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ORIGINAL PAPER

# Transfusion-transmitted hepatitis B virus infection in the UK: a small and moving target

K. Soldan,<sup>1,2</sup> J. A. J. Barbara<sup>2</sup> & B. C. Dow<sup>3</sup>

<sup>1</sup>Public Health Laboratory Service Communicable Disease Surveillance Centre, London, UK

<sup>2</sup>English National Blood Service, North London Blood Centre, Colindale, UK

<sup>3</sup>Scottish National Blood Transfusion Service, Microbiology Reference Unit, West of Scotland Transfusion Centre, Glasgow, UK

## Vox Sanguinis

**Background and Objectives** Transfusion-transmitted hepatitis B virus (TT-HBV) infections, when analysed in detail provide information about the nature and relative frequency of the sources of infectious donations. These cases are therefore used to inform blood safety strategies. This study updates previous reviews of the causes of TT-HBV in order to determine whether a change may have occurred in recent years.

**Materials and Methods** Cases of TT-HBV reported during 1998–2001 were reviewed and the nature of the infectious donations described. These cases were compared to a previously published case series reported during 1991–97.

**Results** Six cases of TT-HBV have been reported in the UK between 1998 and 2001. All were the result of infectious donations collected from donors with acute HBV infection. This is in contrast to the series reported during 1991–97 when only three of 14 similar cases were caused by acute infections in donors, with the majority of incidents being the result of chronic infection in donors.

**Conclusions** There appears to have been a change in the relative importance of acute and chronic HBV infection in blood donors in causing TT-HBV infections. Improvements in the sensitivity of HBsAg assays and/or a decrease in the prevalence of chronic HBV infection in blood donors could explain this observation. This change may have implications for strategies to reduce the risk of TT-HBV infection.

**Key words:** blood donors, hepatitis B, transfusion-transmitted infection.

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## Introduction

The testing of blood donations for hepatitis B surface antigen (HBsAg), and selection of donors at low risk of hepatitis B virus (HBV) infection, has resulted in a decreased frequency of post-transfusion HBV [1]. However, there remain (at least theoretically) three opportunities, or 'windows', for HBV-infectious blood to be collected: very early in the course of acute infection prior to the development of any serological markers of HBV infection; later, in resolving acute infection;

and even later, at the 'tail-end' of chronic carriage of infection. The latter two windows occur when HBsAg falls below detectable levels, but before infectivity (in the large inoculum of a transfusion) is lost [2]. HBV infection in donations collected during these latter two windows may be identified by testing for antibody to hepatitis B core antigen (anti-HBc). Additional risk of infectious donations arises from the occurrence of variants of the HBV virus with atypical markers of infectivity [3]. Such donations may also be identifiable by anti-HBc testing.

Reported cases of transfusion-transmitted infection (generally detected by investigation of symptoms) have provided information about the causes of transfusion-transmitted HBV (TT-HBV). In 1999, a review of post-transfusion acute HBV infections in England and Wales found that 11 of 14 proven transmissions reported between 1991 and 1997

Correspondence: Kate Soldan, Public Health Laboratory Service Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, UK

E-mail: kate.soldan@GRO-C

had been caused by donations collected during late chronic infection [4] (with HBsAg undetectable by one or more of the tests in routine use for donation testing). This was consistent with previous observations made at the North London blood centre.

### Materials and methods

In 1995, an enhanced surveillance system for all post-transfusion infections was established by the National Blood Services and the Public Health Laboratory Service Communicable Disease Surveillance Centre (PHLS CDSC). This surveillance system collates all reports of infections in transfusion recipients that the blood services are informed about, in order to investigate transfusion as a possible source of infection [5]. Reports include recipients with clinical acute HBV infections and recipients with asymptomatic acute infection and chronic or previous HBV infection, who have been diagnosed by routine or investigative testing. Occasionally, this testing is prompted by the discovery of HBV in a donor whose blood has been transfused to recipients. This system does not measure the frequency of transfusion transmission of infection – as many TT-HBV infections are probably unidentified and not reported – but does collate information about identified cases. These cases are expected to be representative of the causes of infectious donations.

Cases reported to this system over the 4 years since a previous study of TT-HBV infections (based on reports of

acute HBV infections to the PHLS CDSC) were reviewed and the causes of the infectious donations in these cases were compared to the previously published observations. In particular, the stage of the implicated donors' infections and the associated markers of infection present in these donors were examined.

### Results

During 1998–2001, six cases of proven TT-HBV infection were reported to the enhanced surveillance system for post-transfusion infections. All of these cases were found to be the result of donations collected from donors subsequently found to have clinical and/or serological evidence of acute HBV infection (see Table 1). Four of these six had an anti-HBc test result available: not surprisingly all were anti-HBc negative. Three of four cases with an HBV DNA test reported for the donation were HBV DNA positive. Of those with an anti-HBc-negative result, two were HBV DNA positive and one was HBV DNA negative [6].

The proportion of TT-HBV cases caused by acute infection from 1998–2001 was significantly higher than the proportion observed during 1991–1997 ( $P = 0.002$ , Fishers exact test).

