VALIDATION OF IMMUNOASSAY FOR THE DETECTION OF HEPATITIS B VIRUS SURFACE ANTIGEN (HBsAg) IN PLASMA POOLS

Introduction

Immunoassays for the detection of hepatitis B virus surface antigen (HBsAg) are qualitative tests for the presence of HBsAg in pooled plasma for fractionation. The validation requirements are laid down in the following documents:

- The test is considered to be a qualitative limit test for the control of impurities. Therefore, according to the "Note for guidance on validation of analytical procedures: definitions and terminology (CPMP/ICH/381/95)", published in "The rules governing medicinal products in the European Union", ICH topic Q2A, the two characteristics regarded as the most important for validation of the analytical procedure are specificity and the detection limit. However, the note for guidance adds "those validation characteristics are regarded as the most important, (...) but occasional exceptions should be dealt with on a case-by-case basis" and requires that robustness needs to be considered.
- The Ph. Eur. Monograph 01/2005:0853 "Human plasma for fractionation" requires the use of HBsAg test methods of suitable sensitivity and specificity for plasma pool testing.
- The "Note for guidance on plasma derived medicinal products" (CPMP/BWP/269/95, 3.2.2) specifies that the sensitivity of the test in relation to pool size has to be stated. The intention of the test is defined to be a safeguard against errors in testing or pooling.
- The Ph. Eur. chapter 2.7.1 "Immunochemical methods" requires the use of international reference material. Furthermore, the chapter suggests the use of commercial assay kits.
- The GMP Guide (Volume 4, Chapter 6, 6.21) as well as ISO 17025 (4.6.2) require critical reagents to be under control.

In accordance with these guidelines, the validation characteristics are described as:

- Specificity is the ability to unequivocally assess HBsAg in the presence of other components which may be expected to be present.
- The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample, which can be detected but not necessarily quantitated as an exact value. In the context of plasma pool testing for HBsAg, the detection limit should be expressed in IU/ml with reference to the International Standard.
- The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal performance.

Validation Guidelines

1. SCOPE

HBsAg assay kits, for single donations purposes, marketed in Europe are CE-marked devices and are classified in Annex II A of the Directive 98/79/EC on in vitro diagnostic medical devices. The kits are therefore subject to the Common Technical Specifications (CTS, 2002/364/EC).

HBsAg assay kits are validated for use in single donation testing either through CE-marking in the EU or through non-EU regulation. The use of such assays for the testing of pooled plasma for fractionation is a change of the intended use and this application is not covered by the validation undertaken by the test kit manufacturer. The application for testing plasma pools for fractionation therefore has to be accompanied by appropriate validation.

If non-CE marked test kits are used for plasma pool testing purposes, equivalent quality to a CE-marked test kit for individual donation testing should be proven in addition to the validation for pool testing described in this guideline.

The CTS defines minimal requirements for diagnostic and analytical sensitivity for assay kits.

Furthermore, the CTS requires that specificity should be demonstrated in a broad variety of patient samples. However, this approach to validation is not necessarily relevant for plasma pool testing purposes, because those patient samples which may give aberrant responses (e.g., those from patients with autoimmune diseases or having cross-reactive infections) will normally have been excluded by the donor selection process. In addition, non-specific interfering factors will be diluted in the plasma pool.

Plasma pool serology is not capable of detecting all contaminated single donations that may have escaped single donation screening. Patients with occult or asymptomatic Hepatitis B infection show low antigen levels that will escape detection after dilution in a manufacturing pool. Moreover, in general plasma pools may contain antibodies to HBsAg (predominantly from vaccinees), that may result in the formation of HBsAg/anti-HBs complexes which may affect the detection limit.

Plasma pool serology should therefore not be considered as a test to ensure viral safety, but as a measure to detect serious GMP failures.

This document describes methods to select and validate commercial qualitative immunoassay test kits for assessing contamination of plasma pools with HBsAg based on the above-mentioned documents.

2. SELECTION OF THE TEST KIT(S)

Commercial kits used for the analytical procedure are validated by the manufacturer for single donation testing only. Selection of a test kit for plasma pool testing should be based on a high analytical sensitivity.

In most cases, the manufacturers' instructions for use of reagents are adequate for the performance of the test procedure on plasma pools.

Any modification of the manufacturer's instructions should be included in the validation of use of a kit for testing plasma pools.

