医薬品 研究報告 調査報告書

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一般的名称	解凍人赤血球濃厚液		研究報告の公表状況	ABC Newsletter. 2006 Sep 22; 16.	公表国	
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社)				EU	

研究報告の概要	使用上の注意記載状況・その他参考事項等
○欧州協議会が伝達性海綿状脳症に関する報告書を発行 欧州協議会は2005年の反芻動物(有蹄動物)における伝達性海綿状脳症(TSE)のモニタリングと検査に関する報告書を発表した。TSE検査を行った1千万頭以上のウシ亜科動物のうち、陽性となったのは561頭のみと報告されている。2005年の調査結果は陽性例が引き続き減少していることを示している。TSE年次報告は、1990年代の食物安全危機を受けて、牛海綿状脳症モニタリングプログラムの一環として行われている。2001年以降5,100万頭のウシがこのプログラムによって検査されている。報告書はECのウェブサイト上で公開されている。	解凍赤血球濃厚液「日赤」 照射解凍赤血球濃厚液「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
欧州協議会が伝達性海綿状脳症に関する報告書を発表し、1千万頭のうち561頭がTSE陽性であったとの報告である。	日本赤十字社は、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より1980年～1996年に1日以上の英国滞在歴のある方からの献血を制限している。今後も、CJD等プリオン病に関する内外の新たな知見及び情報の収集に努める。

INFECTIOUS DISEASE UPDATES

A high school science teacher in Salina, Kansas this week was suspended for allowing students to reuse the same instrument to draw blood from their fingers as part of a class project. Carol Pitts, spokeswoman for the Salina school district, said students in two science classes at Salina High School South were allowed to use the same lancet, or small pin, to prick their fingers for an experiment on Monday. She said about 50 students might have been involved. Ms. Pitts said there was additional concern that some of the students might have come in contact with blood when they washed the science experiment slides. She said it was unclear what experiment the classes were doing, but they may have been checking blood glucose levels. The school district is working with the Saline County Health Department to ensure that the students are tested for diseases such as HIV and hepatitis, both of which can be spread by using a shared instrument to draw blood. "Our recommendation is that the kids get tested now as a baseline for HIV and Hepatitis B and C and have it repeated two or three times," said health department director, Yvonne Gibbons, MD. But she said there likely was little cause for concern. "This is minimal risk," Dr. Gibbons said. "I don't think there is any reason to panic, but we're cautioning the school to take the best possible course they can, and that would be to have the kids tested." (Source: Associated Press, 9/19/06)

vCJD

The European Commission this week released its 2005 report on the monitoring and testing of ruminants (hoofed animals) for the presence of Transmissible Spongiform Encephalopathy (TSE) in the EU. Out of over 10 million bovine animals tested for TSE in 2005, only 561 were positive, EC reports. The 2005 results show a continuous decline in the number of positive tests. The annual TSE report is produced as part of the monitoring program on Bovine Spongiform Encephalopathy (BSE), following the food safety crisis of the 1990s. Since 2001, 51 million cattle have been tested through the program. The report is available on the EC Web site at: ec.europa.eu/food/food/biosafety/bse/-annual_report_tse2005_en.pdf ♦

PEOPLE:

Maria Elena Geyer, vice president of Donor Services at Puget Sound Blood Center, this week was honored as a Women In Science at the *Northwest Asian Weekly's* Women of Color Empowered Luncheon. Ms. Geyer is one of several women being honored for their work in the field of science. *Northwest Asian Weekly* is an English language newspaper published by Assunta Ng, publisher of the *Seattle Chinese Post*. Ms. Ng started the Women of Color Empowered luncheons in 1996 as a networking group and as a way to recognize the accomplishments of women from diverse ethnic backgrounds. Ms. Geyer was also named recipient of the AABB's Chapman Franzmeier Memorial Award. The award was made in recognition of her exceptional leadership in the area of donor recruitment.

Jennifer Taggart is the new chief financial officer for Florida's Blood Centers. Ms. Taggart, whose background is in finance and management, will oversee finances, procurement and employee relations. She previously was vice president and general manager for Orlando Harley Davidson – where she managed revenue growth that went from less than $20 million in 2000 to $48 million in 2005, and year-to-year net income growth of more than 50 percent every year since 2001, including some years of triple-digit growth. She also oversaw the opening of five new retail stores and laid the groundwork for two future sites.

(continued on page 17)

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識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2006. 9. 16	該当なし	
一般的名称	解凍人赤血球濃厚液		研究報告の公表状況	Schmidt M, Nubling CM, Scheiblauer H, Chudy M, Walch LA, Seifried E, Roth WK, Hourfar MK. Vox Sang. 2006 Oct;91(3):237-43.	公表国 ドイツ	
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研究報告の概要