### Discussion

Reports of TT-HBV in the UK over recent years suggest that – in contrast to previous observations – acute infection in

Table 1 Transfusion-transmitted hepatitis B virus (HBV) in the UK, 1991–2001

Year of report	Source of case details		Source of infectious donation	
	PHLS CDSC acute HBV surveillance, England and Wales	Surveillance of all post-transfusion infections, UK	Donor with acute infection	Donor with chronic infection
1991	2		0	2
1992	2		1	1
1993	5		1	4
1994	2		0	2
1995	1		0	1
1996	2		1	1
1997	0		0	0
Subtotal: 1991–1997	14		3	11
1998		2	2	0
1999		2	2 <sup>a</sup>	0
2000		1	1	0
2001		1	1	0
Subtotal: 1998–2001		6	6	0
Total: 1991–2001	14	6	9	11

<sup>a</sup>One case was only detected as a result of the diagnosis of acute infection in the donor.

PHLS CDSC, Public Health Laboratory Service Communicable Disease Surveillance Centre.



donors is a relatively more important cause than low-level chronic infection.

There is no reason to expect any increasing bias to the detection and reporting of TT-HBV infections that are caused by donors with acute HBV rather than low-level carriage. One case reported during 1998–2001 was identified by an investigation that was instigated when the donor subsequently developed clinical acute HBV, i.e. was only identified because the donor had acute infection. Removing this case did not affect our finding of a significant change in the proportion of cases of TT-HBV occurring as a result of acute infections in donors between the two time periods ( $P = 0.005$ , Fishers exact test).

A decrease in the prevalence of chronic infection, and/or an increase in the prevalence of acute infection, amongst selected donors, could account for the observed change. There has been no deliberate effort by the Blood Services to preferentially improve the de-selection of individuals at increased risk of chronic HBV infection over this time, and we are not aware of any changes in recruitment that would be expected to have had this result. The introduction of anti-HCV testing in late 1991 is unlikely to have greatly affected the prevalence of chronic HBV in donors as the major risk factors for HCV (injecting drug use and transfusion) and for HBV carriage (country of birth and ethnic group) differ. (No dual HBsAg- and anti-HCV-positive donors have been reported in the available data since October 1995.) There has, however, been a significant decrease (from 6.5 to 1.9 per 100 000) in the prevalence of HBsAg in all donations in the UK between 1995 and 2001 (NBA/PHLS CDSC Unpublished Six-monthly Infection Surveillance Report, No. 14). If this is a result of changing epidemiology in the general population, with HBV carriage becoming less prevalent with increasing year of birth, we would expect this trend to continue. This may have contributed to the absence of transmissions caused by chronic infections in recent years, and may further lower the risk of TT-HBV in future years. No increase in the incidence of acute HBV amongst selected donors has been demonstrated.

Another probable explanation for a decrease in HBV transmission as a result of chronic infection in donors is the improved sensitivity of tests for HBsAg over recent years, particularly with the introduction of the Abbott/Murex PRISM assay and GE 34/36 ELISA assay (Murex Biotech Ltd, Dartford, Kent, UK) [7]. The previously observed period of 'undetectable HBsAg' late in chronic infection may have been removed, or at least greatly narrowed, by improvements in HBsAg test sensitivity. Unfortunately we do not have appropriate samples from the donations implicated in previous transmissions from chronic carriers in order to test this hypothesis. The late acute window may also have been reduced.

The benefits of introducing anti-HBc testing in addition to HBsAg testing have been debated for a number of years. The

change described here in regard to the relative importance of different causes of TT-HBV over the past decade – whatever the reasons for this change – may have implications for estimates of the effect that anti-HBc testing would have on the risk of TT-HBV. However, the benefit of anti-HBc testing with respect to detecting HBV variants [3] remains unchanged. Also, a retrospective study of recipients of blood from donors found to be chronic carriers negative for HBsAg (i.e. HBsAg negative, anti-HBc positive and with no, or  $< 0.1$  IU/ml, anti-HBs) in 1995–96 identified two recipients with probable TT-HBV and estimated the frequency of HBV transmission by chronic carriers negative for HBsAg to be 1 in 52 000 donations (confidence interval: 0.3–7.8 per 100 000) [8]. Although this study was conducted prior to the routine use of the more sensitive tests mentioned above, all donations identified to be from chronic carriers (who were negative for HBsAg by the assays in use for routine donation testing at that time) were confirmed to be HBsAg negative by the more sensitive Abbott PRISM and Murex HBsAg assays, thus demonstrating that HBV transmission from chronic carriers negative for HBsAg by the most sensitive tests available was occurring in the early 1990s. Furthermore, in Germany, highly sensitive singleton PCR for HBV DNA found seven of 729 (approximately 1%) HBsAg-negative, anti-HBc-positive donor samples to be HBV DNA positive at titres of  $\leq 10$  HBV DNA copies/ml (K. Roth, personal communication). Whether transmission by transfusion from these 'tail-end' chronic carriers with undetectable HBsAg is continuing in the UK is difficult to determine by direct observation, as most HBV infections are asymptomatic. Neither prospective studies of recipients, nor surveillance of identified transfusion-transmitted infections, are able to exclude with confidence the existence of the low frequency of transmission that these data suggest may still be occurring.

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