Uncovering occult hepatitis B in blood donations: a tale of two worlds

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For almost fifty years, improvements in donor selection and screening have led to a continuous reduction in the risk of transfusion-transmitted hepatitis B virus (HBV). However, transmission can still occur when blood is collected from hepatitis B surface antigen (HBsAg) negative donors during the pre-seroconversion window period. Another source of transmission is represented by donors with occult HBV infection (OBI), a condition characterised by persistent HBV carriage in the absence of detectable HBsAg. In many countries, this prompted the introduction of nucleic acid testing (NAT) for HBV and/or antibodies to hepatitis B core (anti-HBc) testing in order to improve detection of infectious donations[1].

In principle, the implementation of both HBsAg and anti-HBc, and HBV NAT provides optimal safety levels as it permits the window phase of acute infection, persistent occult infection, and HBV variant strains to be detected. However, NAT screening is costly, and it is usually beyond the budget of low income countries. On the other hand, anti-HBc has good sensitivity but very low specificity in detecting infectious donations, and therefore its use is limited to regions at lower prevalence, where donor deferral is sustainable in terms of donation wastage[1].

The residual risk of transfusion transmission of HBV varies, therefore, worldwide, being greater in low and intermediate income countries, where the prevalence of the virus is higher and the implementation anti-HBc testing and/or NAT for HBV DNA is not affordable. However, the risk might not be negligible even in developed countries using HBV DNA but not anti-HBc, as the minimal infectious dose of OBI is below the limit of detection of current individual NAT assays[2].

A few months ago, a group of international experts with multidisciplinary backgrounds reviewed the existing knowledge of the biology and clinical impact of OBI[3], providing an update on a landmark paper published ten years ago[4]. It was agreed that transfusion transmission of OBI has a global relevance, the impact of transmissions is frequently underestimated, and the best preventive strategies to improve safety should be tailored to local prevalence and available resources.

This issue of the Journal includes two interesting contributions to the current debate on HBV screening in blood donors.

The article by Claudio Velati *et al*.[5] describes the trends of HBV infection in Italian blood donors over the last decade. In Italy, NAT HBV was introduced in 2008, while anti-HBc, in order to avoid shortages in the blood supply, is not considered mandatory[6]. The data for this study were collected within the Italian Haemovigilance System and included an impressive number of donations (almost 31 million donations from more than 17 million donors), providing solid grounds for risk modelling. According to their estimate, the overall residual risk of transmitting HBV was less than 1 per 2 million donations, i.e., the sum of the risks related to the window period (1 per 6 million) and OBI donations (less than 1 per 4 million). Notably, the risk substantially declined during the study period, and was lower in first time donors than in repeat donors. As argued by the authors, this likely reflects the increasing rate of vaccination coverage among young donors.

Clearly, like any estimate derived from mathematical models, these numbers should be taken with some caution. As a matter of fact, when the impact of OBI was assessed prospectively in European settings where anti-HBc was not performed, it was sufficient to examine thousands (not millions) of donor/recipient pairs to identify various cases of transfusion transmission[2,7]. In the present study, 40% of the units were examined by NAT HBV in minipools of 6-24 donations. With minipooling, at least 50% of OBI donations cannot be identified[7], likely leading to some underestimation of the risk. In addition, risk modelling was based on the optimistic assumption that transfusion transmission occurs only from donors who are negative for anti-HBs (i.e., less than 10 mIU/L) and that, even in these cases, the efficiency of transmission is very low (1.8%). However, recent studies indicate that HBV transmission can occur at higher rates (up to 37.5%)[2,7], and despite concomitant detectable anti-HBs in the donor[8].

Finally, and perhaps most importantly, we should take into account the fact that anti-HBc screening, although not mandatory according to Italian law, was voluntarily adopted by many Italian blood centres during the period of study. For example, in the nine transfusion departments of Lombardy, the most highly populated region in Italy, providing 24% of the total Italian blood supply, anti-HBc has been in place for the selection of

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first time donors since 2016. It is impossible to say to what extent this has contributed to reducing the overall risk of OBI transmission, but we must remember that these reassuring Italian data do not necessarily extend to other countries where no anti-HBc screening is carried out in the blood supply at all.

However, as correctly pointed out by the authors, these data testify that the Italian blood supply has now reached unprecedented levels of safety. Actually, in their article, Velati *et al*. go well beyond their estimates and calculations: they provide a big picture of the successful fight against hepatitis B in Italy. This started almost 30 years ago with universal vaccination of infants and children, and continued with extensive campaigns of case finding and treatment of carriers, and with the building and maintenance of a comprehensive national blood system.

The article by Diderot Fopa *et al*.[9] is an example of co-operation between African, European and North American scientists, producing high quality epidemiological data. The authors examined more than one thousand blood donors in Yaoundé, Cameroon, and found a prevalence of HBsAg and anti-HBc reactivity of almost 8% and 50%, respectively. Among the 522 HBsAg negative, anti-HBc positive donors, 6 (0.52% of all donations) fulfilled the definition of OBI, which means that approximately 1 in 200 blood units released for patient transfusions in Cameroon contain HBV viraemia and could transmit the infection. These figures were not unexpected in an area where HBV is highly endemic, confirming that in sub-Saharan Africa these OBI donations could have a significant impact[10,11]. The study provides an evidence base for policy decisions. Of course, screening based on anti-HBc testing would be unfeasible in this area, as it would halve the number of donors in an area where the blood supply is already insufficient to meet the clinical needs. Implementing NAT-based technologies would certainly improve safety; alternatively, the introduction of pathogen reduction techniques would provide the means to diminish infections from multiple pathogens simultaneously, including HBV[1,3,10]. However, as argued by Fopa *et al.*, any opportunity to introduce expensive and technically demanding procedures in areas with limited logistics and staffing resources needs to be carefully balanced. For example, the introduction of NAT technologies in other sub-Saharan countries a few years ago absorbed a high proportion of the total blood service expenditure, with an ultimately negative impact on the national transfusion system[10]. In this regard, we fully agree with the conclusions of the article by Fopa *et al.* that the African HBV epidemic can only be tackled by comprehensive strategies, including vaccination and treatment programmes. Blood transfusion centres could play an important role in this field, for example, by referring HBsAg positive donors (8% in this study) for counselling and treatment, and by promoting vaccination among donors and their family members. On the other hand, these findings support the decision to test for anti-HBc immigrants from endemic areas, who are likely to remain at higher risk of transmitting the infection in affluent countries.

These two studies, with their profoundly different risk estimates of HBV infection, are reminders of the gap between low- and high-income countries in terms of quality and safety of blood supplies. Blood is recognised as an essential medicine, but the need for safe blood products remains unmet[12].

Disclosures of conflicts of interest

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