

TABLE 3. CMV DNA in plasma samples*

Donor status	Number of samples	CMV DNA		Excluded
		Positive	Negative	
Seronegative donors	150	0 (0%)	150 (100%)	0 (0%)
Donors with seroconversion				
Last seronegative sample	68	2† (3%)	64‡ (94%)	2§ (3%)
First seropositive sample	82	36 (44%)	43 (52%)	3 (4%)
Second seropositive sample	71	4¶ (6%)	66** (93%)	1†† (1%)
Donors who were seropositive for at least 1 year	450	0 (0%)	450 (100%)	0 (0%)
Donors with elevated ALT‡‡ who were seropositive for at least 1 year	148	0 (0%)	148 (100%)	0 (0%)

* Data are reported as number (%).

† Drawn 68 and 98 days before the first seropositive sample (median, 83 days).

‡ Drawn 15 to 1513 days before the first seropositive sample (median, 192 days).

§ One due to ambiguous PCR results and one due to insufficient sample volume for repeated testing after a positive PCR result. Drawn 35 and 105 days before the first seropositive sample (median, 70 days).

|| One due to ambiguous PCR results and two due to insufficient sample volume for repeated testing after a positive PCR result.

¶ Drawn 3 to 84 days after the first seropositive sample (median, 12.5 days).

** Drawn 15 to 798 days after the first seropositive sample (median, 131 days). Fifty-seven of 66 samples (86%) were drawn after an interval of no more than 365 days.

†† Due to insufficient sample volume for repeated testing after a positive PCR result. Drawn 39 days after the first seropositive sample.

‡‡ 76 U/L or more.

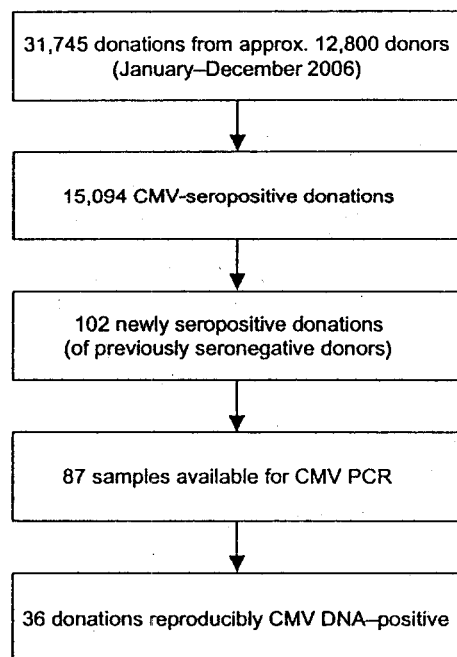


Fig. 2. Prevalence of CMV DNA in plasma of blood donors due to primary CMV-infections. Between January and December 2006, 36 out of 87 donations from newly seropositive donors contained CMV DNA (41%). 44 samples tested DNA-negative and 7 samples were excluded (5 because of ambiguous results and 2 due to insufficient sample volume for repeated testing after a positive PCR result). Assuming the prevalence of CMV DNA in the first seropositive donation to be 41 percent for all 102 seroconversion cases results in a minimum rate of CMV DNA-positive units of 42 out of 15,094 seropositive units (0.28%) or 42 out of 31,745 units (0.13%), if the CMV-serostatus is not considered.

resulting in a sensitivity of 17 percent. A combined screening with neopterin, ALT, and WBC counts would have a sensitivity of 71 percent, if all values outside the normal range are considered (Table 4).

DISCUSSION

The prevalence of CMV DNA in plasma of newly seropositive donors was 44 percent in our study. To our knowledge, the only other study examining CMV DNA in connection with seroconversion of blood donors is the study of Drew and colleagues¹⁷ who detected CMV DNA in only 2 of 192 first-time seropositive donors (1%).