○供血者のHBc抗体スクリーニング:HBc抗体検査9種の比較

【背景および目的】ドイツ赤十字社におけるB型肝炎ウイルス(HBV)に対するミニプール核酸増幅検査(NAT)導入以降、輸血関連HBV感染の残存リスクは1:500,000と推定されているが、これはヒト免疫不全ウイルス(HIV)あるいはC型肝炎ウイルス(HCV)の10倍である。このリスクの高さは、B型肝炎コア抗原に対する抗体(HBc抗体)の慢性陽性、B型肝炎表面抗原(HBsAg)の陰性、ならびにウイルス量が少なくポリメラーゼ連鎖反応(PCR)で陰性を示す供血者が主な原因である。【対象および方法】血液センターの供血者10,000名を対象に、現行のPRISM®HBcおよび新規PRISM®HBcore検査を用いたHBc抗体のスクリーニングを実施し、これらの検査の診断感度および特異性を調べた。PRISM® HBcまたはPRISM® HBcoreで陽性だった検体については、別のHBc抗体検査7種、B型肝炎表面抗原抗体(HBs抗体)検査2種、B型肝炎エンベロープ抗原抗体(HBe抗体)検査1種、およびHBV NAT検査3種を用いて、さらに分析を行った。【結果】合計10,000名の供血者のうち、PRISM® HBc およびPRISM® HBcoreの一方のみに陽性反応を示したのは、それぞれ9および14検体であったが、2つのHBc抗体検査ともに陽性だった検体は165であった。HBc抗体検査が陽性であったこの188検体について、計9種類の抗HBc検査による分析をさらに実施したところ、162(86.2%)検体で一致した結果が得られた。HBc抗体のみ陽性だった検体のHBc抗体のカット・オフ値は、HBs抗体またはHBe抗体も陽性だった検体と比較して、有意に低かった($p < 0.01$)。【結論】PRISM HBc抗体検査はいずれも、ドイツのプレスクリーニング未実施供血者の約1.8%がHBc抗体陽性であることを示した。両PRISMテストの感度は同等であったが、特異性はPRISM® HBcoreの方が有意に高かった。HBc抗体のカット・オフ値が高い検体では、その他のHBVパラメータが陽性であり、9種類のHBc抗体検査結果が一致することが示された。HBc抗体のみ陽性およびHBc抗体/HBs抗体陽性の輸血によるそれぞれの感染リスクを推定するためには遡及調査が必要である。

使用上の注意記載状況・その他参考事項等

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「日赤」

血液を介するウイルス、
細菌、原虫等の感染
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報告企業の意見	今後の対応
現行のPRISM®HBcおよび新規PRISM®Hbcore検査を用いたHBc抗体のスクリーニングを実施し、診断感度および特異性を調べたところ、感度は同等であったが、特異性はPRISM® HBcoreの方が有意に高かった。HBc抗体のカット・オフ値が高い検体では、その他のHBVパラメータが陽性であり、9種類のHBc抗体検査結果が一致することが示されたとの報告である。	日本赤十字社では、HBs抗原検査及びHBc抗体検査を実施することに加えて、HBVについて20プールでスクリーニングNATを行い、陽性血液を排除している。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。また、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。

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ORIGINAL PAPER

Anti-HBc screening of blood donors: a comparison of nine anti-HBc tests

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Vox Sanguinis

Background and Objectives Since voluntary introduction of hepatitis B virus (HBV) minipool nucleic acid amplification technology (NAT) at the German Red Cross, the expected residual risk of a transfusion-associated HBV infection has been estimated to be 1 : 500 000 – about 10 times higher than for human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection. Donors demonstrating chronic positivity for antibody to hepatitis B core antigen (anti-HBc), negativity for hepatitis B surface antigen (HBsAg) and polymerase chain reaction (PCR)-negative with a low virus load are a major cause of this increased risk.

Materials and Methods Ten-thousand blood donors from our blood-donation centre were screened for anti-HBc using the current PRISM® HBc and the new PRISM® HBcore assay to evaluate the diagnostic sensitivity and specificity of these tests. PRISM® HBc- or PRISM® HBcore-reactive samples were further analysed using seven additional tests for anti-HBc, two tests for antibody to hepatitis B surface antigen (anti-HBs), one test for antibody to hepatitis B envelope antigen (anti-HBe) and three HBV NAT assays.

Results From a total of 10 000 donors, nine and 14 samples were reactive only in the PRISM® HBc and the PRISM® HBcore, respectively, whereas 165 samples were reactive in both anti-HBc assays. Further analysis of these 188 anti-HBc-reactive specimens in a total of nine different anti-HBc assays revealed concordant results for 162 (86·2%) specimens. Sample cut-off values for anti-HBc were significantly ($P < 0{\cdot}01$) lower for anti-HBc-only reactive samples compared with specimens that were also reactive for anti-HBs or anti-HBe.

Conclusions Both PRISM anti-HBc assays revealed that ≈ 1·8% of non-prescreened blood donors from Germany were reactive for anti-HBc. Although sensitivity was comparable between both assays, specificity was increased significantly with the PRISM® HBcore. High anti-HBc sample cut-off values were indicative for reactivity in other HBV parameters and for concordant results in the nine different anti-HBc assays. Look-back investigations are necessary to estimate the infection risk both of anti-HBc-only positive and of anti-HBc/anti-HBs-positive blood transfusions.

Key words: anti-HBc assays, anti-HBs, blood screening, HBV DNA.

