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日本赤十字社　血液事業本部

HBV 感染既往の血液に対する更なる安全対策について

1．現在の HBV 関連検査

1）HBs 抗原（CLEIA）
2）スクリーニング NAT（HBV・HCV・HIV）/　20 本プール
3）HBc 抗体及び HBs 抗体

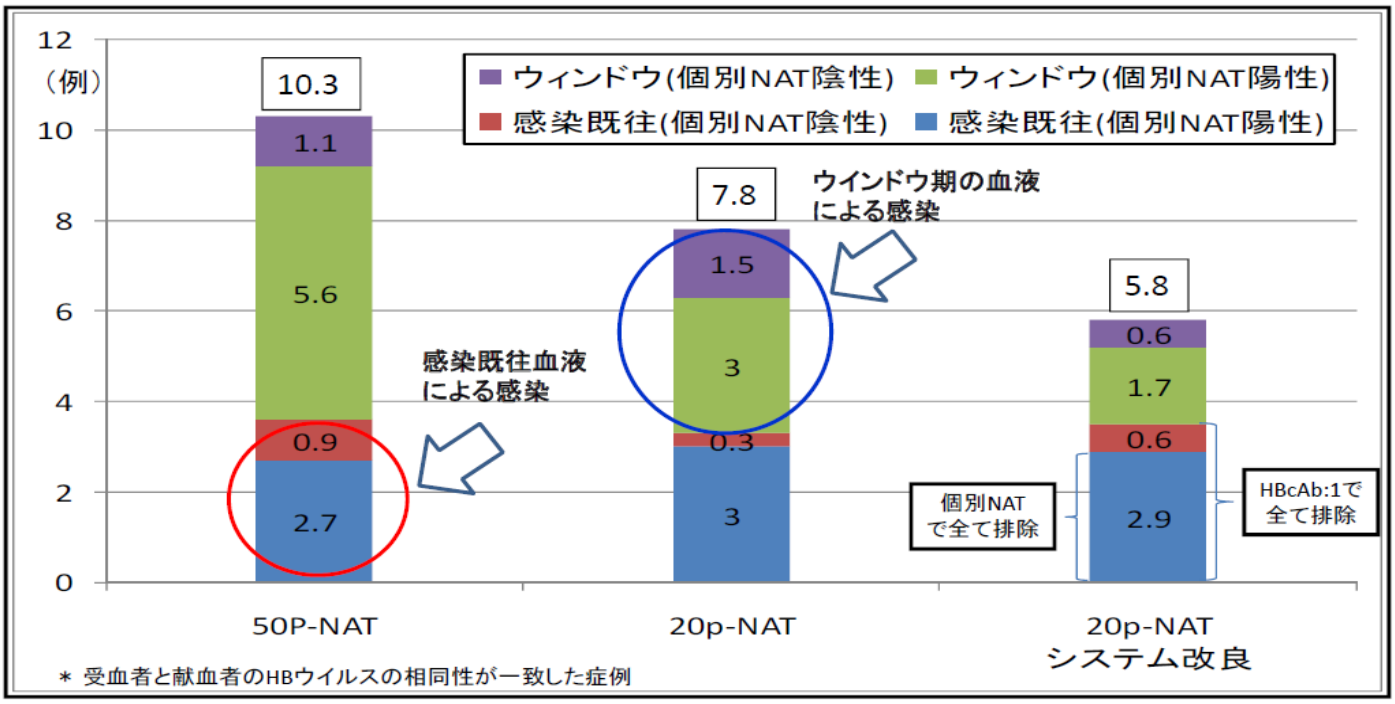
HBc 抗体の判定ロジック

		HBc 抗体（COI）	
		1 以上 12 未満	12 以上
HBs 抗体	200mIU/mL 以上	「適」	「適」
	200mIU/mL 未満	「適」	「不適」

→ 感染性なしとされている

「適」　：輸血用血液製剤等に使用
「不適」：廃棄

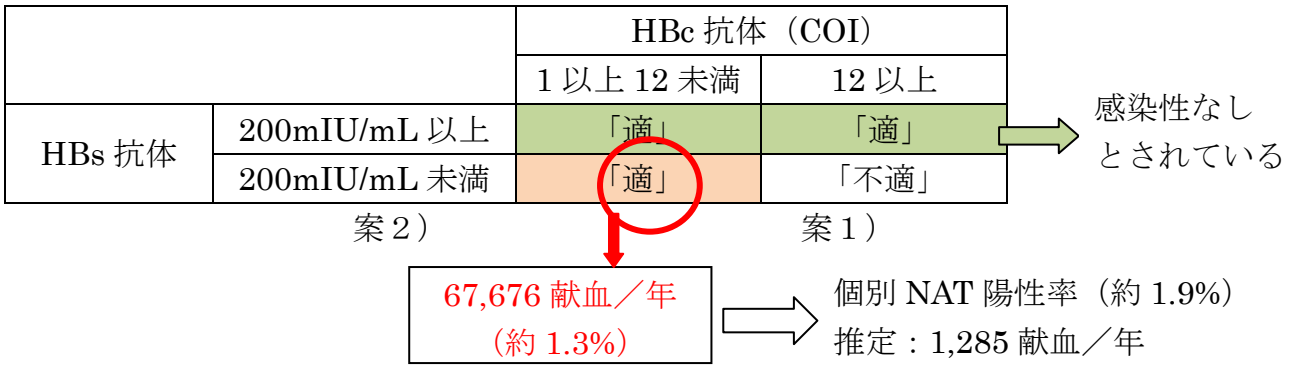
2．輸血 HBV 感染*の原因血液の変遷（1 年あたりの日赤確認症例数）



1）スクリーニング NAT のプール本数縮小及び試薬改良等による検出感度の向上により、ウインドウ期の個別 NAT 陽性血液による感染は減少した。
2）感染既往血液による輸血感染には、変化がなかった。原因となった血液の血清学的検査結果の特徴は、HBc 抗体（COI）1 以上 12 未満で HBs 抗体 200mIU/mL 未満の血液であった。

→更なる、安全性向上には感染既往血液に対策を講じる必要がある。

３．安全対策の考え方



【対策案】

１）HBc 抗体（COI）1 以上 12 未満かつ HBs 抗体 200mIU/mL 未満の検体に個別スクリーニング NAT を実施し、NAT 陽性の血液を「不適」とする。

