

# Need for Quality Assurance Program of Donor Screening Tests

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## 1. Introduction

Transfusion of blood and blood preparations is indispensable in modern medicine, and the processes of delivering a transfusion to a patient provide additional opportunity for risk, despite the remarkable progress. A spectrum of blood-borne infectious agents is transmitted through transfusion of infected blood donated by apparently healthy and asymptomatic blood donors. The diversity of infectious agents includes hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency viruses (HIV-1/2), human T-cell lymphotropic viruses (HTLV-I/II), Cytomegalovirus (CMV), Parvovirus B19, West Nile Virus (WNV), Dengue virus, trypanosomiasis, malaria, and variant CJD<sup>[1]</sup>. Post-transfusion hepatitis caused by HBV or HCV make up the major problems of blood-transmitted infections. Clinical characteristics, such as pathophysiology and clinical progress, of post-transfusion hepatitis are the same as those of hepatitis by other causes, except of transmission route.

HBV presents a higher residual risk of transmission by transfusion than HCV or HIV. While most infectious blood units are removed by new testing methods such as chemiluminescent serologic assays for hepatitis B surface antigen (HBsAg), there is clear evidence that transmission by HBsAg-negative components occurs, in part, during the serologically negative window period, but more so during the late stages of chronic infection that HBV DNA could be detected despite HBsAg seronegativity defined as occult HBV infection (OBI). OBI is a challenging clinical entity, recognized by two main characteristics: absence of HBsAg, and low viral replication. The frequency of OBI depends on the relative sensitivity of both HBsAg and HBV DNA assays. It also depends on the prevalence of HBV infection in the population. OBI may follow recovery from infection, displaying antibody to hepatitis B surface antigen (anti-HBs) and persistent low-level viraemia, escape mutants undetected by currently available HBsAg assays, or healthy carriage with antibodies to hepatitis B e antigen (anti-HBe) and to hepatitis B core antigen (anti-HBc)<sup>[2]</sup>. Over time, in the latter situation, anti-HBe and, later, anti-HBc may become undetectable. Blood donated in the stage of so-called 'window period' after exposure is more infectious than that of OBI. It is reported that blood from donors in window period can infect, even if there might be only 10 virus particles because of its high infectivity. On the other hand, in case of chronic HBV infections in which HBsAg is negative or carriers lasting proliferation of HBV, Dane particles have been developing immune complexes with antibodies like anti-HBs, so infectivity is weaker than acute window period. By look-back study<sup>[3]</sup> reported in Japan, serological responses showing acute infection have been observed in 12 (19%) among 158 patients transfused with HBV-infected blood. Among them, serological responses showing

acute infection have been observed in 11 (50%) among 22 patients transfused with blood donated from HBV-infected window period, on the other hands, observed in only 1 (3%) among 33 patients transfused with blood donated from OBI. However, all forms have been shown to be infectious in immunocompromised individuals, such as organ- or bone marrow-transplant recipients.

HBsAg become positive 50-60 days after infection, preceded by a prolonged phase (up to 40 days) of low-level viraemia. NAT pooling will only detect a small proportion of this pre-HBsAg window period (Fig. 1). Unlike HBV, the risk of HCV transmission by transfusion reduced by introducing HCV nucleic acid testing (NAT) and that of HIV transmission by transfusion also reduced by usage of HIV combined antibody-antigen tests and of HIV NAT. Window period of 16 days (p24 antigen) may be reduced to 11 days by NAT (Fig. 2) and HCV NAT theoretically reduce the window period by 41-60 days (Fig. 3).