Evaluation criteria of the manufacturer may be adapted to plasma pool testing according to validation data relevant to plasma pools (see 3.1. Specificity and determination of a cut-off limit for pool samples, and 4. Quality assurance).

3. VALIDATION

3.1 Specificity and determination of a cut-off limit for pool samples

For commercial kits the cut-off value established by the manufacturer is a compromise between sensitivity and specificity based on results from single donation testing. Many test kit manufacturers also define a 'grey-zone' cut-off which will identify samples which give a response above background but below the cut-off. It is recommended that such samples are re-tested as if they were reactive.

On the basis of previous experience in testing plasma pools, the use of a lower cut-off for pool samples should be considered as non-specific factors present in single donations are diluted in a fractionation pool. The use of such a cut-off will increase the analytical sensitivity of assays and facilitate the detection of a single positive donation in a plasma pool. The grey-zone value recommended by the kit manufacturer may be suitable. Alternatively, a limit could be established by considering the signal distribution of negative pools, e.g. as mean response to cut-off ratios of negative pool samples + 3 standard deviations and routinely expressed as % of single donation cut-off (see 3.2.1). In no case should the pool cut-off be higher than the single donation cut-off.

For all practical applications in the context of this Guideline, if a grey-zone limit is used as the cut-off value for pool samples, this limit is used to identify initially and repeatedly reactive plasma pools (see 5., confirmation strategies).

3.2 Robustness

Robustness of the analytical procedure has to be evaluated, as all methods using biological and biochemical reagents may be subject of considerable batch-to-batch variation of the reagents used and may be influenced by changes in ambient conditions. Special attention has to be focussed on handling and storage of samples before testing.

3.2.1 Inter-assay and intra-assay

Qualitative immunoassays primarily produce a quantitative signal that is compared to the calculated cut-off in an independent step. Reactive plasma pool samples are likely to give low signals due to high dilution in the pool. Batch-to-batch variability of the test kit reagents (including controls) may have a significant influence on results and should be under control, as is foreseen by the GMP guide (chapter 6, 6.21) and ISO 17025 (4.6.2).

Robustness of the method should be demonstrated for a panel of representative negative pool samples (e.g. routine pool samples which have tested negative by both the manufacturer and an OMCL), a low positive sample (e.g. the low positive control, see 4.3) and a freshly prepared titration series of a standard calibrated in IU in a typical plasma pool.

The study should cover:

- Inter-assay variability in 6 independent assays (including variable ambient conditions, equipment if available, preferably using more than one test kit lot if available)
- Intra-assay variability with at least 6 determinations of a low positive control in 1 run

  Intra-assay variability can be expressed as %CV (Relative Standard Deviation, RSD) of the signal of the low positive sample in relation to the cut-off of the individual assay (S/CO, sample to cut-off ratio).

3.2.2 Impact of sample preparation

HBsAg may be masked by complex formation with antibodies to HBsAg (present in any European or US pool, predominantly from vaccinees) in a manner dependent on time, temperature and anti-HBs concentration. Formation of immune complexes in pooled plasma at fractionation temperature is a rather slow process (approx. 3-4 days for 50% signal loss), so efforts should be taken to minimise the time from sampling to freezing, and thawing to testing in order to avoid false negative results. For the same reason, freshly thawed samples should be used for re-testing/confirmation.

3.3 Detection limit

The detection limit with the pool cut-off established according to 3.1 should be determined using reference material calibrated in IU and diluted in an anti-HBs free matrix representative of a plasma pool (e.g., single plasma donation(s) or a pool of 10 single donations). It is expected that this will be considerably lower than the minimum requirement defined by the CTS.

The impact of the anti-HBs containing matrix may be assessed by data comparing the results of a titration of an HBsAg positive sample in anti-HBs positive and anti-HBs negative dilution matrix (see section 3.2.1). Where possible, this should simulate the "worst case scenario" in respect to the time that a typical pool of donations is mixed prior to sampling as well as with respect to anti-HBs concentration, temperature and agitation.

4. QUALITY ASSURANCE

4.1 Standard Operating Procedures for plasma pool testing

The test procedures must be described in detail in the form of standard operating procedures (SOPs). These should cover at least the following operations:

- Storage conditions for samples
- Preparation of samples (e.g. freezing/thawing steps, mixing)

- Description of the equipment and the test kit used
- Incubation procedures (including tolerance limits for time and temperature, e.g. according to the test kit manufacturers specifications/instrument settings)
- Detailed formulae for calculation and interpretation of results
- Validity criteria for the individual assay
- Retesting procedures
- Reference to confirmation procedures, if applicable

4.2 Test kit controls

The test kit manufacturer's controls should always be included in every assay to ensure correct functioning of reagents according to the manufacturers specifications. Validity criteria for modified testing conditions should be defined and documented.