２）HBc 抗体（COI）1 以上 12 未満かつ HBs 抗体 200mIU/mL 未満の血液を「不適」とする。

４．HBV の感染既往に対する安全対策の実施について

	案 1）　1≦HBc 抗体＜12 かつ 個別 NAT 陽性の血液を「不適」（HBs 抗体≧200mIU/mL を除く）		案 2）　1≦HBc 抗体＜12 の血液を「不適」（HBs 抗体≧200mIU/mL を除く）	
	メリット	デメリット	メリット	デメリット
受血者	○年間約 48 人の感染予防が可能。	○感染既往があり個別 NAT 陰性の血液は検出できない。	○年間約 48 人＋α（5～10 人）の感染予防が可能。	－
献血者	○NAT 陽性者について早期発見・早期治療に結びつく。	－	○NAT 陽性者について早期発見・早期治療に結びつく。 ○感染既往であることが認識できる。	○本来であれば健康上問題ない献血者に対しても制限をかけることになり、不安を与える。（特に頻回献血者への丁寧な説明が不可欠） ○献血者数の減少につながる。
医療機関	－	○遡及調査に伴うリスク情報の提供件数が増加（約 1,285 件／年増）		○遡及調査に伴うリスク情報の提供件数が増加（約 42,510 件／年増(実献血者数))
コスト	○検査費用：4 億 8 千万円 ○システム改修：5 千 7 百万円		○検査費用：3 億 5 千万円	

５．1≦HBc 抗体＜12 の血液を「不適」（HBs 抗体≧200mIU/mL を除く）とした場合の献血者数シミュレーション

	2010 年	2011 年	2012 年	2013 年	2014 年	2015 年	2016 年	2017 年	2018 年
① 予測献血者数* （延べ人数=献血数）	5,186,000	5,140,000	5,103,000	5,058,000	5,024,000	4,986,000	4,968,000	4,921,000	4,868,000
② 必要献血者数* （延べ人数=献血数）	（5,318,586） 2010 年実績	―	5,220,000	5,240,000	5,260,000	5,280,000	5,280,000	5,310,000	5,328,817
③ 不足献血数*			117,000	182,000	236,000	294,000	312,000	389,000	460,000
④本措置に伴う実献血不足数 （延べ献血者数）			67,482	49,868	48,648	40,339	39,094	37,044	33,606
⑤ 本措置施行後の 予測献血者数（①-④）			5,035,518	5,008,132	4,975,352	4,945,661	4,928,906	4,883,956	4,834,394
⑥ 本措置に伴う 予測献血者数の比率（⑤/①）			0.9868	0.9901	0.9903	0.9919	0.9921	0.9925	0.9931

＊：①予測献血数、②必要献血者数、③不足献血数：「我が国における将来推計人口に基づく輸血用血液製剤の供給本数と献血者数のシミュレーション」より抜粋

【結論】

① 予測献血者数は、新たな安全対策実施後においても 1%程度の減少にとどまる見込みである。

② 平成 23 年 4 月の採血基準改定で、400mL 採血は「18 歳から 17 歳」に引き下げられ、血小板採血は「54 歳から 69 歳」に引き上げられたことから、安定供給に影響を及ぼすものではないと推定される。

６．HBs 抗体 200mIU/mL 以上の安全性について

１）輸血後 B 型肝炎症例の中で HBV 感染既往の献血が原因と考えられた血液

症例№	原因と考えられた献血血液の情報				
	採血年	年齢	血清学的検査結果		
			HBc 抗体	HBs 抗体	HBV-DNA
1	2008	40	8.1	0.4	陽性
2	2008	60	5.5	0.8	陽性
3	2008	65	8.1	76.5	陽性
4	2008	67	3.9	0.9	陽性
5	2009	42	7.7	0.1	陽性
6	2009	49	8.0	2.3	陰性
7	2009	60	7.3	0.5	陽性
8	2009	63	5.8	18.9	陽性
9	2009	59	2.0	8.7	陽性
10	2009	62	5.4	13.0	陽性
11	2009	69	4.1	0.5	陽性
12	2010	67	8.7	29.6	陽性
13	2010	43	8.1	0.3	陽性

CLEIA 法による感染症スクリーニングが導入された以降の症例

２）日赤が供給してきた HBc 抗体（COI）1 以上・HBs 抗体 200mIU/mL 以上の血液について
1989 年 12 月検査開始より 18 年間

①HBc 抗体（COI）1 以上・HBs 抗体 200mIU/mL 以上の献血数（延べ数）
177,561 献血／年　（平成 22 年度）

②上記献血より医療機関に供給される輸血用血液製剤数
221,951 製剤／年　（177,561 献血×1.25 倍）

③上記製剤による輸血感染例
0 件（1993 年より医薬情報活動開始）

３）参考文献

① Satake.M,et al. Infectivity of blood components with low hepatitis B virus DNA levels identified in a lookback program. Transfusion 2007;47:1197-1205（別添 1）

② Guidelines for the Blood Transfusion Services in the UK 7th Edition　Section 10.4（別添 2）
Tests for antibodies to hepatitis B core(anti-HBc)
Antibody to hepatitis B surface antigen(anti-HBs)

別添1

Infectivity of blood components with low hepatitis B virus DNA levels identified in a lookback program

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BACKGROUND: Japanese Red Cross (JRC) blood centers implemented anti-hepatitis B core antigen (HBc) screening in 1989 and 50-minipool (MP)-nucleic acid testing (NAT) in 2000. A systematic lookback study has been conducted to determine the hepatitis B virus (HBV) transmission risk of donations drawn in the pre-hepatitis B surface antigen (HBsAg) and/or MP-NAT window phase and by donors with occult HBV infection.

STUDY DESIGN AND METHODS: JRC blood centers have been storing aliquots of every blood donation since 1996. On the basis of the complete repository tube archives, all donations from repeat donors received from 1997 to 2004 were subjected to a lookback study. When repeat donors turned positive for HBV viral marker(s), repository tubes from their previous donations were tested for HBV with individual-donation (ID)-NAT. The frequency of ID-NAT-only–positive donations and the HBV transmission risk by the transfusion of those components were investigated.

RESULTS: HBV ID-NAT was performed on 15,721 repository tubes, and 158 tubes (1.01%) were found positive for the presence of HBV DNA. Of these 158 ID-NAT-only–positive donations, 95 (60%) were derived from carriers with low anti-HBc titers. Of 63 patients transfused with ID-NAT-only–positive components, 12 (19%) proved to be infected with HBV. Only 1 of 33 components with low anti-HBc titers could be identified as infectious, whereas 11 of 22 anti-HBc–negative components proved to be infectious. None of the 16 identified hepatitis B surface antibody–positive components showed serologic evidence of infection.

