6.7% dimethyl sulfoxide, and 55 μg per mL bovine serum albumin), 0.3 μmol per L external primers (Set 1), and ultrapure water up to 30 μL final volume. External EBV PCR was performed in a conventional thermal cycler (Peltier, PTC-200, MJ Research, South San Francisco, CA) under the following conditions: 95°C for 2 minutes and 20 amplification cycles of 95°C for 30 seconds, 56°C for 40 seconds, and 72°C for 1 minute, followed by a final 6 minutes' extension at 72°C. EBV internal nested PCR was performed with internal primers (Set 2) and 0.2 μmol per L dual-labeled probe.

For external HHV-6 PCR, 1 μg of sample DNA was added to a preloaded PCR tube (EasyStart micro50, Molecular BioProducts, San Diego, CA) to which was added 5 μL of 1 percent Triton X-100, 2.5 units of *Taq* polymerase (Orbigen), 3 μL of 25 mmol per L $MgCl_2$, 0.32 μmol per L of external primers (Set 1), and ultrapure water up to 50 μL final volume. External HHV-6 PCR was performed in a conventional Peltier thermal cycler (PTC-200, MJ Research) under the following conditions: 94°C for 2 minutes and 20 amplification cycles of 94°C for 30 seconds, 60°C for 30 seconds, and 72°C for 30 seconds, followed by a final 5 minutes' extension at 72°C. HHV-6 internal nested PCR was performed with internal primers (Set 2) and both HHV-6A and HHV-6B type–specific probes (0.2 μmol/L each). For extremely high viral loads (as seen with Case 46), our experience indicates that the use of two PCR procedures, each with a single HHV-6 type–specific probe, is preferable.

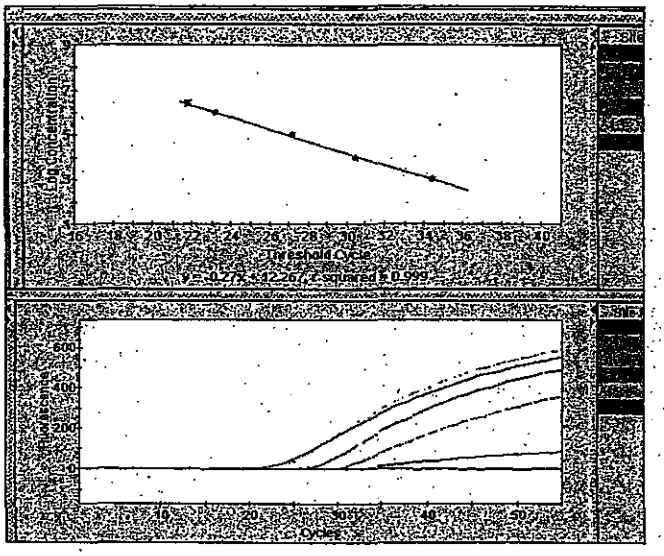

Fig. 2. Real-time PCR standard curve for HHV-6 high-viral-load samples. PCR positivity of extremely high HHV-6 viral loads (>10^6 copies/reaction) was seen only after more than 20 cycles of single-step PCR and yields a highly linear log standard curve with a range of 10^3 to 2.45×10^6 virus copies per reaction. The linearity of the assays allows for viral load quantification of samples with high viral load by one-step PCR.

Virus load calculation

Because each human diploid cell contains approximately 6.6 pg DNA, 1 μg of human genomic DNA from blood was derived from approximately 1.5×10^5 WBCs. One milliliter of whole human blood contains approximately 7×10^6 nucleated cells (WBCs). Thus, the virus copy number (geq) per milliliter of blood is equal to virus copy number per μg of DNA (as determined by the real-time PCR assay) multiplied by 47 μg of DNA per mL blood.

