The Risk of Transfusion Transmitted Infections – Current Aspects*

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Key Words

Blood donor · HIV · HCV · HBV · Infection

Summary

Surveillance of infectious disease markers in the blood donor population is important to recognize trends in prevalence and incidence of relevant infections. These data are essential to calculate the risk of an undetected infectious donation entering the blood supply and to evaluate the potential benefit of new tests shortening the window period, e.g. the introduction of minipool or individual donation nucleic acid amplification technique (NAT). Prevalence and incidence of transfusion-relevant infections are low in the blood donor population in Germany. A careful selection of donors combined with consistent testing of all donations guarantee the very high safety standard of blood transfusions. However, from 1999 to 2003 prevalent HIV infections increased significantly among first-time donors. Further studies are necessary to investigate the observed trend. The risk of a window period donation in the study period 2002/2003 was estimated to be 1 in 4.6 million for HIV, 1 in 4.2 million for HCV and 1 in 260,000 for HBV. Implementation of HCV NAT testing has markedly improved transfusion safety because of the clear shortening of the window period, whereas the calculated benefit of HIV-1 NAT or HBV NAT is not quite so pronounced.

Schlüsselwörter

Blutspender · HIV · HCV · HBV · Infektion

Zusammenfassung

Die Überwachung von Infektionsmarkern in der Blutspenderpopulation in Deutschland ist wichtig, um Trends im Auftreten von relevanten Infektionen zu erkennen. Darüber hinaus können diese Daten genutzt werden um, anhand von mathematischen Modellen, die Wahrscheinlichkeit einer unerkannt infektiösen Spende und den Effekt von neuen Teststrategien zu ermitteln. Prävalenz und Inzidenz von transfusionsrelevanten Infektionen in der Blutspenderpopulation in Deutschland sind niedrig. Die Kombination von sorgfältiger Spenderauswahl und stringenter Testung aller Blutspender mit sensitiven Methoden hat zu einer sehr hohen Transfusionssicherheit geführt. Von 1999 bis 2003 wurde jedoch ein signifikanter Anstieg der HIV-Infektionen unter Neuspendern beobachtet, der einer weiteren Abklärung bedarf. Das Risiko einer «Fensterphasenspende» lag 2002/2003 bei 1 zu 4,6 Millionen für HIV, 1 zu 4,2 Millionen für HCV und 1 zu 260 000 für HBV. Die Einführung der HCV-NAT hat die Transfusionssicherheit durch die erhebliche Verkürzung der diagnostischen Fensterphase merklich erhöht, wohingegen der errechnete Sicherheitsgewinn durch die Einführung von HIV-1- und HBV-NAT nicht so ausgeprägt ist.

Introduction

Preventing transfusion-associated infections presents one of the greatest challenges of transfusion medicine. Thanks to the

combination of strict selection of donors and consistent testing of each blood donation for infective pathogens using validated test procedures, the risk of transmission could be markedly reduced, especially since the most sensitive diagnostic method suitable for donor screening, nucleic acid amplification technique (NAT) testing, has become mandatory for HCV and HIV-1 in Germany in 1999 and 2004, respectively. Still, a 'zero

*Dedicated to Prof. Dr. Peter Hanfland, Bonn, on the occasion of his 65th birthday.

risk' for these infections could not be achieved, and from 1999 to 2002 3 HIV and 9 HBV transmissions have been reported to the Paul Ehrlich Institute [1]. Transfusion-associated virus transmissions can mainly be attributed to donations in the early phase of the infection (the so called window period) during which the infections cannot be detected by screening assays. Other reasons for infective donations such as process errors are considered to be negligible. In order to estimate the risk of infection associated with the transfusion, mathematic models to calculate the risk attributable to window period donations have been developed. They are based upon data on the incidence of relevant infections in the blood donor population. Pursuant to article 22 of the Transfusion Act, the Robert Koch Institute (RKI) collects and evaluates data on the prevalence and incidence of HIV, HCV, HBV and syphilis infections among blood and plasma donors in Germany [2]. These surveillance data permit an assessment of the occurrence of infections in the blood donor population and consequently aid in evaluating the safety of the donations. In Germany blood and plasma donations are collected by more than 100 separate blood donation services, namely the German Red Cross, the community and hospital blood banks, the blood donation services of the German Army, private blood donation services and industrial plasma collection sites. In 2002 and 2003, the years for which data are presented here, all blood and plasma donations services in Germany reported data to the RKI.