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Introduction

Hepatitis B virus (HBV) infection is a serious global health problem affecting two billion people worldwide, and 350 million people suffer from chronic HBV infection [1]. In Germany, ≈ 5–8% of the population has a history of HBV infection, and

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0·4–0·7% are chronic HBV carriers [2]. To provide a safe blood supply, minipool nucleic acid amplification technology (MP-NAT) for hepatitis C virus (HCV), human immunodeficiency virus 1 (HIV-1) and HBV was implemented on a voluntary basis in 1997 at most German Red Cross Blood Donor Services, and subsequently NAT became mandatory in Germany for HCV RNA (in 1999) and for HIV-1 RNA (in 2004) [3–5]. With the introduction of NAT testing, the risk of transfusion-transmitted viral infections was significantly reduced [5]. For Germany the risk of receiving an infectious blood donation is calculated at 1 in 5 540 000 for HIV-1 and 1 in 4 400 000 for HCV. In contrast, the transfusion-associated risk of HBV is estimated at 1 in 620 000 by using MP-NAT and 1 in 820 000 by using individual-donation (ID) NAT [6].

This relatively high risk for HBV in part can be attributed to chronic HBV-infected blood donors with low-level viraemia. The likelihood of chronicity after an acute hepatitis B infection varies with age. Infection at birth is associated with a clinically silent acute infection with a 90% probability of chronic infection, while infection during adulthood is typically associated with clinically apparent acute hepatitis and a low risk of chronicity (≈ 1%) [7].

Heptatitis B surface antigen (HBsAg) [8] assays have been available for blood donor screening since 1971. However, despite the introduction of HBsAg- and MP-NAT testing, cases of HBV transmission via HBsAg-negative blood donations have been reported [9]. This indicates that both screening tests (HBsAg and MP-HBV-NAT) might have limitations for the diagnosis of chronic HBV infections, as the viral load may be below the detection limit of NAT, and that HBsAg may become undetectable only a few months after infection.

Seroconversion to antibody to hepatitis B core antigen (anti-HBc) occurs within the first 1–2 weeks [9] after the appearance of HBsAg and precedes detectable levels of antibody to hepatitis B surface antigen (anti-HBs) by weeks to months. High anti-HBs levels of > 100 IU/l in a donor are currently assumed to be putatively protective against transmission of HBV to a recipient of blood transfusion. However, HBV infections may occur without detectable anti-HBs or with disappearance of anti-HBs, sometimes associated with late-phase reactivation of HBV. Additional screening for anti-HBc could therefore both close the diagnostic gap between the disappearance of HBsAg and the appearance of anti-HBs and detect late-phase HBV infection with potential low-level viraemia.

Isolated anti-HBc does not necessarily indicate active virus replication, as most cases of isolated anti-HBc denote resolved hepatitis B infections of the past [10]. HBV-infected blood donors with a low-level viraemia and without anti-HBs, however, are assumed to be infectious to recipients, and probably contribute to the relatively high residual infection risk compared with HCV or HIV [5,11].

Anti-HBc screening of blood donors is performed in some countries (e.g. the USA, France and Japan) and will become mandatory in Germany from July 2006. Currently available anti-HBc assays, however, are reported to be unsatisfactorily non-specific, with unconfirmed reactive results in ≈ 32% of initially anti-HBc reactives [12–14]. The unnecessary deferral of a high number of non-specific anti-HBc reactive, but otherwise healthy, blood donors could lead to an undersupply of essential blood products.

The objectives of this study were to document the prevalence of anti-HBc reactives in HBsAg-negative donations made to our blood transfusion service and to compare two commercially available anti-HBc assays (PRISM® HBc and PRISM® HBcore) for their diagnostic and analytical specificity and sensitivity. In addition, all 188 samples, which were either PRISM® HBc or PRISM® HBcore reactive, were analysed by comparative testing in a total of nine different anti-HBc tests and by analysis of the HBV parameters anti-HBs, antibody to hepatitis B envelope antigen (anti-HBe) and HBV DNA.

Materials and methods

Blood donors

Whole-blood samples were collected from 10 000 unpaid blood donors at the German Red Cross Institute Frankfurt between January and February 2004. Of these, 10·5% were first-time donors (50·4% female, mean age 36·1 ± 12·4 years; 49·6% male, mean age 37·9 ± 12·8 years) and 89·5% were repeat donors (38·8% female, mean age 44·6 ± 12·5 years; 61·2% male, mean age 46·7 ± 12·3 years). The donor population had not been previously screened for anti-HBc. The study was approved by the ethics committee of the Johann Wolfgang Goethe University, Frankfurt am Main.

Sample preparation and test algorithm

Samples were centrifuged at 3000 *g* for 10 min, and EDTA-plasma was separated within 24 h. Samples involved were tested by the current PRISM® HBc and the new PRISM® HBcore (Fig. 1). Reactive samples were analysed using a total of nine commercially available anti-HBc assays (including the two used for screening), as well as with two anti-HBs assays, an anti-HBe assay and three different NAT assays. Samples with a positive test result in one anti-HBc assay were initially defined as anti-HBc reactive until the results of further testing were available. Samples where the initial anti-HBc result was confirmed by an additional HBV parameter (such as anti-HBs without vaccination, anti-HBe or HBV DNA) were defined as anti-HBc positive. Samples that were anti-HBc-only reactive, or vaccinated donors who were anti-HBc and anti-HBs reactive, were termed anti-HBc indeterminate. The donors were queried about their vaccination status if anti-HBs was the only additional marker.