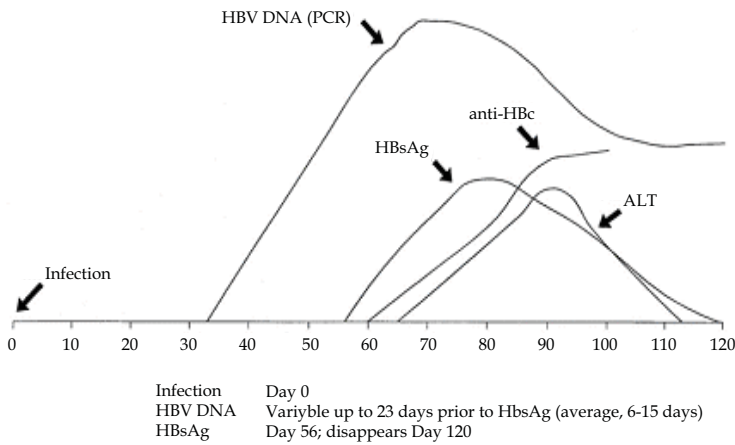


Fig. 1. Estimated window period in each HBV test

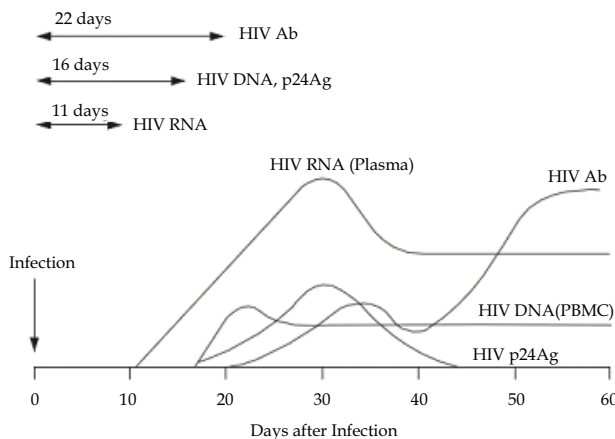


Fig. 2. Estimated window period in each HIV test

The risk of transfusion-transmitted infection (or "residual risk") refers to the chance that an infected donation escapes detection because of a laboratory test's window period (i.e., the time between infection and detection of the virus by that test). The residual risk depends on the prevalence of viremia in the population, especially in blood donors and the sensitivity of the donor screening tests. Prevalence of viremia in blood donors is much less than that of general population. The window period risk can be estimated using the incidence of infection in donors and the length of the window period for tests in use, with an adjustment for atypical inter-donation intervals in seroconverting donors.

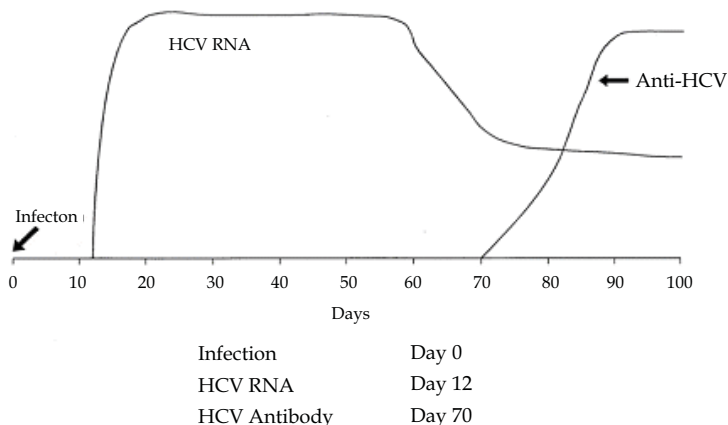


Fig. 3. Estimated window period of each HCV test

Following the introduction of NAT for HIV and HCV, the American Red Cross estimates<sup>[4]</sup> the risk of transfusion-transmitted human immunodeficiency virus to be 1:1,215,000 (per unit transfused) and 1:1,935,000 for transfusion-transmitted hepatitis C virus. Hepatitis B virus nucleic acid testing has not been implemented, and the risk of transfusion-transmitted hepatitis B virus in the United States remains relatively high at an estimated 1:205,000. The risk of transfusion-transmitted human T-cell leukemia virus I/II is 1:2,993,000, based on Red Cross estimates. The residual risk per million donations was 0.10 for HIV, 0.35 for HCV, 13.88 for HBV and 0.95 for HTLV reported by the the Canadian Red Cross Society and Canadian Blood Services in 2003<sup>[5]</sup>. The estimated frequency of infectious donations entering the blood supply during 1996-2003 was 1.66, 0.80 and 0.14 per million for HBV, HCV and HIV respectively, in the United Kingdom<sup>[6]</sup>.