CONCLUSION: The clinically observed HBV infection risk caused by blood components from occult HBV carriers with low anti-HBc titers who slip through the JRC screening system is more than 10-fold lower than the transmission risk by donations in the pre-HBsAg and/or MP-NAT window phase.

Nucleic acid testing (NAT) for hepatitis C virus (HCV) and human immunodeficiency virus (HIV) has been implemented in developed countries for screening blood donated during the window period and plays a critical role in excluding infectious blood components.[1,2] For hepatitis B virus (HBV), Japanese Red Cross (JRC) blood centers have been screening blood with hemagglutination for hepatitis B surface antigen (HBsAg) detection combined with anti-hepatitis B core antigen (anti-HBc) and hepatitis B surface antibody (anti-HBs) testing since 1989 and implemented 50-member-pool NAT (50-NAT) for HBV, HCV, and HIV in February 2000.[3,4] There is still a residual risk of transfusion-transmitted viral infection (TTI), however, because of the limited sensitivity and use of pooled samples in current NAT systems.[5] A precise evaluation of residual risk after NAT implementation is essential in determining whether further strategies for preventing TTI are warranted (e.g., individual donation [ID]-NAT or pathogen reduction).[6,7]

To investigate the cause of reported TTI and to identify and retrieve virus-containing components, JRC has been storing aliquots of every blood donation since 1996 with a plan to preserve repository aliquots for 11 years. A

ABBREVIATIONS: 50-NAT = 50-member-pool nucleic acid testing; HBs = hepatitis B surface antibody; HI = hemagglutination inhibition; ID = individual donation; JRC = Japanese Red Cross; MP = minipool; TTI = transfusion-transmitted viral infection.

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systematic lookback study has been conducted in which repository tubes from previous donations were investigated for the presence of HBV, HCV, or HIV sequences by ID-NAT when repeat donors turned positive for viral antigens, anti-viral antibodies, or screening 50-NAT.[8] In the present lookback study, the proportion of ID-NAT–reactive donations that are not detected by the current JRC blood screening algorithm has been established and the clinically observed HBV transmission risk of the components derived from these donations has been investigated.

MATERIALS AND METHODS

In JRC blood centers, all donated blood samples are first screened for HBsAg by reversed passive hemagglutination,[9] the sensitivity of which is 3 ng per mL. HBsAg-negative samples are further screened for anti-HBc and anti-HBs by hemagglutination inhibition (HI) and particle agglutination, respectively. Only blood having a high anti-HBs titer ($\geq 2^4$ dilution equivalent to 200 mIU/mL) or no or a low anti-HBc titer (HI titer $\leq 2^4$ dilution) is defined as seronegative. The combination of the above serologic screening tests excludes HBsAg-positive donors and most occult carrier donors. Because the cutoff point for HI is set at a higher level than that for enzyme immunoassay (EIA) anti-HBc, there are donations that are accepted while having low anti-HBc titer detectable by EIA but not by HI. Fifty seronegative samples are then pooled for NAT. JRC NAT screening employs a polymerase chain reaction (PCR) system (AmpliNAT, Roche, Indianapolis, IN) that utilizes multiplex reagents for detecting HBV, HCV, and HIV genomes. The detection range limit (95% confidence interval) for HBV is 22 to 60 copies per mL.[10] The sensitivity of current 50-NAT is expected to be 50-fold lower than that described above, that is, 1100 to 3000 copies per mL.

All donations from repeat donors received from 1997 to 2004 were subjected to a lookback study when a subsequent donation turned positive for a 50-NAT, HBsAg, or anti-HBc. Repository samples from donors immediately preceding donations that became positive for the presence of the markers described above were routinely analyzed by ID-NAT. Donors exhibiting a subsequent donation with anti-HBc reactivity above 2^4 dilution in the absence of anti-HBs, or donors with a decrease in their anti-HBs reactivity (to below 2^4 dilution) in the presence of a positive anti-HBc result, were also defined as anti-HBc converters and included in the study. The process of ID-NAT was as follows. Test samples were first screened with the same reagent and method as AmpliNAT except that the system contained a capture probe only for HBV. Positive samples were then subjected to dual-repeat ID-NAT. Doubly positive (+/+) and singly positive (+/–) samples were defined as ID-NAT–positive and further subjected to quantitative NAT. The HBV genome was quantified by a JRC in-house method that utilizes TBF-1 (nucleotides 250-272; 5′-AGACTCGTGGTGGACTTCTCT CA-3′), TBR-1 (nucleotides 428-409; 5′-TGAGGCATAGCA GCAGGATG-3′), and TP-02 (nucleotides 368-392; 5′-TATC GCTGGATGTGTCTGCGGCGTT-3′) as F-primer, R-primer, and probe, respectively. The sensitivity of the quantitative NAT was 100 copies per mL. Samples verified to be ID-NAT–positive were reevaluated for anti-HBc by EIA (AxSYM, Abbott Japan, Tokyo, Japan) as well as semiquantitative HI and for anti-HBs by EIA (AxSYM). Only samples exhibiting concordant results for anti-HBc with $2^1 \leq$ HI $\leq 2^4$ and EIA positivity (>50% inhibition) were defined as samples with low anti-HBc titers. To substantiate the infectious status of the donors in the ID-NAT-only–positive donation, repository tubes obtained in the subsequent donations were also evaluated for HI, EIA-anti-HBc, EIA-HBsAg, and EIA-anti-HBs.

The risk analysis for HBV contamination in blood components was limited to donations obtained from February 1, 2000, to January 31, 2004, all of which had been qualified by the current screening algorithm including 50-NAT. For the analysis of the infectivity of HBV-containing units, components that had not been tested by 50-NAT were also used in the study.

ID-NAT results for the preceding donation were sent with an evaluation form for viral contamination risk to the medical facility that used the donation. On the form, the degrees of viral contamination risk were described with the following classification: the donation was 1) ID-NAT–positive; 2) ID-NAT–negative but with probable HBV contamination because the blood was donated during the potential window period (the window period was defined as 46 days according to the Japanese guideline for lookback investigation issued by the Ministry of Health, Labour and Welfare); 3) ID-NAT–negative but with possible HBV contamination even though the time interval between the preceding donation and the marker conversion was long (>46 days); or 4) ID-NAT–negative and unlikely to have viral contamination because the test result for the subsequent donation was verified to be positive because of the alteration of the cutoff point for anti-HBc during the period between the two donations. The clinical outcome of patients transfused with ID-NAT–positive components was collected by local blood centers. The testing of blood samples from transfused patients, the initial diagnosis of HBV-TTI, and the report of suspected cases to blood centers were basically conducted by physicians who treated the patients. The diagnostic bases for TTI was therefore not uniform regarding the HBV markers tested, the observational period after index transfusion, and the time interval between transfusion and blood testing. In most medical institutions, the presence of anti-HBc or anti-HBs in pretransfusion samples is usually not evaluated. In all documented HBV transmission cases, the diagnosis of HBV infection was established on the basis of

