat donors tested for hepatitis C antibody were being tested by the National Blood Service for the first time. As a previous negative result on testing for hepatitis C antibody test is a prerequisite for seroconversion to positivity for hepatitis C antibody, rates for 1991 and 1992 were not calculated.

The rate of post-seroconversion donations in all donations from repeat donors was calculated by dividing the number of seroconversions by the number of donations from repeat donors. The number of donations from repeat donors tested for hepatitis C antibody during 1993, 1994, and 1995 was obtained from the national system for the surveillance of donation testing. The incidence of seroconversion was calculated by dividing the number of seroconversions by the number of person years at risk. The number of person years was estimated by dividing the number of donations from repeat donors by the average annual number of donations per repeat donor. The average number of donations per repeat donor at one blood centre (which tests 5% of the repeat donor donations in England) was 1.71 over one year and 3.49 over three years (1993-5). The average annual number of donations during the three years from 1993 to 1995 was therefore taken as 1.16 (3.49/3). This is equivalent to an average interval between donations of 0.86 years.

Results

We received 23 reports of putative seroconversion in repeat donors tested between September 1991 and the end of 1995. The test results available for seven of them did not satisfy the case definition. We asked centres to report on only the donors for whom full testing information was available, so these seven reports do not represent all the possible additional cases of recent infection with hepatitis C virus in repeat donors in whom the data are insufficient to satisfy our case definition. Two of the donors who fulfilled the case definition received their diagnosis during 1991 or 1992, and 14 of the cases were diagnosed during the study years, 1993-5 (table 1). The difference in the rates for 1993, 1994, and 1995 was not significant ($P=0.59$). Results from the polymerase chain reaction were available for 10 of the 14 donors: nine donors had positive results and one donor, whose first seropositive donation was

Table 1 Seroconversion to positivity for hepatitis C antibody among repeat donors in England, 1993-5

	1993	1994	1995	1993-5
No of donations from donors who had seroconverted since previous donation	5	3	6	14
No of donations from repeat donors tested for antibody to hepatitis C virus	2 140 712	2 116 178	2 105 038	6 361 928
Frequency of donations from donors who had seroconverted since previous donation	1 in 428 142	1 in 705 393	1 in 350 840	1 in 454 423
Rate of seroconversion per 100 000 person years (95% CI)	0.40 (0.17 to 0.96)	0.24 (0.08 to 0.75)	0.49 (0.22 to 1.08)	0.26 (0.15 to 0.43)

Table 2 Acknowledged probable exposure to hepatitis C virus in 14 repeat donors who became positive for hepatitis C antibody

Probable exposure to hepatitis C virus	Criterion for exclusion of blood donation in 1995	No of seroconverting donors		
		Total (n=14)	Men (n=8)	Women (n=6)
Injecting drug use	Yes	2	2	0
Heterosexual intercourse		5	1	4
Partner with hepatitis C*	Yes	1	1	0
Partner who injected drugs†	Yes	2	0	2
Partner with tattoos	No	1	0	1
Partner from country with high prevalence of hepatitis C	No	1	0	1
Blood contact with person with risk factors	No	1‡	1	0
None identified	No	4	2	2
No information		2	2	0

*At time of donation this selection criterion was not in use.[2]
†In one case, partner was found positive for antibody to hepatitis C after donor was given diagnosis; in other, antibody status of partner was not known.
‡Also reported on in Atrah et al.[3]

taken two years after the last seronegative donation, had negative results.

Five blood centres reported no seroconversions. Three centres reported more than one seroconversion; one centre in one of the Thames regions reported four cases and had the highest rate of seroconversion, and two centres, outside the Thames regions, reported two cases each. There was no significant heterogeneity between the rates by centre (deviance = 15.9, df = 13, P = 0.25).

The average interval between the pre-seroconversion and post-seroconversion donation for the 14 donors was 1.29 years (median 1.38 years, range 0.42-2.33 years). This interval was 1.5 times longer than the average interval in 1993-5 for all repeat donors.

Table 2 shows the reported probable exposures to infection of those who seroconverted (information about ethnic group was not gathered). The average age of all repeat donors was around 40. The mean age of the 14 donors who seroconverted was 30 years 6 months (95% confidence interval 26 years 7 months to 34 years 5 months); the mean age of the men was 31 years 5 months (26 years 1 month to 36 years 8 months) and of the women 29 years 4 months (21 years 1 month to 37 years 6 months).