Virus	Risk of transfusion-transmitted infection per 1,000,000 donations		
	USA	Canada	UK
HBV	4.88	13.88	1.66
HCV	0.52	0.35	0.80
HIV	0.82	0.10	0.14
HTLV	0.33	0.95	

Table 1. Incidence and estimated rates of residual risk for HIV, HCV, HBV and HTLV in blood donors

## 2. Donor screening tests

Donor screening tests to prevent blood-borne virus infections include tests for HBV, HCV, HIV, and HTLV. Accurate detection of HBsAg is an important aid in successful screening blood donors infected with the HBV. Prevention of transfusion-transmitted HBV has historically relied on serological screening of blood donors using progressively more sensitive HBsAg assays; in some countries anti-HBc assays have also been employed to detect chronic carriers with low-level viremia who lack detectable HBsAg. According to the study conducted by the International Consortium for Blood Safety (ICBS) to identify high-quality test kits for detection of HBsAg, seventeen HBsAg enzyme immunoassay (EIA) kits among the 70 HBsAg test kits from around the world had high analytical sensitivity <0.13 IU/ml, showed 100% diagnostic sensitivity, and were even sensitive for the various HBV variants tested<sup>[7]</sup>. An additional six test kits had high sensitivity (<0.13 IU/ml) but missed HBsAg mutants and/or showed reduced sensitivity to certain HBV genotypes. As regards the sensitivity of HBsAg assays, diagnostic efficacy of the evaluated HBsAg test kits differed substantially, and the analytical sensitivity of HBsAg assays may be dependent on the genetic variability of HBV. Laboratories should therefore be aware of the analytical sensitivity for HBsAg and check for the relevant HBV variants circulating in the relevant population<sup>[8]</sup>. HBV mutants are stable over time and can be transmitted horizontally or vertically. The sensitivity of HBsAg assays for mutant detection is continuously improved. Immunoassays based on polyclonal capture antibody show the highest sensitivity for the recognition of recombinant mutants or serum samples harboring mutant forms of HBsAg. However, they do not guarantee full sensitivity. Detection of HBsAg needs to be improved by the introduction of new HBsAg assays able to recognize so far described S-gene mutants and with a lower detection threshold than current immunoassays in order to detect smallest amounts of HBsAg in low level carriers. There is also a need for more complete epidemiological data on the prevalence of HBsAg mutants and strategies for the (differential) screening of mutants need to be developed and evaluated<sup>[9]</sup>.

NAT for HCV and HIV has been successfully introduced to screen donors in many developed countries over the past several years. HCV/HIV NAT screening has been applied to mini-pools (MP) of eight to 96 donor specimens, with only minimal impact of MP dilutions on clinical sensitivity for interdiction of window period donations. HBV NAT was only recently introduced in several countries (e.g., Japan and Germany), to detect HBsAg-negative, anti-HBc-negative blood units donated during early acute infection or from OBI<sup>[10]</sup>, although many countries including England and France are still difficult to introduce HBV NAT because of the cost. HBV NAT in donor screening has been introduced in the Finland and Netherland since 2009 and in Korea since 2011.

Although theoretical benefits of HBV NAT relative to HBsAg has been proven through comparison data on seroconversion panels as been using HBsAg assays of varying sensitivities, benefit of pooled-sample NAT is relatively small in areas of low endemicity, with greater yields in areas highly endemic for HBV<sup>[11]</sup>. Japan is the first country introducing HBV NAT as a donor screening test in 1999, now using 20-MP since 2004. In Japan, frequency of OBI from donors was 1 in 107,000 donations, on the other hands, frequency of OBI from donors in Europe was 1 in 7500~63,000, because of using 6~8 MP. Frequency of OBI is differ from country to country, depending on the prevalence and the number of MP. Frequency of OBI detection in Japan is lower than Europe, so the number of MP should be reduced to increase efficiency of OBI detection.