RESULTS

Herpesvirus DNA was commonly detected, with 94 of 100 donor blood samples positive for the presence of at least one herpesvirus (results summarized in Table 1). No herpesvirus DNA was detected in 6 cases. Four herpesviruses (HSV-1, HSV-2, VZV, HHV-8) were undetected in any sample, and CMV was detected in only a single case. In contrast, EBV (72%), HHV-7 (65%), and HHV-6 (30%) were commonly detected. All 30 cases of HHV-6 were Type B; that is, no HHV-6 Type A was identified. Median viral loads of positive samples (virus geq/mL blood) were 4,371 for HHV-6 (range 188-61,610,713), 3,196 for CMV (1 case only), 1,763 for HHV-7 (range 282-27,401), and less than 47 for EBV (range, <47-550,370). A single donor sample containing more than 80×10^6 geq of HHV-6B DNA per mL was identified. Because 1 mL of normal adult blood contains approximately 7×10^6 WBCs, this extremely high viral load translates to approximately 11 virus copies per WBC. Seventeen donor blood samples were positive for the presence of three herpesviruses (16 with EBV, HHV-6, and HHV-7; 1 with EBV, CMV, and HHV-7).

TABLE 1. Prevalence and virus load of herpesviruses in blood donors

	HSV-1	HSV-2	VZV	EBV	CMV	HHV-6	HHV-7	HHV-8
Total samples	100	100	100	100	100	100	100	100
Positive samples	0	0	0	72	1	30	65	0
Median viral load*				<47	3196	4371	1763	
Viral load range				<47-5.5×10^5		188-6.2×10^7	282-2.7×10^4	

* Expressed as virus copy number per mL of whole blood. Each PCR procedure was performed on 1 μg of whole-blood DNA, representing approximately 1.5×10^5 WBCs.

DISCUSSION

Given that acute infection with human herpesviruses may sometimes lead to serious disease, issues regarding the frequency and clinical significance of blood transfusion–mediated transmission of herpesviruses from chronically infected donors to previously uninfected or immunocompromised recipients have been raised. Although these issues have been addressed in the case of CMV, the frequency and significance of infection with the other herpesviruses have not been as thoroughly detailed.

Little information regarding the frequency and virus load of HSV-1–positive blood donors is available. HSV-1 PCR positivity was not detected in healthy adult blood donors from three independent studies.[2,5,6] With a highly sensitive real-time PCR assay, we detected no HSV-1–positive samples from a cohort of 100 adult blood donors. Our results corroborate the earlier negative reports and suggest that HSV-1 transmission by blood transfusion is likely to be a highly unusual event.

Information regarding detection of HSV-2 in healthy adult blood donors is extremely limited. In one small study,[2] HSV-2 PCR positivity was not detected in 20 adult blood donors. In the current study, we detected no HSV-2–positive samples from 100 adult blood donors. Our results corroborate the earlier negative findings and indicate that HSV-2 transmission by blood transfusion is likely to be a highly unusual event.

Relatively little information regarding the incidence of VZV DNA positivity in donor blood is available. Hoang and coworkers[2] detected only 1 VZV-positive sample (virus load 39,029 geq/mL) from a total of 20 samples, whereas de Jong and coworkers[7] detected no positive samples from a total of 20. In our study of 100 donor samples, no positive samples were identified. Thus, these data suggest that VZV transmission by donor blood is likely to be an infrequent event.