One possible reason for this marked difference is the lower limit of detection of the TaqMan PCR (~13.5 geq/mL) in comparison to the PCR applied by Drew and coworkers (400 geq/mL). In the first part of our study, only 4 of 82 newly seropositive donors (5%) had CMV DNA levels of 400 geq per mL or more in their first seropositive sample. Furthermore, the interval to the last seronegative donation is given as "8 weeks to years" in the study of Drew and coworkers without any mean or medium interval given. A high proportion of donors with long interdonation intervals could have led to a lower number of CMV DNA-positive donors, as the prevalence of CMV DNA in our study was significantly higher after short interdonation intervals. Even an influence of the different target sequence used by Drew and coworkers (pol instead of gB) cannot be excluded.

Zanghellini and colleagues²⁴ reported approximately 45 seronegative adolescents, who were screened for development of CMV antibodies at monthly intervals. They detected 6 seroconversion cases and tested plasma samples from 5 seroconverted adolescents by CMV PCR finding CMV DNA in samples from 4 subjects (80%). This

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 recipients²¹ 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 described²⁰ 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 authors²⁹ 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 colleagues¹⁷ 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 coworkers¹⁷ 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 others³⁸ 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 coworkers³⁹ who found a correlation between anti-CMV IgM-positive donors and TT-CMV. Lamberson and coworkers⁴⁰ 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 colleagues¹⁶ 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 Vamvakas¹³ 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 coworkers⁴⁷ 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) ⁵¹	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) ¹⁷	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 Vamvakas¹³ 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 = $100 \times [1 - (1 - 0.0013)^{\text{number of units}}]$.

‡ 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.

ACKNOWLEDGMENTS

We gratefully acknowledge the excellent technical assistance of Sylvia Greve, Frauke Holznagel, Andrea Reimer, and Silvia Runge-Nissen. For linguistic support we are indebted to Una Doherty.

REFERENCES

1. Klemola E, Kaariainen L. Cytomegalovirus as a possible cause of a disease resembling infectious mononucleosis. *Br Med* 1965;2:1099-102.
2. De Jong MD, Galasso GJ, Gazzard B, Griffiths PD, Jabs DA, Kern ER, Spector SA. Summary of the II International Sym-

