TABLE 4. Neopterin concentration, ALT level, and WBC count as surrogate markers for CMV DNA in plasma of newly seropositive donors

Surrogate marker	CMV DNA–positive donors	CMV DNA–negative donors
Neopterin concentration (n = 56)*	13.6 ± 9.1†	6.8 ± 2.8†
<10 nmol/L	11	24
≥10 nmol/L	17	4
Donor sensitivity (%)	61 (17/28)	
ALT level (n = 79)	43.9 ± 35.7†	23.2 ± 11.2†
≤30 or 40 U/L‡	21	37
>30 or 40 U/L‡	15	6
Donor sensitivity (%)	42 (15/36)	
WBC count (n = 78)§	5.2 ± 1.1†	6.3 ± 1.9†
<4 × 10^9/L	6	3
Between 4 and 10 × 10^9/L	30	38
>10 × 10^9/L	0	1
Donor sensitivity (%)	17 (6/36)	
Combined screening (n = 56)*		
All tests normal	8	21
Any test positive	20	7
Donor sensitivity (%)	71 (20/28)	

* Neopterin was measured in a subset of 59 donors, of whom 3 had ambiguous PCR results.
† $p = 0.001$, $p = 0.002$, and $p = 0.004$ for differences in neopterin concentrations, ALT levels, or WBC counts between DNA-positive and DNA-negative donors, respectively.
‡ Values for female and male donors, respectively.
§ WBC counts for one CMV DNA–negative donor are missing.

high prevalence of CMV DNA must be interpreted with caution owing to the low number of subjects studied, but it could be caused by the short screening interval, which would be in accordance with our results.

In a study of 420 blood donors conducted by Glock and coworkers,[18] CMV DNA in serum was detected solely in an IgG-positive donor with equivocal results for IgM, but not in 185 IgM-negative and IgG-positive donors. No information about the date of seroconversion is supplied by the authors, however.

Detection of CMV DNA in serum or plasma correlates well with presence of infectious virus in transplant recipients[21] and patients with AIDS.[23] Even if assays for detection of viable CMV with detection limits corresponding to 27 geq CMV DNA per mL have been described[20] most viral cultures or shell vial assays have relatively low sensitivities.[19,27] Therefore, detection of CMV DNA in plasma or serum is routinely used for diagnosis and monitoring of CMV infections in transplant recipients.[22] Consequently, CMV PCR has recently been suggested for screening of cord blood samples used for transplantation.[28]

The concerns of some authors[29] about lacking infectivity of CMV DNA–positive blood donations are based on a single study of three renal transplant recipients with active CMV infection showing CMV DNA in plasma to be highly fragmented.[30] But even the authors of this study conclude that, "It is beyond doubt that CMV DNA load measurements are important for prediction and diagnosis of CMV disease." Neutralizing antibodies against CMV could reduce the infectivity of seropositive CMV DNA–positive donations, but they are not expected to achieve complete neutralization as studies of convalescent sera showed neutralization capacities not exceeding 50 percent.[31]

Early studies of CMV DNA showed inconsistent results with some reports of high prevalences even in seronegative donors,[32-34] which could not be reproduced by validated PCR assays.[35] Therefore, the need for appropriate validation of PCR assays was stressed by Roback and associates.[36] Our TaqMan PCR was carefully designed to detect CMV genome with high sensitivity without cross-reaction with other organisms' DNA. Additionally, samples from all study populations were processed in arbitrary order, whereby CMV DNA was detected in connection with seroconversion, but not in plasma of 150 seronegative donors or of 598 donors who had been seropositive for at least 1 year, 148 of whom even had elevated ALT. Also ambiguous results of the TaqMan PCR were detected only in connection with seroconversion. Those results may represent CMV DNA concentrations below the 95 percent detection limit, but to ensure a conservative interpretation of the data, they had been excluded from analysis. The presence of active infection in newly seropositive donors with detection of CMV DNA in plasma is confirmed by a significantly higher percentage of donors with elevated levels of neopterin and ALT compared to seroconverted donors without detection of CMV DNA.