TABLE 1. Numbers of ID-NAT–positive donations and positivities for anti-HBc in repository tubes

Converted markers	Projected number of converted donations for 4-year period	Number of repository tubes positive for ID-NAT within 4 years	Anti-HBc status of ID-NAT–positive repository sample		
			Low titer	Negative	Not tested
50-NAT	329	28 (8.5%)*	13	13	2
HBsAg†	730	16 (2.2%)*	3	13	0
Anti-HBc	14,662	114 (0.78%)*	79	34	1
Total	15,721 (observed number)	158 (1.01%; 39.5/year)	95 (60%)	60 (38%)	3 (2%)

* Percentage of observed ID-NAT–positive samples among projected number of samples for which ID-NAT was performed.
† HBsAg conversion includes those accompanied by anti-HBc seroconversion.

the HBsAg conversion, anti-HBs seroconversion, or HBV DNA conversion.

TABLE 2. Relationship between EIA-anti-HBs and HBV genomic copy number

EIA value for anti-HBs (mIU/mL)	Copies/mL (number of samples)
EIA = 0	<100 (14), 160, 200, 220, 230 (2), 300 (2), 380
0 < EIA < 5.0	<100 (11), 100, 120
EIA ≥ 5.0 (range, 5.7-179.2; median, 24.9)	<100 (18)

RESULTS

Lookback study for HBV

Of the repository tubes that had been aliquoted from the donations obtained from February 1, 2000, to January 31, 2004, a total of 15,721 were subjected to ID-NAT (Table 1). All the donations had been qualified with the current screening algorithm including 50-NAT. Although the total number of tubes investigated by ID-NAT is evident because ID-NAT was performed in one laboratory, the numbers for each of the HBsAg–, 50-NAT–, or anti-HBc–converted repeat donors are not available because of a data management problem where the detail of lookback process for each conversion case was not recorded on a centralized computer system. The exact number for each of the three categories was summed up only for the period between June 13, 2002, and July 21, 2003. From the extrapolation of these 404 days of data, the number of repeat donors who became positive for the presence of the three markers during the 4-year period was estimated (Table 1).

Of the estimated 329 prior donations that became positive for the presence of HBV DNA by 50-NAT in the subsequent donation, 28 (8.5%) were verified to be positive for the presence of HBV DNA by ID-NAT (Table 1). Viral concentrations were available for 18 samples and were fewer than 380 copies per mL. A low anti-HBc titer below the screening cutoff value ($\leq 2^4$ by HI test) was detected in 13 of 26 cases evaluated but not in the remaining 13 (Table 1). This result suggests that a significant number of occult carriers have a fluctuating low-level viremia. Thirteen of the 16 ID-NAT–positive donations in which subsequent donations became HBsAg-positive were thought to have been obtained during the window period because they were anti-HBc–negative (Table 1). The remaining three contained a low anti-HBc titer and were considered to be derived from chronic carriers. Seventy-nine of the 114 ID-NAT–positive donations exhibiting a subsequent donation with anti-HBc seroconversion were considered to have been derived from occult carriers having low anti-HBc titers (Table 1); 82 percent (65/79) of these carrier donors were more than 50 years of age at the time of the repository sample. Thirty-four donations with negative anti-HBc reactivity were thought to have been obtained during the window period of acute infection. These units were donated mostly by young people, with 68 percent (23/34) less than 50 years of age.

In summary, during the 4-year study, we identified 158 HBV ID-NAT-only–positive blood donations that corresponded to 1.01 percent of samples for which ID-NAT was performed. Ninety-five (60%) of them were donated by occult carriers with low-titer anti-HBc and 60 (38%) by anti-HBc–negative or window-period donors (Table 1). Thus, of the repeat donors in Japan, there are an estimated 39.5 donations every year that are ID-NAT-only–positive. Viral concentrations were generally very low in occult carrier donors with 75 (95%) of the 78 samples studied having fewer than 100 copies per mL and only three having at least 100 copies per mL (data not shown). Donations obtained during the window period contained higher viral DNA levels with 12 of the 46 samples studied containing at least 100 copies per mL (range, 100-860 copies/mL).

Anti-HBs titer was measured with EIA in 53 repository tubes for which clinical outcome as a result of transfusion were available (see below). When anti-HBs titer was divided into three categories (=0, between 0 and 5, and ≥5 mIU/mL), there was no sample that contained at least 100 copies per mL of HBV DNA in the category of anti-HBs of at least 5 mIU per mL (Table 2).

Infectivity of ID-NAT–positive component

To establish the infectivity of the ID-NAT-only–positive components, we included donations obtained from 1997

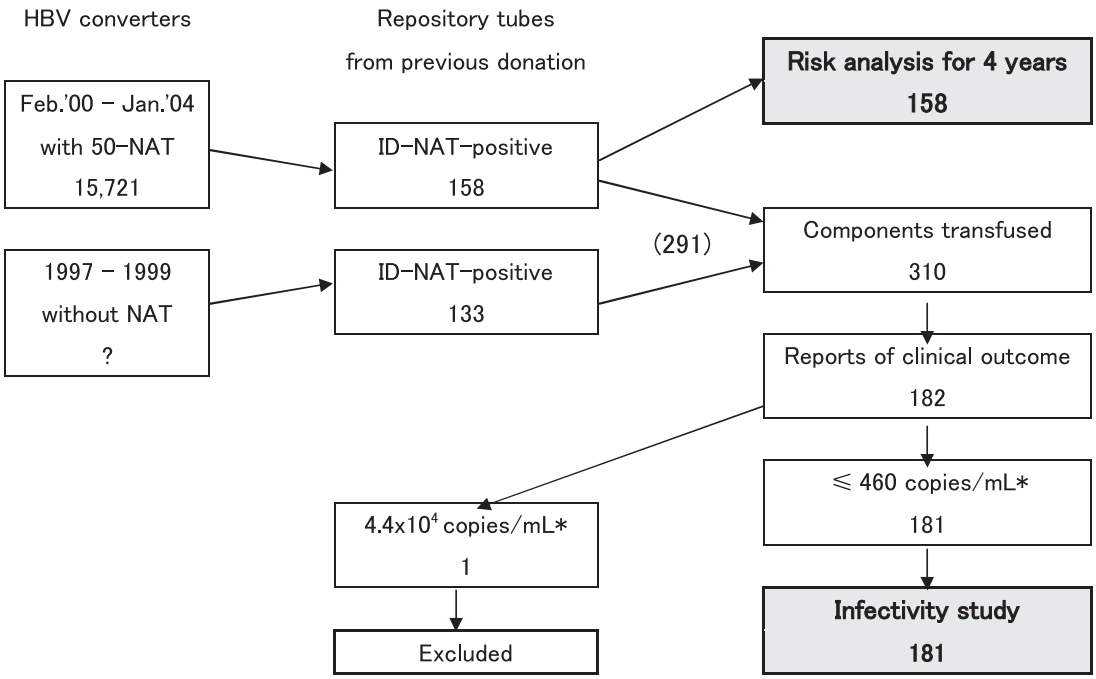

Fig. 1. Donations with HBV conversion obtained from 1997 to 2004. *HBV DNA copy number in repository tubes from prosero-conversion donation.