- posium on cytomegalovirus. *Antiviral Res* 1998;39:141-62.
3. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* 1998;338:1741-51.
 4. Grigoleit U, Riegler S, Einsele H, Laib SK, Jahn G, Hebart H, Brossart P, Frank F, Sinzger C. Human cytomegalovirus induces a direct inhibitory effect on antigen presentation by monocyte-derived immature dendritic cells. *Br J Haematol* 2002;119:189-98.
 5. Sinclair J, Sissons P. Latency and reactivation of human cytomegalovirus. *J Gen Virol* 2006;87:1763-79.
 6. Larsson S, Söderberg-Naucler C, Moller E. Productive cytomegalovirus (CMV) infection exclusively in CD13-positive peripheral blood mononuclear cells from CMV-infected individuals. implications for prevention of CMV transmission. *Transplantation* 1998;65:411-5.
 7. Yeager AS, Grunet FC, Haffleigh EB, Arvin AM, Bradley JS, Prober CG. Prevention of transfusion-acquired cytomegalovirus infections in newborn infants. *J Pediatr* 1981;98:281-7.
 8. Gilbert GL, Hayes K, Hudson IL, James J. Prevention of transfusion-acquired cytomegalovirus infection in infants by blood filtration to remove leucocytes. Neonatal Cytomegalovirus Infection Study Group. *Lancet* 1989;1:1228-31.
 9. Bowden RA, Slichter SJ, Sayers M, Weisdorf D, Cays M, Schoch G, Banaji M, Haake R, Welk K, Fisher L, McCullough J, Miller W. A comparison of filtered leukocyte-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplant. *Blood* 1995;86:3598-603.
 10. Bowden RA, Sayers M, Flournoy N, Newton B, Banaji M, Thomas ED, Meyers JD. Cytomegalovirus immune globulin and seronegative blood products to prevent primary cytomegalovirus infection after marrow transplantation. *N Engl J Med* 1986;314:1006-10.
 11. Miller WJ, McCullough J, Balfour HH Jr, Haake RJ, Ramsay NK, Goldman A, Bowman R, Kersey J. Prevention of cytomegalovirus infection following bone marrow transplantation: a randomized trial of blood product screening. *Bone Marrow Transplant* 1991;7:227-34.
 12. Nichols WG, Price TH, Gooley T, Corey L, Boeckh M. Transfusion-transmitted cytomegalovirus infection after receipt of leukoreduced blood products. *Blood* 2003;101:4195-200.
 13. Vamvakas EC. Is white blood cell reduction equivalent to antibody screening in preventing transmission of cytomegalovirus by transfusion? A review of the literature and meta-analysis. *Transfus Med* 2005;19:181-99.
 14. Narvios AB, Przepiorka D, Tarrand J, Chan KW, Champlin R, Lichtiger B. Transfusion support using filtered unscreened blood products for cytomegalovirus-negative allogeneic marrow transplant recipients. *Bone Marrow Transplant* 1998;22:575-7.
 15. Narvios AB, Shah H, Lichtiger B. Transfusion of leukoreduced cellular blood components from cytomegalovirus-unscreened donors in allogeneic hematopoietic transplant recipients: analysis of 72 recipients. *Bone Marrow Transplant* 2005;36:499-501.
 16. Dumont LJ, Luka J, VandenBroeke T, Whitley P, Ambruso DR, Elfath MD. The effect of leukocyte-reduction method on the amount of human cytomegalovirus in blood products: a comparison of apheresis and filtration methods. *Blood* 2001;97:3640-7.
 17. Drew WL, Tegtmeier G, Alter HJ, Laycock ME, Miner RC, Busch MP. Frequency and duration of plasma CMV viremia in seroconverting blood donors and recipients. *Transfusion* 2003;43:309-13.
 18. Glock B, Schistal E, Mayr WR. CMV DNA in blood donors with IgM and IgG CMV antibodies. *Transfusion* 2003;43:1493-4.
 19. Boeckh M, Gallez-Hawkins GM, Myerson D, Zaia JA, Bowden RA. Plasma polymerase chain reaction for cytomegalovirus DNA after allogeneic marrow transplantation: comparison with polymerase chain reaction using peripheral blood leukocytes, pp65 antigenemia, and viral culture. *Transplantation* 1997;64:108-13.
 20. Jayarama V, Marcello J, Ohagen A, Gibaja V, Lunderville D, Horrigan J, Chapman J, Lazo A. Development of models and detection methods for different forms of cytomegalovirus for the evaluation of viral inactivation agents. *Transfusion* 2006;46:1580-8.
 21. Brytting M, Xu W, Wahren B, Sundqvist VA. Cytomegalovirus DNA detection in sera from patients with active cytomegalovirus infections. *J Clin Microbiol* 1992;30:1937-41.
 22. Einsele H, Ehninger G, Hebart H, Wittkowski KM, Schuler U, Jahn G, Mackes P, Herter M, Klingebiel T, Löffler J, Wagner S, Müller CA. Polymerase chain reaction monitoring reduces the incidence of cytomegalovirus disease and the duration and side effects of antiviral therapy after bone marrow transplantation. *Blood* 1995;86:2815-20.
 23. Spector SA, Merrill R, Wolf D, Dankner WM. Detection of human cytomegalovirus in plasma of AIDS patients during acute visceral disease by DNA amplification. *J Clin Microbiol* 1992;30:2359-65.
 24. Zanghellini F, Boppa SB, Emery VC, Griffiths PD, Pass RF. Asymptomatic primary cytomegalovirus infection: virologic and immunologic features. *J Infect Dis* 1999;180:702-7.
 25. Wandinger K, Jabs W, Siekhaus A, Bubel S, Trillenber P, Wagner H, Wessel K, Kirchner H, Hennig H. Association between clinical disease activity and Epstein-Barr virus reactivation in MS. *Neurology* 2000;55:178-84.
 26. Westermann J, Thiemann F, Gerstner L, Tatzber F, Kozak I, Bertsch T, Kruger C. Evaluation of a new simple and rapid enzyme-linked immunosorbent assay kit for neopterin determination. *Clin Chem Lab Med* 2000;38:345-53.
 27. Revello MG, Zavattoni M, Sarasini A, Percivalle E, Simoncini L, Gerna G. Human cytomegalovirus in blood of immunocompetent persons during primary