Given the very real clinical concerns with transfusion-mediated CMV transmission in immune-compromised recipients, several studies have addressed the issue of CMV positivity in donor blood. Whereas a relatively high frequency of CMV DNA positivity (19%-33%) has been described by some investigators,[5,6,8] other investigators have reported much lower rates of CMV positivity, ranging from 0 to 2.8 percent.[2,9-12] Roback and colleagues[9] identified only 2 positive samples of 1000 samples from the United States whereas Nishiwaki and coworkers[10] identified 27 positive samples of 953 samples from Japan. In the current study, we identified only 1 CMV-positive donor sample of 100 samples from the United States, a result that is consistent with the low prevalence previously reported in US blood donors.[9] In this previous report,[9] the 2 positive samples yielded an estimated 10 to 99 CMV geq per 2.5×10^5 WBCs. In an earlier article,[13] this same group reported donor blood CMV viral loads ranging from 8 to 1560 geq per 2.5×10^5 blood WBCs. Our positive sample contained 3196 CMV geq per mL of blood. Given that 1 mL of blood contains approximately 7×10^6 WBCs, our single positive case contains approximately 114 CMV genomes per 250,000 WBCs, a result remarkably similar to that previously reported.[9]

Give the role of EBV infection in the pathogenesis of posttransplant lymphoproliferative disorders, there has been a great deal of interest in determination of EBV viral load in donor blood. Although EBV infection is very common with greater than 96 percent seroprevalence in adults worldwide,[14] there is a wide range of reported rates for EBV DNA positivity of donor blood, ranging from 5 to 88 percent.[2,5,6,10,15-20] In this study, with a real-time nested PCR method, 72 percent of the donor blood samples contained EBV DNA. The sensitivity of our assay is 1 geq per µg of DNA. We suspect that the lower rates for EBV positivity reported by some investigators were obtained with less sensitive assays. Regarding EBV DNA load in blood, Hoang and colleagues[2] reported 845 geq per mL, Kimura and colleagues[15] reported 585 geq per mL (15.8 geq/µg), and Maurmann and colleagues[19] obtained a range of 3055 to 851,170 geq per mL. The current results indicate that EBV load varies over a wide range, with some donor blood samples containing more than 500,000 geq per mL, a result consistent with those previously reported by Maurmann and colleagues.[19] Qu and coworkers[20] reported the interesting observation that removal of WBCs from 14 EBV DNA–positive whole-blood units rendered all but 1 unit EBV DNA–negative. Thus, although EBV DNA positivity of whole donor blood appears to be quite common, the risk of EBV transmission from red blood cell transfusion is significantly reduced by leukoreduction.

In the current study, HHV-6 DNA was detected in 30 percent of the blood donor samples. At least six previous studies have reported rates of HHV-6 DNA positivity and virus load from adult donor blood samples. In one early study, Wilborn and colleagues[21] reported HHV-6 positivity in only 5.4 percent of donor blood (buffy coat) samples. In four later studies, HHV-6 DNA positivity was detected in 25 to 36 percent of donor blood samples.[2,22-24] Cuende and colleagues[25] made the interesting observation that using 1 µg of DNA, 40 percent of the samples were positive, a rate similar to that reported in the four previously mentioned studies, whereas using 5 µg DNA, 90 percent of the same samples were positive. Assuming that these results are not due to contamination, nonspecificity, or technical error, this finding suggests that detection of extremely low levels of virus may in some cases require amplification of larger amounts of sample DNA. It should be noted, however, that the 30 percent HHV-6 positivity rate obtained in the current study was obtained with an assay with a high sensitivity (5 geq/µg DNA).

Clearly the most surprising finding from the current study was the identification of a single blood donor

sample that contained more than 6.1×10^7 geq of HHV-6 per mL of blood. To ensure the validity of this result the assay was performed four times, with the same result obtained each time. Unusually high levels of HHV-6 DNA were first reported by Luppi and coworkers[26] in peripheral blood mononuclear cells from three patients, two with lymphoproliferative disorders and one with multiple sclerosis. The fact that two of the three patients were HHV-6–seronegative suggested that the virus infection was latent. Luppi and coworkers[26] further demonstrated that the viral genome was integrated into WBC DNA. Clark and colleagues[22] described a single healthy adult with 1.2×10^6 HHV-6 geq per μg DNA (56.4×10^6 geq/mL) in blood that persisted for at least 10 months with no evidence of active disease. These findings have been confirmed and extended by others.[27-31] Tanaka-Taya and coworkers[29] concluded that these levels of viremia translate to more than 1 virus copy per blood WBC. Ward and colleagues[31] identified six patients with a mean of 10^7 geq of HHV-6 per mL of whole blood. These six individuals, ranging in age from newborn to 58 years, presented with a variety of symptoms including neonatal convulsions, EBV-associated encephalitis, and meningitis, while one individual was a healthy adult stem cell donor. Based on demonstration of HHV-6 integration in hair follicle cells and previous reports of vertical transmission of integrated HHV-6,[28,29] Ward and colleagues[31] concluded that the virus was carried by all cells and inherited through the germline.