to 2004 in the analysis (Fig. 1). A total of 291 donations were determined to be ID-NAT–positive and an estimated 310 components were prepared from these donations and distributed to medical institutions. Through the hemovigilance system, we received 182 reports as of August 2005 that showed the clinical outcomes of the transfusions of the components. Although the donations given before February 2000 were not screened by 50-NAT, it is highly unlikely that the ID-NAT–positive donations before February 2000 would have been disqualified by 50-NAT screening considering the very low viral load in these samples (≤460 copies/mL, except for one case). Therefore, they are also referred to in this article as ID-NAT-only–positive donations. One sample donated before NAT screening that contained 4.4×10^4 copies per mL HBV DNA was excluded from this study.

TABLE 3. Clinical outcome of 181 patients transfused with ID-NAT-only–positive components

Clinical outcome	Number of patients (n = 181)
Infected through transfusion	12
Positive for the presence of HBsAg	7
Positive for the presence of HBV DNA	2
Positive for the presence of anti-HBs	3
Positive after transfusion without pretransfusion testing	7
Infected before transfusion	7
No evidence of infection	51
Expired	104

Twelve of the 181 reports were confirmed to be HBV-TTI cases (Table 3); of these, 7 became positive for the presence of HBsAg, 2 became positive for the presence of HBV DNA, and 3 showed anti-HBs seroconversion. All these patients had negative results for either HBsAg or HBV DNA before transfusion. HBV DNA sequences were identical between the blood donors and the transfused patients in all the 8 pairs studied. Seven patients who were positive after transfusion for the presence of anti-HBc (2 patients), anti-HBs (3 patients), or both markers (2 patients) were not classified as TTI cases because of the lack of pretransfusion HBV testing data. The other 7 patients who were also positive for the presence of HBV markers after index transfusion were actually found to have anamnestic HBV infection before transfusion. Fifty-one patients showed no evidence of HBV infection after index transfusion. Because no anti-HBc testing was performed after transfusion in any of the 51 patients, we may have overlooked cases that showed positivity only for anti-HBc as a result of infection. A total of 104 patients had died without any test results recorded regarding HBV infection. Thus, 12 of 63 (of 12 infected and 51 noninfected) patients acquired HBV infection as a result of the transfusion of ID-NAT-only–positive components, suggesting the infectivity of the components to be 19 percent. If all of the 7 positive patients without pretransfusion data were

TABLE 4. Blood donors and components included in study of HBV transmissibility and relationship between HBV-TTI and anti-HBc status of transfused components

Anti-HBc in repository samples	Number of donors	Converted marker	Number of components processed and transfused	Total number of components evaluated	Infection	
					Yes	No evidence
Low titer	29	NAT: 4	5	33	1	32
		Anti-HBc: 25	28			
Negative	20	NAT: 1	1	22	11	11
		HBsAg: 4	4			
		Anti-HBc: 15	17			
Undetermined	6	NAT: 1	1	8	0	8
		Anti-HBc: 5	7			
Total	55	NAT: 6	7	63	12	51
		HBsAg: 4	4			
		Anti-HBc: 45	52			

assumed to be TTI cases, the infectivity of the components would be 27 percent.

Blood components transfused to the 63 patients had been processed from 55 donations (Table 4). The HBV infection status of the 55 donations was determined from the anti-HBc and anti-HBs data and was further confirmed by the serologic data that were obtained with the repository tubes in the subsequent donation when HBV marker(s) converted. Twenty-nine donors with low-titer anti-HBc were judged to be in the occult carrier state (Table 4); 4 donors who became 50-NAT–positive in the subsequent donation were anti-HBc–positive with greater than 95 percent EIA inhibition in both the index and the subsequent donations, and all 25 donors showed weak reactivity for HI and greater than 90 percent (except for one case with 63%) EIA inhibition in the index donation and showed HI positivity and greater than 95 percent EIA inhibition in the subsequent donation. One exceptional donor with 63 percent EIA inhibition for anti-HBc was a 60-year-old woman with 72 mIU per mL anti-HBs in the index donation. Twenty anti-HBc–negative donations were designated as those obtained during the window period (Table 4); 4 donors became strongly positive for EIA-HBsAg with greater than 200 S/N within 2 months; 13 donors became anti-HBc–positive with greater than 90 percent EIA inhibition coupled with HI conversion in the subsequent donations; 1 donor with 5 percent inhibition for EIA-anti-HBc became HI-positive with an increase of up to 65 percent inhibition and anti-HBs conversion; 1 donor with 10 percent inhibition became HI-positive although EIA-anti-HBc remained negative after 14 days with 46 and 38 percent inhibitions in duplicate tests; and 1 donor became positive only for 50-NAT after 33 days, representing a minipool (MP)-NAT window case. For the six donations that had conflicting results between HI and EIA-anti-HBc, the infection status was not determined even if the serologic data in the subsequent donation were taken into consideration. A nonspecific reaction of HI and EIA-anti-HBc or the recovery phase of acute infection with or without prior vaccination are the possible explanation for this category. Because the transfusion of components derived from one donation (e.g., red blood cells [RBCs] and fresh-frozen plasma [FFP]) sometimes caused discrepant results in patients and the total viral loads of the components were different depending on the component types, clinical outcomes resulting from the transfusion of components derived from single donation are described separately in the present analysis.

Note that 11 of the 12 components that caused HBV infection had zero or negligible anti-HBc titers and therefore were considered to have been derived from donations given during the 50-NAT window period (Table 4). One jumbo FFP component (450 mL) identified by 50-NAT conversion in the subsequent donation had low anti-HBc titer with fewer than 100 copies per mL viral concentration. This case represents a TTI case caused by the transfusion of an occult carrier–derived component. Results of anti-HBs testing were available for 9 of the 12 infectious samples (Table 5). All 9 showed negative results including the sample from the occult carrier that had 4.8 mIU per mL, a value defined as negative. Of the repository tubes from 51 noninfectious components, 11 were negative and 32 were positive with low titer for anti-HBc (Table 4). Of the 32 samples with low-titer anti-HBc, 11 were positive and 12 were negative for the presence of anti-HBs (Table 5).

