

Case reports

Lessons from practice

Two cases of asymptomatic HBV “vaccine breakthrough” infection detected in blood donors screened for HBV DNA

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Clinical records

Case 1

A 35-year-old male first-time blood donor who donated in June 2011 tested positive for HBV (hepatitis B virus) DNA (Box). DNA sequencing analysis identified HBV genotype E. The only other HBV marker present was anti-HBs (antibodies to HBV surface antigen), attributable to a full course of vaccination in 2003–2004. A follow-up interview identified heterosexual contact with a new partner as the likely source of infection. HBsAg (HBV surface antigen) remained undetectable throughout the 90-day follow-up period, and the donor was asymptomatic. Viral load peaked at 217 IU/mL and DNA was undetectable by 3 months. Coincident with DNA disappearance, the anti-HBs concentration increased from 101 IU/L to 518 IU/L, with subsequent detection of IgM anti-HBc (IgM antibodies to hepatitis B core antigen) and total anti-HBc indicative of recent infection.

Case 2

A 31-year-old male blood donor, who had donated three times previously, donated again in August 2011 and tested positive for HBV DNA. DNA sequencing analysis identified HBV genotype C. The only

other HBV marker present was anti-HBs, attributable to a full course of vaccination 10 years earlier. The donor had negative HBV screening results for all previous donations, including a negative HBV DNA result at his most recent donation in February 2011. A follow-up interview failed to identify any recent risk situation. The donor was born in Asia and had lived in Australia for 3 years. No family members were known to have HBV infection. The only past risk factor was a needlestick injury 5 years previously. The donor's partner, also born in Asia, had been vaccinated for HBV in the past. Follow-up test results showed subsequent appearance of HBsAg 1 month later, followed by HBeAg (HBV e antigen). Viral load peaked at 160 000 IU/mL (index + 52 days). Three months after the index donation, both HBsAg and HBV DNA were undetectable; however, IgM anti-HBc, total anti-HBc and anti-HBe (antibodies to HBeAg) were present, confirming recent infection. Consistent with Case 1, a marked increase in the anti-HBs concentration (to 894 IU/L) was observed subsequent to DNA disappearance. The donor remained asymptomatic throughout, but a slightly raised level of alanine aminotransferase (73 U/L; reference interval, < 40 U/L) was noted; other liver function test results were normal. ◆

A full course of HBV vaccine results in protective levels of neutralising antibody to HBV (anti-HBs, ≥ 10 IU/L) in over 90% of adults.¹ Rare cases of “vaccine breakthrough” infection in actively vaccinated individuals, mainly involving “vaccine escape mutants”, have been documented.^{2–4} The infecting strain usually carries mutations in the major antigenic region of HBsAg that result in suboptimal detection by HBsAg tests and, on occasion, incomplete neutralisation by vaccine-induced antibodies.⁴ Unless symptomatic, or tested for some other reason, these infections invariably go unrecognised. However, a sensitive HBV DNA assay near the onset of infection may result in an atypical test pattern suggestive of acute infection (ie, HBV DNA detected; HBsAg not detected; anti-HBc not detected; anti-HBs detected [caused by prior vaccination]). With increasing use of HBV DNA assays for blood donor screening, these cases are now more likely to be detected and referred for clinical management.^{5,6}

Nucleic acid amplification testing for HBV DNA reduces the window period for detecting HBV compared with serological screening, which will not identify donors with HBV infection before the appearance of HBsAg. In July 2010, to improve the safety of blood products, the Australian Red Cross Blood Service augmented its HBsAg screening protocol (PRISM HBsAg assay, Abbott Diagnostics) by implementing nucleic acid amplification testing of all donations (ULTRIO HIV-1/HCV/HBV assay, Novartis Diagnostics). The two cases of apparent vaccine break-

through infection that we report were recognised subsequently; both blood donors had a history of HBV vaccination and were found to be HBV nucleic acid reactive with anti-HBs at protective levels (≥ 10 IU/L), and all other serological markers for HBV were initially non-reactive.

To our knowledge, these cases are novel in Australia. Similar occurrences have been reported in paediatric transfusion recipients in Taiwan⁷ and in blood donors in the United States^{5,6} and Thailand.⁸ They are distinct from chronic (ie, anti-HBc positive) occult HBV infection, which is characterised by undetectable HBsAg and very low levels of HBV DNA.⁹ Given the complete absence of detectable HBsAg in one donor, and that neither donor identified a past history of hepatitis (a trigger for anti-HBc testing), at least one case, and probably both cases, would have gone unrecognised before the implementation of universal HBV DNA testing. Consistent with previously published cases with comprehensive follow-up,^{5,6} the immediate and long-term clinical significance of these two cases of infection appears to be inconsequential. Neither donor reported any clinical symptoms of hepatitis, and both remained well during the period of follow-up. A slight rise in alanine aminotransferase level was apparent in Case 2, although all other liver function test results remained normal. Both donors had a transient viraemia followed by an increase in anti-HBs and seroconversion to anti-HBc, with detectable IgM anti-HBc confirming recent infection.

