Editorial

New minimum infectious level of hepatitis B virus proposed and continued testing for HBsAg questioned

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The factors involved in transmission of infection from transfusion are: (I) circulating level of infectious agent; (II) binding of virus to neutralizing antibody in the donor; (III) stage of infection in the donor; (IV) particular blood component transfused; (V) storage duration of infected RBCs; (VI) degree of immunosuppression in the recipient; and (VII) blood volume of the recipient (1). Thus, the level of circulating infectious agent in the donor is important but only one factor in determining the likelihood of infection transmission from a particular unit of blood (1). While a considerable amount of data is available related to infectivity of different levels of circulating virus, a wide range of levels is reported.

High rates of infection have been reported from transfusion of 180–56,000 copies/mL of HBV (2). Moderate rates of infection have been reported from 7, 9, <10 up to 500 copies/mL of HBV (2). Infection has been reported but the likelihood not specified from 2, 5, 10 and up to 620,000 copies/mL (2). In contrast it has been reported that 98, 100, 200 and as much as 19,800 copies/mL of HBV did not transmit infection (2). Thus, infection has been reported from levels as low as 2–5 copies/mL although it is difficult to conclude for certain the likelihood of infection at these low levels because similar levels are known to not lead to infection.

Previous work regarding HBV transmission estimated that the 50% minimum infectious dose of HBV was 1,049 copies/mL with range of 117 to 3,441 copies/mL (3). Weusten *et al.* (4) described a mathematical model estimating 3.3% and 14% infection from 3.4 IU or 18 copies/mL from blood components containing 20 mL (RBCs) and 200 mL (FFP) of plasma respectively.

A recent report by Candotti *et al.* (5) contributes more information regarding the level of circulating HBV that might cause infection. They report a study of nine recipients of blood from three blood donors with chronic undetected hepatitis B infection. In this chronic infection which has been called occult hepatitis B infection (OBI) donors have fluctuating low levels of circulating virus but fail to be detected by all routine screening tests including the usual HBV NAT tests.

The first two patients received fresh frozen plasma (FFP) from the same donor. Several other patients identified through look back were not currently infected although it was difficult to determine when the donor became infected and therefore whether those patients received infected blood. This donor was anti-HBC positive but negative for all other HBV tests.

A second donor was identified because a dialysis patient developed hepatitis following receipt of a unit of plasma from that particular donor. Look back identified post transfusion HBV infection in three of six recipients of FFP and one of three recipients of red cells from the donor's previous donations.

A third donor was identified when patients who had undergone cardiac and thoracic surgery developed hepatitis B. Lookback revealed that the patients had been transfused with a unit of FFP and RBCs from this same donor who later was found to have anti-HBc.

Altogether 47 patients were transfused with blood from the three implicated donors. Information was obtained from 31 of the 47 recipients. Seven of these had anti-HBs

and none of these became infected. Of the 24 remaining susceptible patients 9 (37.5%) were definitely, five (21%) probably, three (12.5%) possibly infected. Infection rates were 64% and 20% in possibly susceptible that is anti-HBs negative patients transfused FFP and RBCs respectively. The authors used very elegant phylogenetic trees of HBV sequences from the infected donors and patients showing identity of virus in donors and recipients. In summary, nine cases of HBV transmission are defined from three infected blood donors who were undetected with current sensitive HBsAg and HBV DNA screening methods. These donors had HBV virus levels of <3 IU/mL or <16 copies/mL. This would project to infection from RBCs containing 320 virions and FFP containing 3,200 virions based on the amount of plasma in these blood products. The authors propose that the minimum infectious dose of HBV is as low as 16 copies.

Candotti *et al.* (5) summarize by saying that their data show evidence of HBV transmission in nine of 31 or 29% of recipients from donors undetected by currently the most sensitive NAT methods. They emphasize that mostly infection was found from units of FFP presumably because of the larger volume of plasma compared to red cells.

One difficulty with determining the infectivity of a particular level of circulating agent is that "there is variability across recipients in whether infection occurs as result of transfusion of a blood component with a given nucleic acid concentration" (1). Several factors determine whether a particular unit of blood will transmit infection and only one of these is the circulating level of infectious agent. Even the same circulating level may have different infectivity at different stages of infection in the donor. In chronic HBV infection, there is a prolonged carrier state with low level viremia that could be missed by NAT screening. Anti-HBc testing could be valuable in detecting these silent HBV carriers but Candotti *et al.* (5) point out that while screening for anti-HBc would have identified the infectious donors they described but such screening is not feasible because in this particular situation it is estimated that 3% of blood donors would have been deferred due to anti-HBc most of whom would not be infectious.

In some situations, the level of virus differs very little between infectious and non-infectious blood. For instance, a viral load of 1,500 (180–56,000) copies/mL has been infectious in some patients while a viral load of 900 (200–19,800) copies/mL was not (2,3). There has been lack of infection from 1,200–1,500 copies from window phase donors and the 50% infectious dose was estimated as 400 virions (2,3).

Candotti *et al.* (5) continue to build information and experience on the likelihood of infection transmission for donors who are not detected as infectious with current sensitive testing methods, who may have fluctuating low levels of virus and whose blood can transmit HBV at virus levels as low as 16 copies (3 IU). This adds valuable information to the existing extensive but diverse experience on transfusion transmission of HBV.

Thus, in summary, current HBV mitigation strategies using NAT are effective in detecting most levels of viremia, but some low levels of viremia can be infectious some infections can be transmitted by test negative blood. However, Dodd *et al.* (6) have recently shown that elimination of HBsAg screening would have a negligible impact with a risk of less than 1 per 4 million donations. As a result, Katz and Sayers (7) urged that this new data be evaluated as an opportunity to determine the ongoing need for such testing.

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