In summary, of the 33 components with low-titer anti-HBc, only 1 could be identified that caused infection, whereas of the 22 anti-HBc–negative components, 11 had proved to cause infection (Table 5). If the 8 anti-HBc–undetermined cases were also considered, the infectivity range of low-titer anti-HBc components was 2.4 to 3.0 percent and that of anti-HBc–negative components was 37 to 50 percent, showing that the HBV transmission rate of window period–derived components observed in our hemovigilance system is more than 10-fold higher than the rate caused by occult carriers with low-titer anti-HBc

TABLE 5. Relationships between anti-HBc, anti-HBs, and HBV-TTI

Anti-HBc	Infection	Anti-HBs			Total
		Positive	Negative	Undetermined	
Low titer	Yes	0	1 (1)*	0	1
	No†	11 (17)	12 (15)	9 (0)	32
Negative	Yes	0	8 (9)	3 (2)	11
	No	0	8 (10)	3 (1)	11
Undetermined	Yes	0	0	0	0
	No	5 (5)	2 (2)	1 (1)	8
Total	Yes	0 (0)	9 (10)	3 (2)	12
	No	16 (22)	22 (27)	13 (2)	51

* Number in parentheses is the number of donations that include ones whose anti-HBs status was estimated with the data obtained from subsequent donation.
† No evidence of infection.

who have slipped through the JRC screening system. It is also clear that there was no HBV-TTI in patients who were transfused with anti-HBs–positive components. When anti-HBc–undetermined cases were included, none of 16 anti-HBs–positive components exhibited evidence of infection (Table 5). When anti-HBs–undetermined cases were reevaluated with the anti-HBs and/or anti-HBc data in the subsequent donation and time interval between the two donations, the cases were successfully divided into anti-HBs–positive or –negative groups (numbers in parenthesis in Table 5). When the estimated numbers were also taken into account, it is calculated that the infectivity of components with and without anti-HBs was 0 of 22 and 10 of 37, respectively (Table 5).

In both the low-anti-HBc-titer group and the anti-HBc–negative group, the same HBV DNA levels were measured in the components with and without evidence of infection (Table 6). This is true even when viral load is adjusted to total viral copy number contained in the components with mean plasma volume of each component (data not shown). There was also no clear correlation between the type of blood components transfused and the infection outcomes observed in the recipients. There were two cases where components from one donation caused discrepant results in two patients transfused (Table 6 footnote). The distribution of age or sex showed no difference between the patients with and without serologic evidence of infection (data not shown).

The basic disease conditions of the TTI cases were available for nine patients: multiple trauma in one, surgical operation in three, shock due to trauma and burn in one, great vessel diseases in two, hematologic malignancies in two, and disease unknown in three (Table 7). The results show that patients prone to infection were not limited to heavily immunocompromised people. Four patients showed elevated alanine aminotransferase (ALT) of more than 100 IU per L. Although the number of patients was limited, there was a tendency that a high ALT was associated with a high total viral load infused.

DISCUSSION

The sample repository of all donations stored since 1996 enabled us to perform a lookback study and identify the blood donations that were ID-NAT–positive with low HBV DNA levels but had not been detected by the regular 50-NAT, HBsAg, and anti-HBc screening tests. Although the serologic testing of pre- and posttransfusion blood samples of patients who had received the ID-NAT HBV DNA–reactive blood components was often incomplete, we were able to show a difference in the transmissibility of HBV between donations in the pre-HBsAg and/or MP-NAT window phase and blood from donors with occult HBV infection whose anti-HBc titers were below the exclusion limit of the JRC screening system.

We performed HBV ID-NAT on 15,721 repository tubes and identified 158 (1.01%) DNA-positive samples, of which 95 were anti-HBc–reactive with low titer, indicating that, under the Japanese screening algorithm, 60 percent of the ID-NAT-only–positive donations from repeat donors are derived from occult carriers. The viral loads of the samples from occult carriers were very low with 75 of 78 samples having fewer than 100 copies per mL. Such concentrations cannot be detected with pool-NAT systems[11] suggesting the need to develop and implement ID-NAT systems for screening.[12] When no ID-NAT systems are available, sensitive anti-HBc testing is currently the only measure for identifying these very low viral loads from occult carrier donations.[13,14]

Of the 63 patients transfused with ID-NAT-only–positive components, 12 (19%) were confirmed as HBV-TTI cases. This number is unexpectedly low relative to the high HBV infectivity observed in clinical settings and animal experiments.[15,16] Possible reasons for this include the following: 1) anti-HBs or anti-HBc testing before and after transfusion is not routinely performed in medical facilities; thus some patients might have immunity against reinfection from past exposure to HBV or vaccination, whereas a relatively large proportion of HBV infections may not have been recognized in the current hemoviligance system in the hospitals. It is, however, unlikely that most noninfected patients maintained immunity by past infection given the hepatitis marker frequency of first-time donors in Japan, where the highest prevalence of anti-HBc (6.82%) has been observed in donors in their sixties.[17] Assuming that this percentage represents the mean anti-HBc prevalence among patients who received transfusions and that all anti-HBc–positive people have immunity against reinfection, prior protection would have contributed very little to the observed incidence of HBV-TTI. 2) The viral copy number obtained

TABLE 6. Relationship between HBV infectivity, HBV viral loads, and types of components

Anti-HBc status	Infectivity	Viral loads (copies/mL); component type(s)
Low titer (33)	Infectious (1)*	<100; FFP (1)
	Without evidence of infection (32)	<100 (27), 93, 98, 100, 120, NT†; RBCs (17), FFP (14), PC‡ (1)
Negative (22)	Infectious (11)	<100 (6), 160, 170, 230§, 300‖, 380; RBCs(5), FFP(4), PC(2)
	Without evidence of infection (11)	<100 (8), 170, 230§, 300‖; RBCs (5), FFP (4), PC (2)
Undetermined (8)	Without evidence of infection (8)	<100 (6), 200, 460; RBCs (2), FFP (6)

* Number in parentheses is the number of components.
† NT = not tested.
‡ PC = platelet concentrate.
§ RBCs and FFP were processed from the donation and transfused to a patient undergoing orthopedic surgery and a gastric cancer patient, respectively. The former patient acquired HBV infection and the latter did not.
‖ FFP and RBCs were processed from the donation and transfused to a patient with dissecting aneurysm and a patient undergoing orthopedic surgery, respectively. The former patient acquired HBV infection and the latter did not.