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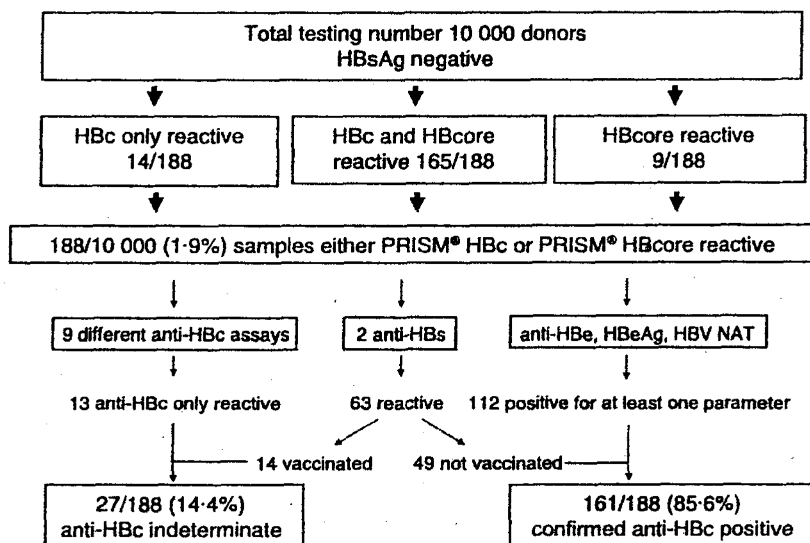

Fig. 1 Testing procedure. A total of 10 000 hepatitis B surface antigen (HBsAg)-negative donors were screened with PRISM® HBc and PRISM® HBcore. Reactive samples were analysed by nine different tests for antibody to hepatitis B core antigen (anti-HBc) and tested for antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis B envelope antigen (anti-HBe) and hepatitis B virus by nucleic acid amplification technology (HBV NAT). Samples that were also positive for anti-HBe, hepatitis B e antigen (HBeAg), HBV NAT or anti-HBs without vaccination were interpreted as confirmed anti-HBc positive. Samples that were anti-HBc-only reactive or anti-HBs with vaccination were interpreted as anti-HBc indeterminate.

HBV NAT

Samples diagnosed as anti-HBc reactive by PRISM® HBc or PRISM® HBcore were tested using an in-house real-time HBV DNA polymerase chain reaction (PCR) assay with primers targeted to the surface (S) gene (nucleotides 338–430) [15]. To increase sensitivity of the in-house NAT, we performed enrichment of viruses from 9·6 ml of single-donor plasma by centrifugation at 58 000 *g* for 1 h before extraction (single-sample enrichment PCR). After centrifugation, supernatants were decanted and the pellets were subjected to nucleic acid extraction using the QIAamp DNA blood mini kit (Qiagen, Hilden, Germany). Nucleic acids were eluted from the Qiagen columns in a final volume of 50 µl. Aliquots of 20 µl were subjected to amplification by HBV PCR in duplicate. Single-sample enrichment PCR was independently repeated at least four times. The analytical sensitivity (95% detection limit) of the single-sample enrichment PCR was 1·86 IU/ml, based on the World Health Organization (WHO) International Standard for HBV DNA (NIBSC Code 97/746). Furthermore, all anti-HBc-reactive specimens were tested in two commercially available HBV DNA screening NAT assays by ID-NAT, HBV Cobas AmpliScreen (Roche Molecular Systems, Pleasanton, CA, USA) and TMA Ultrio (Chiron, Emeryville, CA, USA), according to the manufacturers' instructions. The test systems HBV Cobas AmpliScreen and TMA Ultrio yield a sensitivity of 6·7 IU/ml [16] and 11 IU/ml [17], respectively.

Serological testing

A total of 10 000 blood donors were screened with PRISM® HBc, as well as with PRISM® HBcore. Samples that were positive in at least one of the assays were additionally tested in the following seven anti-HBc assays: AxSym Core™ (Abbott, Wiesbaden, Germany); Immulite® 2000 Anti-HBc (DPC, Bad Naunheim, Germany); Enzygnost® Anti-HBc Monoclonal (Dade Behring, Marburg, Germany); Ortho™ HBc ELISA (Ortho Clinical Diagnostic, Neckargemuend, Germany); Cobas® Anti-HBc (Roche Diagnostics, Mannheim, Germany); Murex® Anti-HBc (Abbott/Murex Biotech Ltd, Dartford, Great Britain); and ADVIA Centaur HBc® (Bayer Health Care, Tarrytown, NY, USA). To determine HBsAg, hepatitis B envelope antigen (HBeAg), anti-HBs and anti-HBe, the following tests were used: PRISM HBsAg®, AxSYM HBe 2·0®, AxSYM AUSAB®, and AxSYM anti-HBe 2·0®, respectively (all Abbott); ADVIA Centaur Anti-HBs (Bayer Health Care); and Architect Anti-HBe (Abbott). All serological tests were conducted strictly in accordance with the manufacturers' instructions. All anti-HBc assays were competitive tests, with the exception of ADVIA Centaur HBc® and Ortho™ HBc ELISA, which were non-competitive anti-HBc assays.