4.3 Test kit independent controls

The positive controls in many commercial test kits are highly reactive and therefore do not reflect the low level of reactivity likely to be found in contaminated pool samples. In addition, as for all biological reagents, these controls are subject of batch-to-batch variation. Therefore it is strongly advised to include an independent low positive control (in the dynamic range of the assay, e.g. 2-3 times the single donation cut-off) in every test used for on-going data monitoring.

4.4 Proficiency testing

Regular participation in an appropriate proficiency testing scheme which include diluted samples with low reactivity to assess the analytical sensitivity of kits is encouraged.

5. CONFIRMATION STRATEGIES

A validated confirmation strategy for initially reactive results should be in place. A pool is considered negative if a fresh aliquot of the initially reactive sample gives a negative result when retested in duplicate. Repeat reactive samples have to be considered positive unless proven otherwise with a validated serological method using different antibodies (alternative assay, neutralization with neutralization reagent).

For HBsAg testing, a neutralization test should always be used on repeat reactive samples. The neutralization test has to be validated for pool plasma samples, considering the neutralization effect of antibodies already present in the pool (self-neutralization) in comparison to the neutralized sample (incubated with additional anti-HBs).

As HBsAg may be present in donors with low or undetectable nucleic acid plasma levels, NAT should not be considered as a confirmation assay as a negative NAT results does not invalidate a positive serological result. On the other hand, positive NAT results do confirm the serological detection of contaminations.

6. IMPLEMENTATION OF THIS GUIDELINE

This guideline has been developed to respond to inadequacies in the validation of plasma pool testing for HBsAg observed during evaluation of dossiers. Marketing Authorisation Holders and Plasma Master File Holders should review the validation of their pool testing methods in the light of this guidance. If the key aspects described in the guideline have already been covered by existing validation, no further validation is needed. If this is not the case, pool testing should be validated in accordance with this guideline and reported in the next annual update of the documentation on the plasma starting material.

医薬品 研究報告 調査報告書

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販売名(企業名)	合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社) 合成血-LR「日赤」(日本赤十字社) 照射合成血-LR「日赤」(日本赤十字社)			日本

研究報告の概要

○個別核酸増幅検査は、全ての輸血によるB型肝炎ウイルス伝播を防止することにはならない
2004年10月、神奈川県赤十字血液センターは、輸血後HBV感染疑いの報告を受けた。受血者は急性骨髄芽球性白血病の51歳の男性で、2004年1月に骨髄移植を受けた。受血者に輸血された血液を供血した33人の供血者の凍結検体を回収した。供血当時の検査では50プールNAT陰性だったにも関わらず、凍結検体がHBV個別NAT陽性となった54歳日本人男性の供血者を特定した。供血者は、これ以前の11年間に78回の血小板成分供血を行っていた。
この供血者の以前の供血に関する遡及調査にあたって、異なる病院で発生した未解決の輸血後B型肝炎疑いの3症例を調査した。患者は3名とも複数回の血小板輸血を受けており、製剤のうちそれぞれ1製剤はこの供血者由来だった。後方視的検査では、この3回の供血血液の凍結検体はHBV個別NAT陰性だった。しかし、供血者と患者4名のHBVの塩基配列を比較したところ、全てジェノタイプCで相同性は99.8%だった。
供血者の過去の供血の40の凍結検体について個別NAT を行うことができた。受血者の面接調査とHBVマーカー検査により、過去のHBV感染が更に2例特定された。これらの患者のうち臨床的に明らかな輸血後B型肝炎の既往のある者はいなかった。回収された検体のうち幾つかは陰性、幾つかは陽性だった。この供血者におけるHBV DNAの量は50コピー/mL未満から200コピー/mLの間で増減していた。
本症例は、供血前に個別NATを行ったとしても、全てのオカルトHBVキャリアを排除できないことを示している。