TABLE 7. Basic disease conditions of TTI cases

Age (years)	Sex	Basic disease status	Converted marker	Highest ALT (IU/L)	Types of components transfused	Viral copies/mL in components	Total viral loads infused*
65	Male	Multiple trauma	HBsAg	2281	FFP-2 (WP)†	1.7×10^2	27,200
66	Female	Knee joint replacement (rheumatoid arthritis)	Anti-HBs	1109	RBCs-2 (WP)	2.3×10^2	5,750
49	Female	Dissecting aneurysm	HBsAg	992	FFP-2 (WP)	3.0×10^2	48,000
71	Male	Gastrectomy (gastric cancer)	HBsAg	148	RBCs-2 (WP)	<100	UD‡
62	Male	Acute myelogenous leukemia	HBV DNA	66	PC§-15 (WP)	3.8×10^2	95,000
63	Male	Carotid artery stenosis	HBsAg	56	RBCs-2 (WP)	<100	UD
74	Female	Shock due to trauma and burn	HBsAg	33	FFP-1 (WP)	<100	UD
68	Male	T-cell lymphoma	HBsAg	27	PC-10 (WP)	<100	UD
78	Male	Gastrectomy (gastric cancer)	HBV DNA	17	RBCs-2 (WP)	<100	UD

* Total viral load in the component was calculated with the plasma volume of each component; FFP-2, 160 mL; RBCs-2, 25 mL; PC-15, 250 mL; FFP-1, 80 mL; PC-10, 200 mL.
† Components obtained during the window phase (WP).
‡ UD = undetermined.
§ PC = platelet concentrate.

by PCR may include replication-incompetent DNA fragments and therefore may not directly relate to infectivity. 3) A protective effect may be induced by passively transferred anti-HBs from index components or components from other antibody-positive donors transfused close to the time of HBV exposure. 4) The infectivity of HBV may be reduced during storage of the blood components.

Despite these limitations we were able to compare the outcomes of HBV transmission of components derived from 55 donations and compare the infection outcomes in 63 recipients. The results that were retrievable in the hemoviligance system indicate that the donations in the pre-HBsAg and/or MP-NAT window phases are at least 10-fold more infectious than the donations with low anti-HBc titers from occult carriers. Eleven of 22 (50%) components derived from window-phase donations proved to have caused seroconversion of HBV markers in the recipients, whereas only 1 of 33 (3%) anti-HBc–reactive donations showed serologic evidence of infection. The infectious anti-HBc–reactive FFP component came from an anti-HBs–negative occult HBV carrier with fluctuating viremia. None of 11 anti-HBc–reactive and anti-HBs–positive units proved to have caused infection. When the anti-HBc–undetermined units were taken into consideration, it was revealed that there was no evidence of infection in any of the 16 patients transfused with anti-HBs–positive components. To establish the relationship between the titer of anti-HBs and the infectivity of occult carrier–derived blood, more clinical reports are needed for the category of patients who acquired infection as a result of transfusion of low titer anti-HBc components. When the clinically observed HBV transmission rate of anti-HBs–negative donations with and without low-titer anti-HBc was compared, it turned out that the transmission rate caused by the presumed tail-end carriers with occult HBV infection (1/13, 8%) was still significantly lower than the rate of the window-phase donations (8/16, 50%; $p < 0.05$). There were three components having at least 200 copies per mL of HBV sequence that did not cause infection even in the absence of detectable anti-HBs. It may be that the infectivity of donors with higher anti-HBc titers (that are screened out of the Japanese blood supply) have a higher risk to be infectious, particularly in the tail-end chronic carriers without circulating

neutralizing anti-HBs. More research needs to be done to understand the infectivity of HBV in donors with chronic occult infection or with persistent or recurrent viral replication after recovery. In chronic and perhaps more in recovered occult HBV infection, mutations in the genome may reduce the capacity of viral entry, replication, and secretion.[18-24] It has been reported that a portion of patients who recovered from acute hepatitis harbor HBV in their liver and may exhibit intermittent viremia even after complete clinical resolution and HBsAg clearance.[25-28]

There was essentially no difference in copy number between the infectious and the presumed noninfectious components, indicating that the viral load is not the only factor for infectivity. The infectious load is dependent on the amount of plasma and 3- to 20-fold higher in platelet concentrate or FFP than in RBCs, but we were unable to demonstrate a difference in transmission risk between these components. It may be that other factors affecting the observed infectivity in recipients (see above) have masked the known relationship between infectivity and viral load in the transfused components. Unfortunately we have no means to confirm whether indeed half of the anti-HBs–negative window-phase units were not infectious even though viral loads above 10^2 to 10^5 HBV particles have been infused. It may be that we would have found these donations to be infectious when anti-HBc and anti-HBs was routinely tested in the pre- and posttransfusion samples of the recipients. Our estimates for the infectivity of ID-NAT-only–positive units may thus be underestimated. We also could not find any clear differences between the patients' susceptibility profiles in terms of disease status, age, and sex. Although we could not find clear relationship between infectivity and viral load in components, some degree of association was suggested between patients' high ALT value during the course of infection and the high total viral load contained in the component, the result reminiscent of the report by Barker and Murray.[29]

JRC has been collecting voluntary reports on TTI from hospitals and has already established a database for isolated TTI cases.[30] Combining these data and those obtained from this lookback study, it is estimated that the total number of HBV-TTI cases is 17 to 20 per year (1/0.27-0.32 million donations) in Japan with 5.4 million annual blood donations and that approximately 85 percent of the HBV infections are caused by the transfusion of window period–derived components. Although it is obvious that combined screening with ID-NAT and sensitive anti-HBc testing would ultimately reduce the HBV-TTI cases, a decision on whether the anti-HBc screening is implemented or not should be made considering the local prevalence of HBV in the area considered, the number of donors who would be disqualified as a result of anti-HBc screening, and the relative low infectivity of occult carrier–derived components described in this report.[31] One must bear in mind, however, that in our study only the infectivity of low-titer anti-HBc carriers was examined and that the picture can be completely different for anti-HBs–negative occult carriers with higher anti-HBc titers. It should also be mentioned that JRC's serologic test, especially hemagglutination for HBsAg, has lower sensitivity than EIA and that the rate of screening NAT yield and ID-NAT-only–positive donation can be different in other areas.