CMV DNA in plasma of seronegative donors during the "window period" of CMV infections was rare in our study, because CMV DNA was detected in the last seronegative sample of only 2 of 68 donors (3%). This is confirmed by Drew and colleagues[17] who studied the last seronegative sample of 192 seroconverting donors, finding only 1 DNA-positive sample (0.5%). In contrast, 2 donors in our study were CMV DNA–positive for at least 84 or 98 days, respectively. Further studies are necessary to determine the duration of CMV DNAemia in asymptomatic immunocompetent persons and to calculate the risk of window-period donations.

Even if the percentage of donors with abnormal surrogate markers like elevated ALT, elevated neopterin, or low WBC count was significantly higher in CMV DNA–positive donors compared to CMV DNA–negative donors, the sensitivity for detection of CMV DNA–positive donations with all these unspecific markers for infectious diseases was no more than 71 percent. Usually, cutoff limits for surrogate markers are set beyond the normal range to

prevent the exclusion of unnecessarily high numbers of donors.[37] This would further decrease the sensitivity of ALT and WBCs, especially, with for example only 11 percent of CMV DNA–positive donors having ALT values outside the former German limits for blood donation. This is in contrast to the results of Drew and coworkers[17] who reported both seroconverted donors with CMV DNA as being excluded from donation because of elevated ALT (92 and 117 U/mL, respectively). As reported by others[38] neopterin could be an option for blood donor screening with a sensitivity of 61 percent in our study. More effective prevention of CMV transmission could be achieved by transient exclusion of newly seroconverted donors. This was already suggested by Beneke and coworkers[39] who found a correlation between anti-CMV IgM-positive donors and TT-CMV. Lamberson and coworkers[40] confirmed that IgM-positive donors were responsible for TT-CMV in 7 of 70 seronegative neonates, whereas the only case of TT-CMV in 87 seronegative neonates after transfusion of anti-CMV IgG-positive and IgM-negative blood was explained by a false-negative result of the IgM assay.

The period of exclusion is difficult to determine on the basis of our data. The last CMV DNA–positive sample was drawn 84 days after the first seropositive donation, but additional samples were only available for 2 of 4 donors who tested CMV DNA-positive in their second seropositive sample. Thus, we cannot determine the possible duration of CMV DNAemia after seroconversion. In contrast, DNA-negative samples were available from 59 of 82 newly seropositive donors earlier than 1 year after the first seropositive sample. Furthermore, 598 donors (148 of whom even had elevated ALT), who had been seropositive for at least 1 year, tested negative for the presence of CMV DNA. This results in a 95 percent CI for the prevalence of CMV DNA–positive donors of less than 0.5 percent in this donor population. So exclusion of newly seroconverted donors for a period of 1 year after seroconversion seems to be sufficient to avoid TT-CMV.

A seasonal reactivation of latent CMV infections reported by Dumont and colleagues[16] could not be found in our donors. CMV reactivation in response to environmental allergens, which was suggested by Dumont and colleagues, could account for the differences, because a correlation between reactivation and pine tree pollen season was reported and those pollen are not a relevant allergen in Germany. A simpler explanation would be the use of systemic steroids in hay fever therapy,[41] which is very rare in Germany, but no data are available on this.

Given that 1 of every 1,000 or 10,000 peripheral blood monocytes from healthy CMV-positive individuals is supposed to be latently infected with a range of 2 to 13 geq per cell,[42,43] the number of latently infected monocytes in WBC-depleted red blood cell (RBC) units was estimated to be up to 50 and the CMV DNA concentration equals approximately 10^2 to 10^3 geq per unit.[44] Our study yielded comparable results for the mean CMV DNA concentration in connection with seroconversion ranging from 10^3 geq per unit in plasma-reduced RBC units to 10^4 geq per unit in fresh-frozen plasma or platelet (PLT) concentrates.