報告企業の意見	今後の対応
供血者の個別NATは陰性だったが、塩基配列から輸血による感染が確認された輸血後B型肝炎の症例が発生したとの報告である。	HBV感染に関する新たな知見等について今後も情報の収集に努める。日本赤十字社では、これまでの凝集法と比べて、より感度の高い化学発光酵素免疫測定法(CLEIA)の導入を予定している。また、NATの精度向上についても評価・検討している。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」
合成血-LR「日赤」
照射合成血-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

自発報告:1-04000222、1-03000103、1-0400072、1-04000269、1-04000271、1-04000278、1-04000348

LETTERS TO THE EDITOR

Individual nucleic amplification technology does not prevent all hepatitis B virus transmission by blood transfusion

We report a case of posttransfusion hepatitis B for which the donor's pretransfusion 50-minipool hepatitis B virus (HBV) nucleic amplification technology (NAT) test result was negative, but retrospective testing of the same sample by individual-donation (ID) NAT was positive. We were able to test 40 frozen samples from prior collections from this donor using HBV ID-NAT and to test current blood samples from pertinent recipients for evidence of prior HBV infection. We believe that the results of this study show that predonation testing by HBV ID-NAT would not have prevented all HBV transmissions by this donor.

In October 2004, the Kanagawa Red Cross Blood Center received a report of a suspected case of posttransfusion hepatitis B. The patient was a 51-year-old man with acute myeloblastic leukemia who had received a marrow transplant in January 2004. We retrieved frozen samples from 33 donors whose blood was transfused to this patient. We identified one donor, a 54-year-old Japanese man, whose frozen sample from the implicated donation tested positive by HBV ID-NAT, although it had tested negative by 50-sample minipool NAT at the time of donation. This person had donated 78 apheresis platelet (PLT) units during the prior 11 years.

To initiate a lookback study of prior donations by this donor, we began with a review of three unresolved cases of suspected posttransfusion hepatitis B from three different hospitals. All three patients had received multiple PLT transfusions, including 1 unit each from the implicated donor. Retrospective testing of frozen blood samples from these three donations was negative by HBV ID-NAT. DNA sequences of the HBV of this donor and the four patients who had developed posttransfusion hepatitis B, however, were analyzed. All were genotype C and had 99.8 percent homology. We were able to test 40 frozen samples from this donor's prior donations (Table 1). Interviews with recipients and the results of HBV marker testing of these samples identified two additional cases of prior HBV infection. None of these patients had a history of clinically apparent post-transfusion hepatitis B. Some of these retrieved samples tested negative and some tested positive by HBV ID-NAT (Table 1). The quantitative HBV DNA in this donor blood fluctuated between less than 50 copies per/mL to 200 copies per/mL.

The results of this study raise serious and difficult issues for Japanese blood banks. Although the existence of HBV carriers has been known, it has been anticipated that most HBV-infective donations would be detected by minipool NAT.[1] Our case study shows that even ID-NAT does not detect all occult HBV carriers. Unfortunately, HBV is endemic in Japan and certain other countries in Asia. Our present strategy to eliminate hepatitis B surface antigen (HBsAg)-negative and /HBV-infective donors is based on the method of Mosley and colleagues,[2] namely, excluding antibody to hepatitis B core (anti-HBc)-positive donations, unless HBsAg antibody is unequivocally positive. Our anti-HBc assay is hemmagglutination inhibition with a twofold step dilution (cutoff level, $>2^5$). This assay eliminates 1.6 percent of our donors, but less than 2 percent of donors excluded by this approach tested positive by HBV ID-NAT. We cannot implement more and more sensitive anti-HBc assay, such as enzyme immu-

TABLE 1. Results of HBV ID-NAT testing of frozen blood samples of implicated donor and responses of recipients of his blood

Number of blood donations	Date of donation	Component	ID-NAT	Recipient
1	04/12/04	PC	+	Not infected
2	03/25/04	PC	+	
3	03/10/04	PC	+	Suspected SC
4	02/23/04	NT	+	
5	02/06/04	PC	+	
6*	01/19/04	PC	+	Acute hepatitis
7	12/29/03	PC		SC
8	12/04/03	PC		
9	10/22/03	PC	+	Suspected SC
10	09/22/03	PC		Infected
11	07/28/03	NT		
12	07/14/03	PC		Not infected
13	06/09/03	PC	+	
14	01/13/03	PC		
15	12/12/02	NT		
16	08/28/02	Whole blood		
17	06/15/02	PC		Acute hepatitis
18	05/22/02	PC		
19	04/22/02	PC		Acute hepatitis
20	03/14/02	NT		
21	01/21/02	PC		Not infected
22	12/28/01	NT		
23	11/21/01	PC		
24	10/29/01	NT		
25	10/09/01	PC		
26	09/14/01	PC		
27	08/25/01	PC		
28	07/31/01	NT		
29	07/17/01	PC		
30	06/26/01	PC		
31	06/07/01	PC		Not infected
32	05/22/01	PC		
33	08/16/99	NT	+	
34	07/29/99	PC		
35	07/31/98	NT		
36	10/16/97	FFP		
37	08/17/97	PC		
38	07/05/97	PC		
39	06/08/97	NT		
40	05/17/97	PC		Acute hepatitis