Statistical analysis

The standard deviation (SD) and coefficient of variation (CV) of the antibody assays were calculated with Excel 2000. The Student's unpaired *t*-test was performed with the data from sample cut-off (S/Co) values. Fisher's test was performed for sensitivity, specificity, positive and negative predictive value between PRISM® HBc and PRISM® HBcore. Statistical significance was considered if the P-value was < 0·05. Results were highly significant if the P-value was < 0·01.

Results

Prevalence of anti-HBc in the German Red Cross donor population

A total of 10 000 HBsAg-negative donors from our blood donation service were screened, in parallel, with PRISM® HBc

Table 1 Characterization of 188 antibody to hepatitis B core antigen (anti-HBc)-reactive samples by nine different anti-HBc assays

		Anti-HBc reactivity in nine different assays		
		Class A (9 assays)	Class B (5–8 assays)	Class C (1–4 assays)
Group 1				
Anti-HBc only	13	0	8	5
Group 2[a]				
Anti-HBc + anti-HBs	63	50	11	2
Anti-HBc + anti-HBe	7	7	0	0
Group 3[b]				
Anti-HBc + anti-HBs + anti-HBe	105	105	0	0
Total	188 [168 (89·4%) anti-HBs positive]	162 (86·2%)	19 (10·1%)	7 (3·7%)

[a]One second marker positive.
[b]Both second markers positive.
All 188 samples reactive by PRISM® HBc and/or by PRISM® HBcore were re-analysed by seven additional assays for anti-HBc. Samples were categorized into three groups [1 = anti-HBc-only reactives; 2 = one second marker positive for antibody to hepatitis B surface antigen or antibody to hepatitis B envelope antigen (anti-HBs or anti-HBe); 3 = samples reactive for anti-HBc and anti-HBe + anti-HBs). The samples were further classified into three classes (class A = reactive in all nine anti-HBc assays; class B = reactive in five to eight anti-HBc tests; class C = reactive in four or fewer anti-HBc tests).

and PRISM® HBcore (Fig. 1). One-hundred and eighty eight of 10 000 (1·88%) samples were either PRISM® HBc or PRISM® HBcore reactive. The majority of these samples were additionally positive for anti-HBs (168/188, 89·4%) or for anti-HBe (112/188 59·6%) (Table 1). All of these anti HBc-reactive samples were HBeAg negative. Only one sample, which was anti-HBc reactive in all nine assays, negative for anti-HBs and positive for anti-HBe, was HBV DNA positive by single-sample enrichment NAT. Quantification yielded a virus load of 2·5 IU/l. However, both commercial HBV NAT systems designed for NAT blood screening (Cobas Ampliscreen and TMA Ultrio) gave negative results after triplicate testing of the individual plasma.

Sensitivity and specificity of PRISM® HBc and PRISM® HBcore assays

One-hundred and sixty five of 188 samples were reactive in both anti-HBc screening assays, whereas 14 and nine samples were only PRISM® HBc and PRISM® HBcore reactive, respectively. Ten of 14 PRISM® HBc-only reactive samples were not confirmed by other HBV parameters. The remaining four samples were positive for anti-HBs. Three of nine PRISM® HBcore-reactive samples were not confirmed by other HBV parameters. The remaining six samples were positive for anti-HBs.

Diagnostic sensitivity is defined as the ratio of positive tested samples divided by all positive samples, whereas diagnostic specificity is defined as the ratio of negative tested samples divided by all negative samples. Based on 'anti-HBc-positive' samples (samples that were also positive for an additional HBV parameter after exclusion of vaccination), diagnostic sensitivity was equal for both screening assays (96·9% and 99·4% for PRISM® HBc and PRISM® HBcore, respectively; not significant $P = 0{\cdot}5$; 159/161 samples reactive for PRISM® HBc and 160/161 samples reactive for PRISM® HBcore). In contrast, diagnostic specificity was significantly higher for PRISM® HBcore (9812/9822 samples negative for PRISM® HBc and 9812/9815 samples negative for PRISM® HBcore; $P = 0{\cdot}046$) and the positive predictive value was also significantly increased for PRISM® HBcore (159/169 samples positive for PRISM® HBc and 160/163 samples positive for PRISM® HBcore; $P = 0{\cdot}049$).

Detailed investigation of 188 anti-HBc reactive samples

Samples that were either PRISM® HBc or PRISM® HBcore reactive were tested in parallel with seven additional anti-HBc assays, two anti-HBs tests and three NAT assays. Arbitrary confirmation of anti-HBc reactivity was either decided on the basis of additional detection of anti-HBs, anti-HBe or HBV-DNA, or in conjunction with the frequency of reactivity in the total of nine different anti-HBc assays. As shown in Table 1, the samples were categorized into three groups in regard to the presence of additional serological HBV markers. The first group represented anti-HBc-only reactive samples (no additional serological HBV marker), the second group consisted of samples that had exclusively anti-HBs or anti-HBe as a second HBV marker, and the third group was made up of anti-HBe- and additional anti-HBs-reactive samples.