- infection: prognostic implications for pregnancy. *J Infect Dis* 1998;177:1170-5.
28. Albano MS, Taylor P, Pass RF, Scaradavou A, Ciubotariu R, Carrier C, Dobrila L, Rubinstein P, Stevens CE. Umbilical cord blood transplantation and cytomegalovirus: post-transplant infection and donor screening. *Blood* 2006;108:4275-82.
29. Preiksaitis JK. Prevention of transfusion-acquired CMV infection: is there a role for NAT? *Transfusion* 2003;43:302-5.
30. Boom R, Sol CJ, Schuurman T, Van Breda A, Weel JF, Beld M, Wertheim-Van Dillen PM, De Jong MD. Human cytomegalovirus DNA in plasma and serum specimens of renal transplant recipients is highly fragmented. *J Clin Microbiol* 2002;40:4105-13.
31. Speckner A, Glykofrydes D, Ohlin M, Mach M. Antigenic domain 1 of human cytomegalovirus glycoprotein B induces a multitude of different antibodies which, when combined, results in incomplete virus neutralization. *J Gen Virol* 1999;80:2183-91.
32. Larsson S, Söderberg-Naucler C, Wang FZ, Moller E. Cytomegalovirus DNA can be detected in peripheral blood mononuclear cells from all seropositive and most seronegative healthy blood donors over time. *Transfusion* 1998;38:271-8.
33. Nitsche A, Steuer N, Schmidt CA, Landt O, Ellerbrok H, Pauli G, Siegert W. Detection of human cytomegalovirus DNA by real-time quantitative PCR. *J Clin Microbiol* 2000;38:2734-7.
34. Zhang LJ, Hanff P, Rutherford C, Churchill WH, Crumacker CS. Detection of human cytomegalovirus DNA, RNA, and antibody in normal donor blood. *J Infect Dis* 1995;171:1002-6.
35. Roback JD, Drew WL, Laycock ME, Todd D, Hillyer CD, Busch MP. CMV DNA is rarely detected in healthy blood donors using validated PCR assays. *Transfusion* 2003;43:314-21.
36. Roback JD, Hillyer CD, Drew WL, Laycock ME, Luka J, Mocarski ES, Slobedman B, Smith JW, Soderberg-Naucler C, Todd DS, Woxenius S, Busch MP. Multicenter evaluation of PCR methods for detecting CMV DNA in blood donors. *Transfusion* 2001;41:1249-57.
37. Brinkmann T, Dreier J, Diekmann J, Gotting C, Klauke R, Schumann G, Kleesiek K. Alanine aminotransferase cut-off values for blood donor screening using the new International Federation of Clinical Chemistry reference method at 37 degrees C. *Vox Sang* 2003;85:159-64.
38. Schennach H, Hessenberger G, Mayersbach P, Schönitzer D, Fuchs D. Acute cytomegalovirus infections in blood donors are indicated by increased serum neopterin concentrations. *Med Microbiol Immunol* 2002;191:115-8.
39. Beneke JS, Tegtmeier GE, Alter HJ, Luetkemeyer RB, Solomon R, Bayer WL. Relation of titers of antibodies to CMV in blood donors to the transmission of cytomegalovirus infection. *J Infect Dis* 1984;150:883-8.
40. Lamberson HV Jr, McMillian JA, Weiner LB, Williams ML, Clark DA, McMahon CA, Lentz EB, Higgins AP, Dock NL. Prevention of transfusion-associated cytomegalovirus (CMV) infection in neonates by screening blood donors for IgM to CMV. *J Infect Dis* 1988;157:820-3.
41. Ostergaard MS, Ostrem A, Soderstrom M. Hay fever and a single intramuscular injection of corticosteroid: a systematic review. *Prim Care Respir J* 2005;14:124-30.
42. Soderberg-Naucler C, Fish KN, Nelson JA. Interferon-gamma and tumor necrosis factor-alpha specifically induce formation of cytomegalovirus-permissive monocyte-derived macrophages that are refractory to the antiviral activity of these cytokines. *J Clin Invest* 1997;100:3154-63.
43. Soderberg-Naucler C, Fish KN, Nelson JA. Reactivation of latent human cytomegalovirus by allogeneic stimulation of blood cells from healthy donors. *Cell* 1997;91:119-26.
44. Roback JD, Bray RA, Hillyer CD. Longitudinal monitoring of WBC subsets in packed RBC units after filtration: implications for transfusion transmission of infections. *Transfusion* 2000;40:500-6.
45. Galea G, Urbaniak SJ. Cytomegalovirus studies on blood donors in north-east Scotland and a review of UK data. *Vox Sang* 1993;64:24-30.
46. Hecker M, Qiu D, Marquardt K, Bein G, Hackstein H. Continuous cytomegalovirus seroconversion in a large group of healthy blood donors. *Vox Sang* 2004;86:41-4.
47. Ohto H, Ujii N, Hirai K. Lack of difference in cytomegalovirus transmission via the transfusion of filtered-irradiated and nonfiltered-irradiated blood to newborn infants in an endemic area. *Transfusion* 1999;39:201-5.
48. Murphy MF, Grint PC, Hardiman AE, Lister TA, Waters AH. Use of leucocyte-poor blood components to prevent primary cytomegalovirus (CMV) infection in patients with acute leukaemia. *Br J Haematol* 1988;70:253-4.
49. Bowden RA, Sayers M, Cays M, Slichter SJ. The role of blood product filtration in the prevention of transfusion associated cytomegalovirus (CMV) infection after marrow transplant. *Transfusion* 1989;29(Suppl):57S.
50. de Graan-Hentzen YC, Gratama JW, Mudde GC, Verdonck LF, Houbiers JG, Brand A, Sebens FW, van Loon AM, The TH, Willemze R, et al. Prevention of primary cytomegalovirus infection in patients with hematologic malignancies by intensive white cell depletion of blood products. *Transfusion* 1989;29:757-60.
51. De Witte T, Schattenberg A, Van Dijk BA, Galama J, Olthuis H, Van der Meer JW, Kunst VA. Prevention of primary cytomegalovirus infection after allogeneic bone marrow transplantation by using leukocyte-poor random blood products from cytomegalovirus-unscreened blood-bank donors. *Transplantation* 1990;50:964-8.
52. Bowden RA, Slichter SJ, Sayers MH, Mori M, Cays MJ, Meyers JD. Use of leukocyte-depleted platelets and cytomegalovirus-seronegative red blood cells for preven-