* The propositus case.
† Infection report from hospital.
PC = PLT concentrate; SC = seroconversion; NT = not transfused.

noassay, because loss of 20 percent of our donors is not feasible for a national blood program. Other measures will be necessary to further decrease posttransfusion HBV infection. Some of the options include prophylaxis using HBV immunization or high-titer hepatitis B immunoglobulin before beginning chemotherapy or monitoring transfusion recipients for HBV DNA by ID-NAT monthly to detect HBV infection in time to administer anti-HBV drugs, such as lamivudine or adefovir dipivoxil.

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Are weak D red blood cells really immunogenic?

In a recent letter to the editor, Kumpel[1] questioned the immunogenicity of weak D red blood cells (RBCs). Kumpel described five case reports that were published during the prior 6 years that offered neither evidence that single units of weak D can immunize in the absence of other alloantigens nor evidence of clinical significance. That letter was followed by replies from the authors who had published the five case reports. Of the 28 references cited in the discussion, only one, listed in both the first and the last of the exchanged communications, described any clinical trial of antigenicity.[2] That research was performed under circumstances remarkably like those pertaining today; that is, there had been a redefinition of what was then called D^u, just as DNA typing is now redefining weak D. The circumstances of 50 years ago are just as pertinent today. In 1956, the blood bank (now Department of Transfusion Medicine) at the National Institutes of Health (NIH) Clinical Center was part of the Division of Biologics Standards that held the licensing authority for reagents now vested in the Food and Drug Administration. We began to study the licensed technology of the day by applying it in the actual care of patients at the clinical center hospital. In the practice of many blood bankers then, D^u still had the specter of an antigen in its original 1946 definition; that is, RBCs not agglutinated by complete (saline) anti-Rh but agglutinated by incomplete (high protein) anti-Rh.[3] At NIH, we had progressed to calling D^u only those RBCs not agglutinated by incomplete reagents but agglutinated in the indirect antiglobulin (Coombs) test.

Our trial of D^u took several years and it has never been repeated. We transfused 68 units of D^u RBCs to 49 D– patients who had no evidence of any prior immunization. The survival of the transfused RBCs was followed by the Ashby (differential agglutination) technique. Three-fourths of the patients were studied for longer than 5 months. The study has been challenged because 15 of the patients were receiving therapy that might have interfered with an antibody response, but none of the D– recipients of D^u made anti-D. Some were certainly presented simultaneously with other alloantigens, with one patient making anti-K and another anti-E.[2]

The argument continued for 30 more years until a half-solution came out of an informal meeting of parties in Raritan, New Jersey, with Peter Agre (he received his Nobel Prize for something else). The successful idea that resulted was to simply castrate D^u by changing its name to weak D.[4]

Now with molecular typing, weak D can be sorted into dozens of alleles, but Kumpel[1] points out that none of the five case reports of immunization by weak D describe any mortality or morbidity. Despite earlier cautions,[5] there are proposals that all weak D types found in blood donors be sorted into their multiple possibilities. Even with availability of the valuable new DNA typing, that redefinition of D^u should not be translated into burdensome limita-

医薬品 研究報告 調査報告書

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販売名(企業名)	合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社) 合成血-LR「日赤」(日本赤十字社) 照射合成血-LR「日赤」(日本赤十字社)			米国

研究報告の概要

○血液の安全性に危険を及ぼす可能性から供血停止となった供血者における特定のウイルス感染症の有病率

【背景】健康歴の問診により、感染症伝播のリスクを高めると考えられる供血者が特定される。本試験は、現在この問診が血液の安全性に及ぼす影響を、感染症マーカーを示すことにより評価する。