The current case represents to our knowledge the first report of this unusual phenomenon in a healthy adult blood donor. Because the virus appears latent and unable to provoke a humoral immune response, we believe that this phenomenon likely poses no serious risk to an immunocompetent recipient. It is most likely that in a fully immunocompetent recipient, transfused WBCs carrying latent integrated HHV-6 will be normally cleared from the recipient with no residual infected donor cells. On the other hand, the outcome in immunocompromised recipients or in those who receive stem cell transplants is less certain. In an immunodeficient patient the possibility of viral activation of latent integrated virus leading to acute virus infection cannot be absolutely excluded. Assuming that integrated virus is present in hematopoietic stem cells, it seems likely that recipients of stem cell transplants from donors that carry integrated HHV-6 will permanently carry integrated virus in their hematopoietic cells. The clinical implications of this phenomenon are not known.

HHV-7 infection, like EBV infection, is very common, with a reported seroprevalence of 96 percent.[32] In an early study, no HHV-7 DNA positivity was detected in 20 donor blood samples.[2] In a more recent study,[33] HHV-7 DNA was detected in peripheral blood mononuclear cells from 87 percent of blood donors. In the present study, HHV-7 DNA was detected in 65 percent of donor blood samples, a result similar to the previous study.[33] The earlier negative results[2] were obtained with a nonnested PCR assay coupled with gel detection of product, whereas the current results were obtained with a real time PCR assay. Because the limits of detection of the assays utilized by Hoang and colleagues[2] ranged from 222 (VZV) to 1738 (HSV-2), it is likely that the marked difference in HHV-7 DNA prevalence obtained by these studies is due to the relative insensitivity of the earlier assays.

HHV-8, the most recently discovered human herpesvirus, is also the least commonly encountered in the United States in terms of seroprevalence, with a range of less than 1 to 24 percent depending on geographic region and serologic technique.[1] In terms of HHV-8 DNA positivity of healthy adult blood donors, there is relatively little information. In two independent studies, Hudnall and colleagues[34] and Hoang and colleagues[2] identified no HHV-8 DNA positivity from an aggregate total of 40 donor whole-blood samples, and Broccolo and coworkers[35] identified no HHV-8 DNA positivity from 36 donor plasma samples. The current study extends and corroborates these negative findings by identifying no HHV-8 DNA positivity from 100 donor blood samples with a highly sensitive assay capable of detecting a single virus copy. These results indicate that HHV-8 DNA positivity of adult donor blood in the United States is likely to be a rare phenomenon.

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SUPPLEMENTARY MATERIAL

The following supplementary material is available for this article:

Appendix S1. Real-time PCR reagents (Word document).

This material is available as part of the online article from: http://www.blackwell-synergy.com/doi/abs/10.1111/j.0041-1132.2008.01685.x
(This link will take you to the article abstract.)