Inaba and coworkers[32] recently reported about another anti-HBs–negative occult carrier with borderline detectable anti-HBc levels who was found some of the time to be ID-NAT–positive and some of the time to be ID-NAT–negative.[32] This may be caused by fluctuating viremia in the donor or stochastic sample variability in the NAT assay typical with low viral load. Lookback study showed that some of the previous donations, both ID-NAT–positive and ID-NAT–negative units, had caused HBV infection in the recipients and that some had caused clinical hepatitis. This donor only would have been detected with more sensitive anti-HBc screening or with ultrasensitive ID-NAT. JRC is currently exploring which options remain to further reduce the risk of posttransfusion hepatitis B.

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Welcome

Guidelines for the Blood Transfusion Services in the UK

7th Edition

Update notice: text HIGHLIGHTED has changed following the issue of Change Notification 12 - 2010

The JPAC Standing Advisory Committee on Care and Selection of Donors has redrafted chapters 3, 4, 5 & 6 of the Red Book. The 4 chapters have been re written into 3 more focused chapters reflecting the fact that care and selection of donors is similar whether they are whole blood or component donors. Outdated prohibitions have been removed. The repetition of the Donor Selection Guidelines (DSG) in the chapters has also been removed as the DSG is an appendix to the Red Book.

Other changes reflect an updated understanding of apheresis, actual adult blood volumes and the new technology now being used. This results in changes to a reduced safe Extra Corporeal Volume (15% rather than 20%) and improved charts and appendixes. Following legal advice on Consent, more information on competence (following the Mental Capacity act 2005), confidentiality and Donor Adverse events has been added.

For further information please see Change Notification 12 2010

The 'Red Book' (as the printed version of these guidelines are known) aims to define guidelines for all materials produced by the United Kingdom Blood Transfusion Services for both therapeutic and diagnostic use. The guidelines reflect an expert view of current best practice, provide specifications ofproducts, and describe technical details of processes .Every effort has been made to ensure thatthe guidelines reflect the legally binding requirements of the Blood Safety (and Quality) and Regulations, UK Statutory Instrument 2005 No. 50.

Chapter 1 provides an introduction to the 'Red Book', the regulatory environment, the Blood Safety (and Quality) regulations, and relevant EU Directives.

The publication of the Red Book and its appearance on the website does not necessarily mean that the practices outlined are brought into use in the Services simultaneously. For operational reasons, the implementation dates may be decided separately by the 4 UK Services. Please consult your relevant Service (England, Northern Ireland, Scotland or Wales) for details of implementation dates.

This site provides:
A portable document file (pdf) version of the current printed version of the Guidelines (7th edition, October 2005).
An online (browser) version. This is updated periodically by means of Change Notifications (view)The printed book can be purchased from:
The Stationery Office (www.tsoshop.co.uk)
Direct link: http://www.tsoshop.co.uk/bookstore.asp?FO=1160007&DI=557693).

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Section 10.4

10.4 Additional microbiological testing of selected donations

There is an increased risk of system error affecting tests that are not performed routinely on donors/donations. Reliable systems must be in place that ensure that errors do not occur where such tests are to be used as a basis for product release.

Antibody to cytomegalovirus (anti-CMV)

The presence or absence of anti-CMV should be determined by examination of the serum or plasma of the donor. The UK specification for the minimum level of sensitivity for the performance of anti-CMV screening has not yet been defined beyond the requirement that in each series of tests a positive result be obtained with the national anti-CMV working standard when it becomes available.

Although it is advisable to have panels of CMV seronegative donors, a donation must not be considered anti-CMV negative and be labelled as such unless it has been tested and found to be anti-CMV negative.

- Quality control of anti-CMV tests:
- each batch of anti-CMV test kits should be shown to conform with locally established minimum criteria for specificity and sensitivity
- in addition to the test kit manufacturer's controls, quality control measures should be taken to demonstrate acceptable sensitivity of the test method
- no series of tests should be considered acceptable unless the result of the test manufacturer's and the additional quality control samples have satisfied the criteria laid down.

Tests for malarial antibodies

The exclusion period for donors from malarial areas is given in the JPAC Donor Selection Guidelines[1]. The JPAC Donor Selection Guidelines specify some situations where donations may only be released if a test for malaria antibody is negative. Such testing must only be undertaken using a test that has been validated for use in this setting. The presence or absence of malarial antibodies should be determined by examination of the serum or plasma of the donor. No series of tests should be considered acceptable unless the manufacturer's control tests have satisfied the criteria laid down.

Tests for antibodies to Trypanosoma cruzi

The deferral criteria for donors from T. cruzi areas are given in the JPAC Donor Selection Guidelines[1]. Donors at risk of T. cruzi must be tested for T. cruzi antibodies and negative results obtained prior to the release of any blood component for clinical use. Such testing must only be undertaken using a test which has been validated for use in this setting.

The presence or absence of T. cruzi antibodies should be determined by examination of the serum or plasma of the donor.

No series of tests should be considered acceptable unless the manufacturer's control tests have satisfied the criteria laid down.

Tests for West Nile Virus (WNV)

The exclusion criteria for donors from a WNV risk area is given in the JPAC Donor Selection Guidelines[1]. The JPAC Donor Selection Guidelines[1] specify some situations where donations may only be released if a test for antibody to WNV is negative. WNV NAT tests can be performed on donations provided by donors within the exclusion period and negative results obtained prior to the release of any blood component for clinical use. Such testing must only be undertaken using a test that has been validated for use in this setting. Normally plasma from the donor would be examined for the presence of WNV RNA.

Any reactive donor would be permanently deferred. No series of tests should be considered acceptable unless the manufacturer's control tests have satisfied the criteria laid down.

Tests for antibodies to hepatitis B core (anti-HBc)

The exclusion period for donors who have had body piercing, acupuncture, etc. are given in the JPAC Donor Selection Guidelines.[1] Certain of these categories may require donations to be tested for anti-HBc and negative results obtained prior to release of any blood component for clinical use. Such testing must only be undertaken using a test that has been validated for use in this setting. The presence or absence of anti-HBc should be determined by examination of the serum or plasma of the donor. No series of tests should be considered acceptable unless the manufacturer's control tests have satisfied the criteria laid down.

Antibody to hepatitis B surface antigen (anti-HBs)

Donations found to be reactive for anti-HBc should be anti-HBs tested and those with levels <100 IU/L are deemed unsuitable for use; whereas those with levels >100 IU/L can be considered safe. Such testing must only be undertaken using a test that has been validated for use in this setting. The level of anti-HBs should be determined by examination of the serum or plasma of the donor. No series of tests should be considered acceptable unless the manufacturer's control tests have satisfied the criteria laid down.

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