【試験デザインおよび方法】健康歴の問診によって供血延期となった供血者を、4つの米国赤十字血液センターで募集し、血液感染症の血清マーカーについて血液検体を検査した。

【結果】登録された供血停止者497名のうち、29名は"11歳以降の黄疸、肝臓疾患、肝炎"の発症のために供血停止となった。このうち1名はC型肝炎ウイルス(HCV)抗体陽性かつB型肝炎コア抗体(HBc抗体)陽性、2名はHBc抗体陽性、1名はHCV抗体陽性だった(両マーカーともp<0.05)。

"過去の肝炎検査で陽性であった"ため供血停止となった37名のうち、1名はB型肝炎表面抗原陽性かつHBc抗体陽性、3名はHBc抗体陽性であった(両マーカーともp<0.05)。

"これまでに(1度でも)非合法、非処方薬を投与するための注射針を使用したことがある"ために供血停止となった14名のうち、1名はHCV抗体陽性、ヒトT-リンパ球向性ウイルス1型抗体陽性かつHBc抗体陽性であり、1名はHCV抗体陽性かつHBc抗体陽性、2名はHCV抗体陽性であった(いずれのマーカーもp<0.05)。

【結論】ウイルス肝炎リスクおよび静注薬物使用歴に関する標準的な供血者用問診にて供血停止となった供血者は、供血停止とならなかった供血者よりも肝炎マーカー陽性率が高い場合が多かった。その他のマーカーおよび質問について有意な知見は認めなかった。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」
合成血-LR「日赤」
照射合成血-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
ウイルス肝炎リスクおよび静注薬物使用歴に関する問診にて不適となった供血者は、供血可能となった者よりも肝炎マーカー陽性率が高い場合が多かったとの報告である。	日本赤十字社は、輸血感染症対策として、慢性B型肝炎・C型肝炎キャリア、非合法薬物の注射については 献血不可としている。今後も引き続き情報の収集に努める。

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Prevalence of selected viral infections among blood donors deferred for potential risk to blood safety

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BACKGROUND: Health history questions identify blood donors believed to pose a higher risk of transmission of infectious diseases. This study assesses the current impact of some of these questions on blood safety as reflected by infectious disease markers.

STUDY DESIGN AND METHODS: Donors who were deferred from donating blood due to health history question(s) were recruited at four different regions of the American Red Cross Blood Services. A blood sample was tested for serologic markers of blood-borne infections as performed for accepted blood donors.

RESULTS: Of 497 deferred donors enrolled, 29 donors were deferred for having had "yellow jaundice, liver disease, or hepatitis since the age of 11" (Question 3), 1 of whom had hepatitis C virus antibodies (anti-HCV) and hepatitis B core antigen antibodies (anti-HBc), 2 had anti-HBc, and 1 had anti-HCV ($p < 0.05$ for both markers). Among 37 donors deferred for having "ever tested positive for hepatitis" (Question 4), 1 had hepatitis B surface antigen and anti-HBc and 3 had anti-HBc ($p < 0.05$ for both markers). Of 14 donors deferred for "having ever used a needle, even once, to take any illegal or nonprescription drug" (Question 12), 1 had anti-HCV, human T-lymphotropic virus-I antibodies and anti-HBc, 1 had anti-HCV and anti-HBc, and 2 had anti-HCV ($p < 0.05$ for all three markers).

CONCLUSIONS: Blood donors deferred for standard blood donor questions regarding risk of viral hepatitis as well as those with a history of intravenous drug use were more likely to have higher hepatitis marker rates than those who were not deferred. No significant findings were identified for other markers or questions.

The safety of blood collected for transfusion is ensured through appropriate procedures for donor recruitment, education, health history, and testing of donated blood units.[1] Safe donors are encouraged to donate their blood whereas at-risk donors are encouraged to self-defer from blood donation. At blood collection sites, presenting donors are informed of known or newly identified risks of blood-borne infections to help their decision making regarding donation. Presenting donors are further interviewed for history of potential exposure to transmissible diseases that are caused by blood-borne infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human T-lymphotropic virus (HTLV). Donors who are believed to be at an increased risk for those infections are deferred from making a donation.

During the blood donor interview, donors are screened through medical examination and a questionnaire for health history. The examination and questions

ABBREVIATIONS: ARC = American Red Cross; IVDU = intravenous drug use; UDHQ = universal donor history questionnaire.

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