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番号：2

別紙様式第２－１

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 平成20年10月20日	新医薬品等の区分 該当なし	機構処理欄
一般的名称	ﾃｸﾈﾁｳﾑ人血清ｱﾙﾌﾞﾐﾝ(99mTc)		研究報告の公表状況	WHO ／ EPR ／ Disease Outbreak News,13 October 2008	公表国 ザンビア、南アフリカ	
販売名（企業名）	テクネアルブミンキット（富士フイルムＲＩファーマ株式会社）					
研究報告の概要	要約：南アフリカ共和国、ザンビア共和国におけるアレナウイルス科の新型ウイルス： 南アフリカ共和国とザンビア共和国で原因不明の疾患で死亡した３名はアレナウイルス科のウイルスによるものであることが検査の結果判明した。					使用上の注意記載状況・その他参考事項等 特になし
報告企業の意見			今後の対応			
アレナウイルス科の新ウイルスにより、３名が死亡したとの報告であり、また、初発症例はおそらくげっ歯類からの感染であるが、その後の症例は、ヒトーヒト感染による感染であること、及び新規かつ重大な感染症の研究報告と判断しております。また詳細は不明であるが、ヒト血液を原料とする血漿分画製剤とは直接関係するものではなく、現時点では、とくに措置等は必要ないと判断する。			現在、アレナウイルスの型を含めて、さらに詳細な調査が進められているところであり、今後とも追加・関連情報に注目し、情報入手次第、必要に応じて、再評価を行う予定とする。			

MedDRA/J Version(11.1)

World Health Organization

New virus from Arenaviridae family in South Africa and Zambia - Update

13 October 2008 -- The results of tests conducted at the Special Pathogens Unit, National Institute for Communicable Diseases (NICD) of the National Health Laboratory Service in Johannesburg, and at the Special Pathogens and Infectious Disease Pathology branches of the Centers for Disease Control in Atlanta, USA, provide preliminary evidence that the causative agent of the disease which has resulted in the recent deaths of 3 people from Zambia and South Africa, is a virus from the Arenaviridae family.

Analysis continues at the NICD and CDC in order to characterize this virus more fully. CDC and NICD are technical partners in the Global Outbreak Alert and Response Network (GOARN).

Meanwhile, a new case has been confirmed by PCR in South Africa. A nurse who had close contact with an earlier case has become ill, and has been admitted to hospital. Contacts have been identified and are being followed-up.

WHO and its GOARN partners continue to support the Ministries of Health of the two countries in various facets of the outbreak investigation, including laboratory diagnosis, investigations, active case finding and follow-up of contacts.

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 2008年9月1日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称	別紙のとおり	研究報告の公表状況	ProMED-mail, 20080828.2697	公表国 インド	
販売名（企業名）	別紙のとおり				

研究報告の概要

問題点：インド東部において、原因不明のウイルス感染を原因とする急性脳炎症候群により、この数週間におよそ800人の患者が発生し150人が死亡している。

インド東部のウッタルプラデシ（Uttar Pradesh）州で小児を死亡させている原因不明のウイルスは、インド保健省の専門家らにより「acute encephalitis syndrome；急性脳炎症候群」（PT；感染性脳炎）と診断された。ウッタルプラデシ州の13の地区では、数週間におよそ800人の患者が発生し150人が死亡したと報告され、その数は増加すると見られている。
血液検査で、毎年この地方で大きな流行が発生する日本脳炎が陽性となったのは5%以下である。
通常、感染流行中は、15～20%以上の検体が日本脳炎陽性となる。しかし、2008年は低率であることが混乱を生じている。
2008年、ウッタルプラデシ州27地区の4000万人がJEワクチン接種を受けたが、なぜ発熱が抑えられなかったのかに専門家らはとまどっている。中国製ワクチンSA 14-14-2には問題はなく、WHOにより日本脳炎に対する防御作用が確認されている、と保健省当局者は述べた。
日本脳炎陽性が5%以下であることから、日本脳炎と、2006年以来脳炎の原因となっている水系感染のエンテロウイルスとの混合感染について調査が行われている。

使用上の注意記載状況・その他参考事項等

記載なし

報告企業の意見	今後の対応
別紙のとおり	今後とも関連情報の収集に努め、本剤の安全性の確保を図っていきたい。

MedDRA/J ver.11.0