Summary test results for two donors with hepatitis B virus (HBV) infection and a history of HBV vaccination

	HBsAg	HBV DNA	Viral load (IU/mL)	Anti-HBs (IU/L)	Total anti-HBc	IgM anti-HBc	HBeAg	Anti-HBe	ALT	Genotype
Donor 1 (first-time donor)										
Index HBV DNA-positive sample	ND	D	85.6	101.2	ND	ND	ND	ND	NT	E
Index + 53 days	ND	D	217	131	ND	ND	ND	ND	NT	NT
Index + 90 days	ND	ND	–	518	D	D	ND	ND	NT	NT
Donor 2										
184 days before index donation	ND	ND	NT	NT	NT	NT	NT	NT	NT	NT
Index HBV DNA-positive sample	ND	D	210	23.7	ND	ND	ND	ND	NT	C
Index + 11 days	ND	D	633	28.6	ND	ND	ND	ND	NT	NT
Index + 34 days	D	D	9 690	NT	ND	NT	ND	ND	Normal	NT
Index + 52 days	D	D	160 000	32	ND	ND	D	ND	NT	NT
Index + 67 days	D	NT	–	> 100	ND	ND	D	ND	NT	NT
Index + 94 days	ND	ND	–	894	D	D	ND	D	73 U/L*	NT

ALT = alanine aminotransferase. D = detected. ND = not detected. NT = not tested. * Reference interval, < 40 U/L; other liver function test results were within normal range. ◆

Lessons from practice

- These atypical cases indicate the need to consider possible acute infection when hepatitis B virus (HBV) DNA is present with anti-HBs at apparently protective levels in an individual with a history of HBV vaccination (“vaccine breakthrough”).
- This may be relevant to clinicians when investigating a recent risk event, for example, high-risk sexual contact or a needle-stick injury, including vaccinated individuals with an anti-HBs level ≥ 10 IU/L.
- The immediate and longer-term clinical significance for the two donors appears to be inconsequential, and, since both cases were detected by routine HBV DNA screening these blood donations posed no safety risk.
- While the donors may pose a temporary risk to close personal contacts, the risk level is substantially lower when compared with classical acute infections. ◆

The viraemic period may mean that such individuals represent a temporary risk to others (for example, sexual partners and recipients of their blood). From the limited published data, it appears that the risk of transfusion transmission is substantially reduced compared with conventional window-period HBV infection. A number of studies confirm the infectivity of blood with detectable HBV DNA. Two cases of transmission where anti-HBs exceeds 10 IU/L have been reported, but none with levels above 30 IU/L.^{10,11}

The underlying mechanism of vaccine breakthrough in our donors is uncertain. Their genotypes (E and C) may be significant; one study noted that non-A2 genotypes were significantly more prevalent among five vaccine breakthrough cases,⁵ and the authors speculated that the HBV vaccine (with A2 parent strain) provides suboptimal protection against infection with non-A2 genotypes but sufficient protection to prevent clinical disease.

Since both donors had detectable DNA at their index donations and were therefore identified by our improved routine screening strategy, their donations posed no risk to the safety of the blood supply. Case 2 required a risk assessment of three prior donations, the most recent of which was 6 months before the positive index donation.

Since this previous donation was negative for HBsAg and HBV DNA, the components were considered not to have posed a transfusion risk. Our cases indicate the need to consider possible acute infection when HBV DNA in the presence of anti-HBs is demonstrated in an individual with an apparently protective anti-HBs level (vaccine breakthrough). In settings outside the Blood Service, this may be relevant to clinicians when investigating a recent risk event, for example, high-risk sexual contact or a needle-stick injury, including those situations where the anti-HBs level is ≥ 10 IU/L.

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Online-only box. Production please delete from print version of article**Important information for consumers from the Australian Red Cross Blood Service**

The addition of a new blood donor screening test for hepatitis B (HBV DNA) in Australia has identified rare cases of infection despite the donor being fully vaccinated (referred to as “vaccine breakthrough”). In the cases to date, the course of infection has been mild without any clinical symptoms of hepatitis. The immediate and longer term clinical significance appears to be inconsequential, and, since all cases to date were detected by routine HBV DNA screening, these donations pose no risk to the safety of the blood supply. While the donors may pose a temporary risk to close personal contacts, the risk level is substantially lower when compared to classical acute HBV infections. ◆