The seroconversion rate of 0.8 percent in our donor population corresponds well to the results of others, who found a seroconversion rate among healthy blood donors of between 0.2 and 1.2 percent.[38,45,46] In a recent meta-analysis Vamvakas[13] reports the risk of TT-CMV after transfusion of WBC-reduced components as being 2.73 percent versus 1.45 percent after transfusion of components from seronegative donors. He concludes that CMV-seronegative blood components are more efficacious in preventing TT-CMV than WBC-reduced components. Reviewing the included studies as well as other studies about TT-CMV after transfusion of WBC-reduced blood components shows great variations both in the rate of TT-CMV and in the amount of blood products transfused (Table 5).

Under the assumption that the prevalence of CMV DNA in blood products due to primary CMV infections was equal in the studies' donor populations to the minimum prevalence calculated for our institution (0.13%), the percentage of patients who had been transfused with CMV DNA–positive blood can be calculated with the previously explained equation:

$$\%\text{Patients} = 100 \times [1 - (1 - 0.0013)^{\text{number of units transfused}}].$$

With the exception of the study of Ohto and colleagues,[47] this percentage is about equal to or even higher than the percentage of patients actually developing TT-CMV. There is no correlation between the rate of TT-CMV and the proportion of patients potentially transfused with CMV DNA–positive blood. This may be due to differences between patient populations as well as donor populations, because no study provides information about the rate of CMV DNA–positive blood components or about factors influencing it such as, for example, the proportion of newly seroconverted donors relative to all seropositive donors or the length of interdonation intervals of first-time seropositive donors.

The study of Ohto and coworkers[47] differs from the other studies, because 94 percent of the studied neonates were fed with milk from their seropositive mothers. Therefore, the authors conclude that the observed CMV infections are probably unrelated to transfusions.[47]

In the retrospective study of Nichols and associates,[12] only 6 percent of the transfused units had been WBC reduced of CMV-seropositive donors, whereas 94 percent were unfiltered units of seronegative donors. A multivariate analysis identified only filtered RBCs from seropositive donors associated with an elevated risk for TT-CMV of a 32 percent relative or about 1 percent (0.2%-2%) absolute

TABLE 5. CMV infection after transfusion of WBC-depleted blood products and patients potentially transfused with CMV DNA–positive blood due to primary CMV infections*

Report (year)	Sample size	Mean number of transfused units	Percent with CMV infection	Percentage of patients potentially transfused with CMV DNA–positive blood†
Murphy et al. (1988)[48]	11	43	0	5.6
Bowden et al. (1989)[49]	17	153	0	18.4
De Graan-Hantzen et al. (1989)[50]	59	69	0	8.8
Gilbert et al. (1989)[8]	30	2	0	0.3
De Witte et al. (1990)[51]	28	52	0	6.7
Bowden et al. (1991)[52]	35	189‡	0	22.2
Eisenfeld et al. (1992)[53]	48	9	0	1.2
Van Prooijen et al. (1994)[54]	60	65	0	8.3
Bowden et al. (1995)[9]	250	102	1.2-2.4§	12.7
Narvios et al. (1998)[14]	45	141‖	2.2	17.1
Ohto et al. (1999)[47]	33	3	9.1¶	0.4
Pamphilon et al. (1999)[55]	62	Not specified	0	Not applicable
Nichols et al. (2003)[12]	807	24**	3.0	3.1
Narvios et al. (2005)[15]	72	55-77††	2.8	7.1-9.7

* This table summarizes studies included in the meta-analysis of Vamvakas[13] as well as two additional studies.[14,52]

† Estimated according to the mean number of units blood transfused in the respective study and to an assumed prevalence of CMV DNA in the whole donor population due to primary CMV infections of 0.13 percent, with the previously explained formula: %patients = 100 × $[1 - (1 - 0.0013)^{\text{number of units}}]$.

‡ 164 units of WBC-reduced PLTs and 25 unfiltered RBC units from seronegative donors.

§ Dependent on whether infections occurring between Day 0 and Day 20 are counted.

‖ Approximately 30 percent from unscreened donors and 70 percent from seronegative donors.