Single-sample NAT would offer more significant early window period closure and could prevent a moderate number of residual HBV transmissions not detected by HBsAg assays. Although the major vendors of NAT systems (Roche and Chiron/Gen-Probe) have been developing triplex assays that include HBV DNA detection capacity without compromising HIV or HCV detection, there is controversy over the magnitude of the incremental yield and clinical benefit of HBV MP-NAT over serological screening strategies, as well as the impact of implementation of HBV NAT on need for retention of HBsAg and anti-HBc screening. Fully automated, high through-put single-sample HBV NAT systems are needed for blood donor screening, now being developed in Korea.

Each country will need to develop its blood screening strategy based on HBV endemicity, yields of infectious units detected by different serologic/NAT screening methods, and cost effectiveness of test methods in ensuring blood safety.

### **3. Need for quality assurance program of donor screening tests**

Serological tests and NAT implemented as donor screening tests for transfusion-transmitted viruses should be most accurately performed, because their false positive results might hinder the effective use of blood and their false negative results might cause the risk of blood-transmitted infections<sup>[12,13]</sup>. Therefore, systematic quality assurance program is required to minimize false positive or false negative results, keeping the accuracy of donor screening tests strictly.

Quality Assurance program for donor screening tests is composed of 4 steps. The first step for quality assurance is in registration/licensing step of in vitro diagnostic reagents for donor screening tests. In the US or Europe, special licensing is required after validating safety and clinical effectiveness in order to be used as donor screening tests, even if it might be the same virus markers as those for diagnostic purpose. The second step for quality assurance is in production/distribution process of in vitro diagnostics for donor screening tests. There is a system verifying each lot of products for donor screening tests in the US or Europe. The third step for quality assurance is to monitor the quality of carrying out donor screening tests. For this, each process should be performed according to standard operating procedures (SOP) and accredited by inspecting institution or society. The last step for quality assurance is to conduct the external proficiency program verifying the accuracy of results of donor screening tests.

The external proficiency program for donor screening tests should be operated to verify the ability detecting low level of viral antibodies or antigens including genetic variability. To do this, wide range of the quality control specimens, including standard serum panels or low titer panels made from patients' sera, should be used for the external proficiency program. Ability for detecting low titer of antibodies or mutant viral antigens should be also confirmed, because blood transfusion by low titer or variant virus has been reported<sup>[14,15]</sup> all over the world. Two blood donors with mutant HBsAg have been also reported in Korea. World Health Organization recommends each country to develop national standard materials for donor screening tests for its people and make use of them for quality evaluation, if possible. In England and Australia, national standard materials of biological medicines have been established at national level, being used for the external proficiency program. These standard materials can be also provided to other countries asking for. Singapore enforces outside and inside quality assurance by using national standard materials made by National Standard Reference Laboratories in Australia. Each country should develop its quality assurance program for donor screening tests.