Discussion

Estimating seroconversion rates

A total of 412 repeat donors who were positive for hepatitis C antibody were identified by English blood centres during 1993-5. Only 14 of them were proved to be incident infections with hepatitis C virus. This survey estimates the minimum rate of seroconversion to positivity for hepatitis C antibody in repeat donors in England during 1993-5. Our case definition excluded spurious seroconversion due to changes in test format and performance. The sensitivity and specificity of ELISAs and recombinant immunoblot assays used to test for hepatitis C antibody changed between 1991 and 1995, and third generation tests were introduced during 1993. By the time of this survey many of the archived samples from the pre-seroconversion donations under investigation had been used for repeat and supplementary tests or had been discarded, depending on each blood centre's protocol. Therefore, repeat and supplementary testing of pre-seroconversion donations was limited. Because we required evidence of comparably confirmed negativity for the last seronegative donation, we may have excluded some cases of true seroconversion. Previous reports of seroconversion to positivity for hepatitis C antibody with less strictly applied case definitions[4] have been justifiably challenged,[5] and we chose to identify clear cut rather than probable cases. Also, our survey was retrospective and relied on retrieval of blood centres' records of tests performed up to four years previously. For these reasons, this study may underestimate the number of donors who seroconvert and therefore the rate of seroconversion among repeat donors in England. Donations from repeat donors who were being tested for hepatitis C antibody by the national blood service for the first time during 1993-5 could not be excluded from the denominators that we used. A study conducted on donations during 1993 by one blood centre found 1.8% of donations from repeat donors to be from donors not previously tested for hepatitis C antibody by the blood centre.[6] This inaccuracy in our denominator is likely to result in a further, although slight, depression of the seroconversion rates as estimated from these data.

One blood centre has published reports about three cases diagnosed during 1993[3] and a further four cases diagnosed during 1994 and 1995[6] in which seroconversion was thought to have occurred. The blood centre obtained denominators of previously negative donors tested for hepatitis C antibody during 1993 and estimated the seroconversion rate during 1993 to be

2.78 per 100 000 (1 in 35 937) previously negative, repeat donors[3]: more than 10 times the estimate from our national study. However, the case definition used by this centre may have been flawed[7 8]; only one of the cases described satisfied the case definition that we used. We consider the estimate of the rate of seroconversion in repeat blood donors derived by this single centre to be erroneously high.

Blood donor sample

Selection criteria for donors aim at selecting a sample of the population that does not report a recognised risk for bloodborne infections before donation.[9] Since the early 1980s potential donors have been given explanatory literature, and since 1989 all new donors and donors who have not attended for two years or more have been directly questioned about risk factors. One centre has additionally asked donors to complete a questionnaire. The procedure for eliciting information about exposures to risk of infection with hepatitis C virus from infected donors has varied throughout the United Kingdom. A standard questionnaire for interviewing donors is soon to be introduced. Information obtained after donation from infected donors may be affected by bias related to the interviewer and the donor. Most blood donors infected with hepatitis C virus have reported a history of injecting drug use,[10–15] typically many years before donating blood. Almost one third of those who seroconverted in this study had no risk factors for infection with hepatitis C virus identified by the blood service. Testing the sexual partners of donors who seroconverted may help to establish the true extent of heterosexual transmission in the donor population. Uncommon routes of transmission and possible exposures that are not thought to be associated with risk of infection with hepatitis C should also be investigated.

Seroconversion for hepatitis C virus among repeat blood donors in England is rare. This implies that the incidence of hepatitis C in the population represented by repeat blood donors is now low or that selection criteria for donation of blood effectively exclude most repeat donors with current exposure to hepatitis C virus. During 1993-5, 14 donations (less than 1 in 450 000 donations) were obtained from donors who had seroconverted for hepatitis C virus since a previous donation was negative for antibody. During the same period 15 donations were obtained from donors who had developed detectable HIV antibody since their previous donation. The number of repeat donors who become infected with hepatitis C virus or other bloodborne infections but do not return to donate after their seroconversion cannot be ascertained by donation testing. In the future, tests for nucleic acids may enable detection of infectious donations that test negative for antibody.

Recipients and new donors

We did not determine infection with hepatitis C virus in those who received the seronegative pre-seroconversion donations. Tracing recipients of potentially infectious donations is conducted by blood centres, and one of the 14 pre-seroconversion donations has been shown to have transmitted infection with hepatitis C virus.[2]

Key messages

- The rate of seroconversion for positivity to hepatitis C antibody in English blood donors is low—0.26 per 100 000 person years during 1993-5 (95% confidence interval 0.15 to 0.43)
- The probable route of infection was unknown in a third of the blood donors who seroconverted during 1993-5 and who provided information on risk factors
- The exclusion of blood donors with a history of probable exposure to hepatitis C remains an important strategy to help keep the blood supply free of infection

Donations from new donors contributed 12% of the total number of donations collected in England during 1993-5. Seroconversion rates in new donors cannot be directly measured, and there are reasons to expect that recent infections in new donors may be more frequent than in repeat donors; repeat donors have been tested for negativity for markers of infection with hepatitis C virus, hepatitis B virus, HIV, and *Treponema pallidum*, and new donors may be more likely to donate blood to obtain testing after having been exposed to infection.