- tion of primary cytomegalovirus infection after marrow transplant. *Blood* 1991;78:246-50.
53. Eisenfeld L, Silver H, McLaughlin J, Klevjer-Anderson P, Mayo D, Anderson J, Herson V, Krause P, Savidakis J, Lazar A, et al. Prevention of transfusion-associated cytomegalovirus infection in neonatal patients by the removal of white cells from blood. *Transfusion* 1992;32:205-9.
54. van Prooijen HC, Visser JJ, van Oostendorp WR, de Gast GC, Verdonck LF. Prevention of primary transfusion-associated cytomegalovirus infection in bone marrow transplant recipients by the removal of white cells from blood components with high-affinity filters. *Br J Haematol* 1994;87:144-7.
55. Pamphilon DH, Foot ABM, Adeodu A, Steward CG, Cornish JM, Marks DI, Oakhill A. Prophylaxis and prevention of CMV infection in BM allograft recipients: Leukodepleted platelets are equivalent to those from CMV-seronegative donors. *Bone Marrow Transplant* 1999;23(Suppl 1):S66. ■

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	厚生労働省処理欄
一般的名称		研究報告の公表状況	2008年2月25日	該当なし	
販売名（企業名）	タココンプ（CSL ベーリング株式会社）		West nile virus and blood product safety in Germany Journal of Medical Virology March 1, 2008, 80/3 (557-563)	公表国 米国	
研究報告の概要 137	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 TCID₅₀ 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。				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则认为られる。		今後とも情報収集に努める所存である。			