#### 4. References

- [1] Allain JP, Stramer SL, Carneiro-Proietti AB, Martins ML, Lopes da Silva SN, Ribeiro M, Proietti FA, Reesink HW. Transfusion-transmitted infectious diseases. *Biologicals*. 2009;37:71-7.
- [2] Allain JP. Occult hepatitis B virus infection: implications in transfusion. *Vox Sang*. 2004;86:83-91.
- [3] Satake M, Taira R, Yugi H, Hino S, Kanemitsu K, Ikeda H, Tadokoro K. Infectivity of blood components with low hepatitis B virus DNA levels identified in a lookback program. *Transfusion*. 2007;47:1197-1205.
- [4] Pomper GJ, Wu Y, Snyder EL. Risks of transfusion-transmitted infections: 2003. *Curr Opin Hematol*. 2003;10:412-8.
- [5] Chiavetta JA, Escobar M, Newman A, He Y, Driezen P, Deeks S, Hone DE, O'Brien SF, Sher G. Incidence and estimated rates of residual risk for HIV, hepatitis C, hepatitis B and human T-cell lymphotropic viruses in blood donors in Canada, 1990-2000. *CMAJ*. 2003;169:767-73.
- [6] Soldan K, Davison K, Dow B. Estimates of the frequency of HBV, HCV, and HIV infectious donations entering the blood supply in the United Kingdom, 1996 to 2003. *Euro Surveill*. 2005;10:17-9.
- [7] Scheiblauer H, El-Nageh M, Diaz S, Nick S, Zeichhardt H, Grunert HP, Prince A. Performance evaluation of 70 hepatitis B virus (HBV) surface antigen (HBsAg) assays from around the world by a geographically diverse panel with an array of HBV genotypes and HBsAg subtypes. *Vox Sang*. 2010;98(3 Pt 2):403-14.
- [8] Huh HJ, Chae SL, Cha YJ. Comparison study with enzyme immunoassay and chemiluminescence immunoassay for hepatitis B virus surface antigen detection. *Korean J Lab Med*. 2007;27:355-9.
- [9] Weber B. Genetic variability of the S gene of hepatitis B virus: clinical and diagnostic impact. *J Clin Virol*. 2005;32:102-12.
- [10] Busch MP. Should HBV DNA NAT replace HBsAg and/or anti-HBc screening of blood donors? *Transfus Clin Biol*. 2004;11:26-32.
- [11] Kuhns MC, Busch MP. New strategies for blood donor screening for hepatitis B virus: nucleic acid testing versus immunoassay methods. *Mol Diagn Ther*. 2006;10:77-91.
- [12] Oh DJ, Cho YJ, Kwon SY, Cho NS, Kwon SW, Um TH, et al. A proposal for developing a national quality assurance program for donor blood assays. *Korean J Blood Transfus* 2008;19: 197-206
- [13] Cha YJ. The results of external proficiency tests to prevent transfusion-transmitted virus infection: there is a need for a quality assurance program for donor screening tests to prevent blood-borne virus infections. *Korean J Blood Transfus* 2010;21:25-35
- [14] Hou J, Wang Z, Cheng J, Lin Y, Lau GK, Sun J, et al. Prevalence of naturally occurring surface gene variants of hepatitis B virus in nonimmunized surface antigen-negative Chinese carriers. *Hepatology* 2001;34:1027-34
- [15] Levicnik-Stezinar S. Hepatitis B surface antigen escape mutant in a first time blood donor potentially missed by a routine screening assay. *Clin Lab* 2004;50:49-51



## **Wide Spectra of Quality Control**

Edited by Dr. Isin Akyar

ISBN 978-953-307-683-6

Hard cover, 532 pages

**Publisher** InTech

**Published online** 07, July, 2011

**Published in print edition** July, 2011

Quality control is a standard which certainly has become a style of living. With the improvement of technology every day, we meet new and complicated devices and methods in different fields. Quality control explains the directed use of testing to measure the achievement of a specific standard. It is the process, procedures and authority used to accept or reject all components, drug product containers, closures, in-process materials, packaging material, labeling and drug products, and the authority to review production records to assure that no errors have occurred. The quality which is supposed to be achieved is not a concept which can be controlled by easy, numerical or other means, but it is the control over the intrinsic quality of a test facility and its studies. The aim of this book is to share useful and practical knowledge about quality control in several fields with the people who want to improve their knowledge.

### **How to reference**

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Young Joo Cha (2011). Need for Quality Assurance Program of Donor Screening Tests, Wide Spectra of Quality Control, Dr. Isin Akyar (Ed.), ISBN: 978-953-307-683-6, InTech, Available from:  
<http://www.intechopen.com/books/wide-spectra-of-quality-control/need-for-quality-assurance-program-of-donor-screening-tests>

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