Opportunities for further work

Surveillance of donation testing and of donors who seroconvert for hepatitis C virus between donations continues to be an important component of monitoring the safety of the blood supply. Study of possible exposures to infection that are associated with seroconversion for hepatitis C virus and of the course of infection in seroconverting blood donors who have a known date of infection should further contribute to our understanding of the epidemiology and clinical course of hepatitis C.

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Contributors: JAJB initiated the survey, reviewed the test results and evidence for seroconversion for each reported case, contributed to the interpretation of the data and to writing the paper, and is guarantor for the paper. KS coordinated the survey, collated the data, conducted the analyses, and contributed to the interpretation of the data and to writing the paper. JH discussed core ideas and contributed to the interpretation and presentation of the data and to writing the paper.

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Screening for human T cell leukaemia/lymphoma virus among blood donors in Sweden: cost effectiveness analysis

Elsa Tynell, Soren Andersson, Eva Lithander, Malin Arneborn, Jonas Blomberg, Hans Bertil Hansson, Aud Krook, Mats Nomberg, Kristina Ramstedt, Agneta Shanwell, Anders Bjorkman

Abstract

Objective: To analyse the cost effectiveness of a national programme to screen blood donors for infection with the human T cell leukaemia/lymphoma virus.
Design: Three models for calculating the costs and benefits of screening were developed. The first model analysed the cost of continuously testing all donations; the second analysed the cost of initially testing new blood donors and then retesting them after five years; the third analysed the cost of testing donors only at the time of their first donation. Patients who had received blood components from donors confirmed to be infected with the virus were offered testing.
Setting: Sweden.
Main outcome measures: Prevalence of infection with the virus among blood donors, the risk of transmission of the virus, screening costs, and the outcome of infection.
Results: 648 497 donations were tested for the virus; 1625 samples tested positive by enzyme linked immunosorbent assay. 6 were confirmed positive by western blotting. The prevalence of infection with the virus was 2/100 000 donors. 35 patients who had received blood infected with the virus were tested; 3 were positive. The cost of testing every donation was calculated to be $3.02m (£1.88m); this is 18 times higher than the cost of testing new donors only, and only 1 additional positive donor would be discovered in 7 years. Regardless of the model used, screening was estimated to prevent only 1 death every 200 years at a minimum cost of $36m (£22.5m).
Conclusion: Based on these estimates the Swedish National Board of Health and Welfare decided that only new blood donors would be screened for infection with the virus.

Introduction

Human T cell leukaemia/lymphoma viruses types I and II were identified in the early 1980s[1 2]; serological tests for these retroviruses became available in 1986.[3] Infection with the virus is associated with tropical spastic paraparesis,[4] adult T cell leukaemia/lymphoma, and some inflammatory disorders.[5 6] The virus is primarily sexually transmitted,[7] but it may also be transmitted from mother to child either perinatally[7] or through breast feeding.[8 9] The virus may also be transmitted through blood transfusions.[10]

Japan began screening blood donors for infection with the virus in 1986.[11] Similar screening was introduced in the United States in 1988 and in France in 1991. Screening also occurs in Canada, Holland, Australia, Finland, Denmark, Portugal, Greece, and Luxemburg.

In Sweden, after a pilot screening of blood donors in 1993 the National Board for Health and Welfare decided to test all blood donations for one year starting in March 1994. We present an analysis of the cost effectiveness of this screening programme.

Subjects and methods

Blood donation—National data on blood donors and donation practices were obtained from the Swedish Society for Transfusion Medicine and the National Board for Health and Welfare. Before registering for their first blood donation potential donors complete a written questionnaire and are interviewed to assess possible risk factors for infectious diseases. All blood donations are tested for HIV, and hepatitis B and C; only the first donation is tested for syphilis.

Recipients of transfusions—There are no detailed national data on the recipients of blood transfusions. A pilot study was done at the blood bank at South Hospital which serves several other hospitals in the region. Data on 255 randomly selected patients who had received blood components during February 1992 were collected; this data included the age of the patient, survival time after transfusion, and which blood components were received.

National screening programme—In March 1994, a national one year programme to screen every blood and plasma donation for the human T cell leukaemia/lymphoma virus was launched. Screening tests were performed at blood banks, local microbiological

Division of Infectious Diseases, Karolinska Institutet, Danderyd University Hospital, Danderyd, Sweden
Elsa Tynell, *specialist, infectious diseases*
Anders Bjorkman, *associate professor*
Swedish Institute for Infectious Disease Control and Karolinska Institutet, Stockholm, Sweden
Soren Andersson, *immunologist*
Malin Arneborn, *nurse epidemiologist*
Kristina Ramstedt, *epidemiologist*
National Board for Health and Welfare, Stockholm, Sweden
Eva Lithander, *senior officer*
Section of Virology, Department of Medical Microbiology, University of Lund, Lund, Sweden
Jonas Blomberg, *associate professor*
Regional Centre for Communicable Disease Control, University Hospital MAS, Malmo, Sweden
Hans Bertil Hansson, *county medical officer*

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