To address the theoretical possibility that the reactive anti-HBc screening result might be non-specific (false-positive) and the anti-HBs reactivity caused by an HBV vaccination with recombinant HBsAg vaccine, we interviewed 63 of the

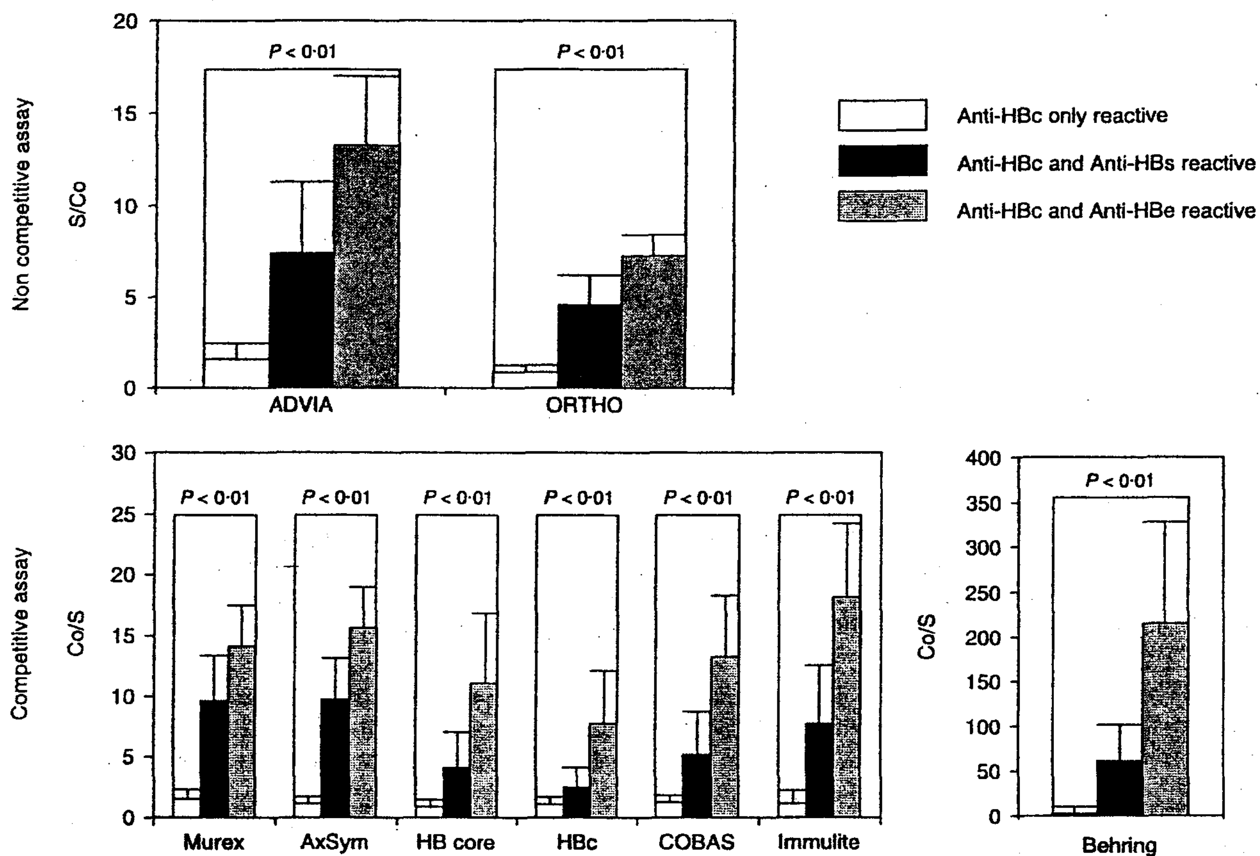

Fig. 2 Analysis of 188 antibody to hepatitis B core antigen (anti-HBc)-reactive samples: comparison between nine anti-HBc assays. Anti-HBc assays were divided into competitive (Murex, AxSYM, PRISM® HBcore, PRISM® HBc, COBAS Immulite and Behring) and non-competitive (ADVIA and Ortho) assays. Sample cut-off values (S/Co) differed significantly between anti-HBc-only reactive samples and anti-HBc + antibody to hepatitis B envelope antigen (anti-HBe)-reactive samples.

anti-HBc/anti-HBs dual-reactive donors about their vaccination history: 14 (22·2%) reported having had an HBV vaccination in the past.

All 112 anti-HBe-reactive samples were also concordantly reactive in the nine anti-HBc assays, providing strong evidence for anti-HBe as the most specific marker for a past HBV infection. Figure 2 shows S/Co values for each group according to the different anti-HBc assays. One might also consider the S/Co ratio of anti-HBc results as an indication of distinguished true and false-positive anti-HBc results: significantly lower anti-HBc signals were obtained with the anti-HBs- and/or anti-HBe-negative samples compared with anti-HBs- and/or anti-HBe-reactive samples (Fig. 2, $P < 0·01$). The student's unpaired t-test was performed for the S/Co values between these groups of samples and differed significantly ($P < 0·05$) in all nine anti-HBc tests.