¶ 94 percent of neonates were fed with milk from CMV–seropositive mothers.

** 0.3 WBC reduced units from CMV-seropositive donors and 23.7 unfiltered units from seronegative donors.

†† Dependent on the number of donations pooled for random PLT concentrates.

increase per RBC unit. This is comparable with the rate of units from newly seropositive donors containing CMV DNA estimated for our donor population (0.28%). Because free CMV cannot be removed efficiently by WBC reduction, transmission of cell-free virus from newly seroconverted donors could be an explanation for at least some of the cases of TT-CMV after transfusion of WBC-reduced components.

We did not analyze whether residual WBCs in WBC-depleted blood components of newly seroconverted or latently infected donors contained CMV DNA. Nevertheless, it cannot be ruled out that the residual risk of TT-CMV with WBC-depleted blood components is mainly due to viremia in connection with seroconversion of blood donors. In this instance, transfusion of WBC-reduced blood components from seronegative donors would imply a greater risk of TT-CMV than transfusion of WBC-reduced blood from donors who have been seropositive for at least 1 year, because window-phase donations but no reactivation could be detected in our study. Therefore, there is an urgent need for further studies comparing the risk of TT-CMV after transfusion of WBC-reduced blood from seronegative donors and donors who have been seropositive for at least 1 year.

In conclusion, the detection of CMV DNA was closely related to the first detection of CMV IgG antibodies in up to 62 percent of our newly seroconverted donors, depending on the interval to the last seronegative donation. Otherwise, the probability of detection of CMV DNA in plasma of blood donors at least 1 year after seroconversion was lower than 0.5 percent. Window-phase donations occurred in only 3 percent of seroconversion cases. On the whole, the main source of blood products containing free CMV DNA were newly seroconverted donors. Thus, it is necessary to discuss whether those donors should be excluded transiently from blood donations. Furthermore, transfusion of WBC-reduced blood components from seronegative donors could imply a greater risk of TT-CMV than transfusion of WBC-reduced blood from donors who have been seropositive for at least 1 year, because window-phase donations but no reactivation could be detected in our study.

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医薬品 研究報告 調査報告書

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販売名（企業名）	タココンブ（CSL ベーリング株式会社）						

研究報告の概要

問題点（WNV の献血への混入）

本研究プロジェクトは、ドイツの Robert-Koch 研究所、Bernhard-Nocht 研究所と Paul-Ehrlich 研究所の共同で実施され、WNV がドイツにおいて国民の健康と血液供給にとって脅威となりうるかを調査した。

9976 名のドイツの健康なドナー、78 名のドイツの薬物使用者及び 198 名の米国の抗 WNV 抗体陽性患者から採取された検体を用いて WNV-RNA を NAT で測定した結果、全て陰性であった。

欧州で採取された血漿分画製剤用の原料血漿 96 件及び東アジアで採取された血漿分画製剤用の原料血漿 51 件は全て陰性であったが、米国で採取された原料血漿は 174 件中 32 件が陽性であった。

さらに本研究プロジェクトは、パスツリゼーションの WNV の不活化を実験室レベルで評価した。人血清アルブミンに安定剤を加え、WNV をスパイクした各々の溶液を 60℃で 1-10 時間加熱し、ウイルス不活化を $TCID_{50}$ で評価したところ、同実験系で測定した SFV と BVDV に似た不活化過程が確認された。

血漿分画製剤の不活化で良く用いられるパスツリゼーション処理、S/D 処理、低 pH 処理は、原料血漿のエンベロープで覆われたウイルスを不活化するのに十分であることが過去の研究で証明されている。

血漿分画製剤の製造工程にウイルス不活化工程が含まれていれば、血漿プール中に WNV が混入していても、感染リスクは無いと結論している。

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使用上の注意記載状況・その他参考事項等

報告企業の意見	今後の対応
本剤はドイツや米国の原料血漿を使用している。万一、原料血漿に WNV が混入していても、本論文のとおり本剤のパスツリゼーション処理により不活化されると考えられる。	今後とも情報収集に努める所存である。

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