Discussion

Blood donors chronically infected with HBV, but without detectable HBsAg, contribute to the residual risk of transfusion-transmitted HBV infections, which is higher for HBV than for HIV or HCV [6]. Blood donor screening with HBsAg assays and HBV MP or single-donation NAT may fail to detect chronic HBV-infected persons, because the low virus burden may remain undetected by these assays. However, a significant proportion of these HBV infections might be detected by testing for anti-HBc.

In this study we first compared two anti-HBc assays (PRISM® HBc and PRISM® HBcore) with each other. One-hundred and sixty one of 188 anti-HBc-reactive samples were confirmed by other HBV markers. This corresponds to a prevalence of 1·61% of confirmed anti-HBc-positive donors in our population. The diagnostic sensitivity was comparable between both assays, whereas the diagnostic specificity was significantly enhanced for the PRISM® HBcore. Based on these data, we suggest the use of the PRISM® HBcore for blood donor screening in order to enhance the specificity of the anti-HBc assay without compromising sensitivity.

Screening for anti-HBc is considered a potential measure to improve blood safety further. However, because of presumed non-specificity of assays, the implementation of anti-HBc as

a screening marker for blood donors is the subject of controversial discussion. A golden rule for the confirmation of anti-HBc reactivity as an indicator of a past HBV infection has not yet been established. It is likely that anti-HBc reactivity, in conjunction with both anti-HBs and anti-HBe, indicate a past HBV infection. In our study, 105/188 (55·9%) of the donors showed this. Anti-HBe as the only second marker also suggests a past HBV infection. This conclusion is supported by the fact that all anti-HBe-reactive samples, with or without anti-HBs coreactivity, were clearly anti-HBc reactive in all nine anti-HBc assays used in this study.

Under this premise, 112/188 (59·6%) anti-HBc-reactive samples were truly anti-HBc positive. At first glance, one might also consider anti-HBs as the only second marker as a confirmation for anti-HBc positivity (group 2). However, both the reactivity of some of these specimens in only a few anti-HBc assays, and the low anti-HBc S/Co values combined with very high anti-HBs titres, raised some doubts. Indeed, in interviews, 14/63 donors confirmed that past HBV vaccinations with recombinant HBsAg were presumably responsible for the high anti-HBs titres. Therefore, we cannot retrospectively differentiate between vaccinated donors who comprise non-specific anti-HBc reactivity and vaccinated donors with anti-HBc as a marker of past HBV infection. Both constellations seemed to be represented in our population. After exclusion of all anti-HBs-positive donors with a vaccination history (including most of the weak anti-HBc reactives), probably 49/63, both anti-HBs and truly anti-HBc-positive donors remain. Altogether, 27/188 (14·4%) of anti-HBc-reactive samples remain as probably non-specific anti-HBc reactive (false-positive), and 161/188 (85·6%) of anti-HBc-reactive samples appear to be truly positive.

A total of 160/161 and 159/161 of these samples were reactive with PRISM® HBcore and PRISM® HBc, respectively. This low percentage of unconfirmed anti-HBc results contrasts previous reports [12,14] and may be explained, in part, by the use of modern, more specific, assays for our blood donor screening.

In an attempt to classify the anti-HBc status by the S/Co values, the samples were classified into three groups according to the level of the S/Co values. The highest S/Co values were found for samples that were at least anti-HBc and anti-HBe reactive, followed by samples that were anti-HBc and anti-HBs reactive (Fig. 2). S/Co values for anti-HBc-only reactive samples were higher for those detected by five to nine assays than those which were reactive in only one to four tests. Therefore, the analysis of the S/Co values enabled us to define confidence intervals for each anti-HBc test in order to classify unknown samples to be potentially confirmed, indeterminate, or potentially negative. There were, however, two samples that could not be classified in this manner because they were both anti-HBc weak and anti-HBs highly reactive. The weak anti-HBc result could be a non-specific finding in donors recently vaccinated for HBV. These preliminary conclusions, however, should be challenged by studies that use a larger number of samples.

In this study, only one anti-HBc-positive donation was found to be positive for HBV DNA in one of the three NAT tests, and again only in three of four respective test runs. Clearly, HBV DNA in this plasma would have hardly been detected with state-of-the-art NATs, even when performed on a single-donation basis. The donor was a repeat donor who had previously donated 18 times, with a normal alanine aminotransferase (ALT) value obtained at each time point. HBV infection has not occurred in the recipients (six of 18 were retested by antibody screening and ultrasensitive NAT; 12 were already dead at the time of the look-back). In a previous study, Roth *et al.* [5] reported on seven HBV-positive samples among 729 HBsAg-negative, anti-HBc-positive donors. Six of these seven donors were also positive for anti-HBs. Kleinman and colleagues [13] found four HBV DNA-positive samples by testing 395 anti-HBc-positive samples with anti-HBs titres of < 100 IU/l. The risk associated with transfusion of those low-level viraemic donations is difficult to assess. Look-back examinations could eventually offer some clarification of this issue.

Based on the data presented, all anti-HBc assays tested were suitable for blood donor screening. However, we prefer a highly sensitive and specific screening test, such as PRISM® HBcore. Confirmation with a second anti-HBc test might be one strategy to identify non-specific reactivity, but we must bear in mind that many assays use the same antigens for testing. Therefore, a sample that could be confirmed with a second assay might well be a result of the non-specificity of both tests. In this study, confidence intervals for S/Co values were defined for each assay, allowing differentiation between truly anti-HBc-positive samples and anti-HBc-indeterminate samples. In very rare cases, however, anti-HBc-only reactive samples with a very weak S/Co value may represent a past HBV infection where anti-HBs and anti-HBe disappeared and anti-HBc waned to low levels. These cases might be outside the confidence intervals for the S/Co values defined in this study. Currently, there were no data, based on look-back examinations, that these donors were infectious.

In summary, ≈ 1·88% of our blood donors were initially reactive for anti-HBc, as determined by screening with PRISM® HBc and PRISM® HBcore, and, in 161/188 donors, anti-HBc reactivity was confirmed by additional HBV parameters. The diagnostic specificity and positive predictive value of PRISM® were significantly enhanced for PRISM HBcore® when compared with the PRISM® HBc. The approach to define confidence intervals for anti-HBc S/Co values might be useful for classifying an unknown sample as anti-HBc positive or anti-HBc indeterminate. The infection risk resulting from anti-HBc-positive donors is under examination in a separate study by the German Red Cross Research Foundation in which ≈ 1300 look-back analyses are being conducted. Results of

these look-back examinations are eagerly awaited and may allow us to assess the impact of donors, chronically infected with HBV, on blood safety more accurately.

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医薬品
医薬部外品　　研究報告　調査報告書
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				2006 年 9 月 4 日	該当なし	
一般的名称	人ハプトグロビン	研究報告の公表状況	肝臓 2006;47(8):384-391		公表国 日本	
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研究報告の概要	わが国の E 型肝炎の実態を明らかにする目的で、全国から総数 254 例の E 型肝炎ウイルス感染例を集め、これを解析した。 その結果、以下の知見を得た。 1)HEV は全国に浸透している。 2)感染者の多くは中高年（平均年齢約 50 歳）で、男性に多い(男女比約 3.5 対 1)。 3)我国に土着の HEV の遺伝型は 3 型と 4 型であり、後者は北海道に多い。 4)年齢と肝炎重症度との間に相関がある。 5)遺伝型 3 型に比べて、4 型は顕在化率も重症化率も高い。 6)発症時期は無季節性である。 7)感染経路は、動物由来食感染が約 30%、輸入感染が 8%、輸血感染が 2%、不明が約 60%であった。

報告企業の意見	今後の対応
日本におけるE型肝炎ウイルス感染の統計学的･疫学的･ウイルス学的特徴を求めた調査の解析結果報告である。 万一原料血漿にHEVが混入したとしても、EMCをモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意
(1) 本剤の原材料となる献血者の血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体、抗 HTLV-Ⅰ抗体陰性で、かつ ALT(GPT)値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査(NAT)を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohn の低温エタノール分画で得た画分から人ハプトグロビンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及び濾過膜処理(ナノフィルトレーション)を施しているが、投与に際しては、次の点に十分注意すること。

③

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
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研究報告の概要

○ヒトヘルペスウイルス8型の輸血伝播

背景:ヒトヘルペスウイルス8型(HHV-8)が輸血によって伝播するかどうかについては明らかにされていない。HHV-8の流行地域であるウガンダにおいてHHV-8の輸血伝播のリスクを検討した。

方法: ウガンダのKampalaで、2000年12月～2001年10月に輸血を受けた患者を登録した。HHV-8抗体について輸血前の血液検体と複数の輸血後検体(6ヶ月の期間中で最高9回行われた来院調査時に採取)を検査した。HHV-8血清反応陰性血液の受血者と比較した、HHV-8血清反応陽性血液受血者におけるセロコンバージョンの超過リスクを経時的に算出した。

結果:登録した受血者1811名のうち、輸血前のHHV-8血清反応が陰性で、必要な追跡調査を完了した患者は991名であった。991名のうち、43%はHHV-8血清反応陽性の血液の輸血を、57%はHHV-8血清反応陰性の血液の輸血を受けた。HHV-8セロコンバージョンは991名中41名に発現した。HHV-8血清反応陽性血液受血者の方が、HHV-8血清反応陰性血液受血者よりも、セロコンバージョンのリスクが有意に高く(超過リスク2.8%; $P<0.05$)、また、リスクの増加は、主に輸血3～10週後にセロコンバージョンを起こした患者に認められ(超過リスク2.7%; $P=0.005$)、このウイルスの輸血による感染に合致する結果であった。保存期間が4日を越える血液製剤と比較して、保存期間が4日以内の血液製剤では、セロコンバージョンの頻度が高かった(超過リスク4.2%; $P<0.05$)。

結論:本試験は、HHV-8が輸血によって伝播する強力なエビデンスを示す。伝染リスクは、血液の保存期間が長くなるほど低下する可能性がある。

使用上の注意記載状況・その他参考事項等

赤血球M・A・P「日赤」
照射赤血球M・A・P「日赤」
赤血球濃厚液-LR「日赤」
照射赤血球濃厚液-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
ヒトヘルペスウイルス8型が輸血によって伝播する疫学的証拠が示されたとの報告である。	今後も引き続き情報の収集に努める。