Materials and Methods

All blood donation services in Germany report quarterly data to the RKI on the number of donors for the different types of donations (whole blood, plasmapheresis, cytapheresis), broken down by type of donor (prospective donor/first-time donor/repeat donor), sex and age group, and average interdonation interval. Also the total numbers of those donors who have been tested confirmed positive for HIV, HCV, HBV or syphilis are reported. Additional information is collected anonymously for each infected donor, i.e. demographic data, individual donation intervals, information on the possible cause of infection, use of confidential self-exclusion, and detailed laboratory results of the viral infections. An infection was considered to be confirmed if a screening test was supplemented by an additional confirmatory assay (e.g. an immunoblot) or detection of viral genome by NAT. Donations that were NAT-only positive were considered to be confirmed positive if later seroconversion was documented or an independently drawn blood sample was also only positive using NAT. Prevalence was calculated as confirmed HIV, HCV, HBV and syphilis infections per 100,000 first time donors per year, and the rate of seroconversions was calculated per 100,000 donations of repeat donors per year. Using these data residual risk calculations were performed by means of a modified incidence rate / window period model [3, 4]: Briefly, the residual risk attributable to window period donations was calculated as

$$\text{residual risk} = (\text{window period}) \times (\text{adjusted incidence} / \text{person years at risk}) \quad (1).$$

Window periods for testing procedures were derived from published data [3, 5]. Since the tests for hepatitis B surface antigen (HBsAg) used in

Fig. 1. Prevalence of HIV, HCV, HBV and syphilis infections among first-time blood donors in Germany 1999–2003.

Fig. 2. HIV, HCV, HBV and syphilis seroconversions among blood donors in Germany 1999–2003.

Germany have a higher sensitivity than those licensed by the Food and Drug Administration (FDA) in the USA (which are commonly used for the determination of the window period) the window period for HBsAg was reduced by 9 days to 50 days [6]. Incidence was calculated as number of seroconversions for HIV, HCV and HBV reported to the RKI in the study period ('crude incidence'). Donations which would not have entered the blood supply due to an additional positive test result (elevated liver enzymes, syphilis) or a confidential self-exclusion were subtracted from the number of seroconversions to determine the 'adjusted incidence' used in the model. For HBsAg, the risk was calculated both with and without the correction factor to compensate for the transient nature of HBsAg [7]. The correction factor was determined to be 2.73 calculated from the individual interdonation intervals of the HBV-positive donations from German blood donors. Person years at risk were derived from the number of repeat whole blood donations from donors who had given at least 2 donations within the 2-year study period 2002–2003 ('regular donors') divided by the mean interdonation interval (0.52 years).

Results

A total of 6.63 million and 7.09 million donations or blood samples from prospective donors were screened in 2002 and 2003, respectively. In 2002 the prevalence of the relevant in-

Table 1. Estimated risk of an undetected infectious donation entering the blood supply 2002–2003 using a modified incidence/WP-model

Virus	Adjusted incidence / 10 ⁵ person years	Test	Window period, days	Risk (rate of undetected infectious donations)
HIV	0.78	anti-HIV 1/2 EIA	22	1:2,300,000
		minipool NAT	11	1:4,600,000
HCV	0.86	anti-HCV EIA	66	1:640,000
		minipool NAT	10	1:4,200,000
HBV	1.2	HBsAg (no correction)	50	1:710,000
		HBsAg (corrected)	50	1:260,000
		minipool NAT	45	1:790,000
		single donation NAT	34	1:1,050,000

fections among first-time donors was 7.5/100,000 donors for HIV, 97.4/100,000 donors for HCV, 164.1/100,000 donors for HBV, and 31.9/100,000 donors for syphilis. The rate of seroconversions/100,000 donations was 0.7 for HIV, 1.5 for HCV, 1.2 for HBV, and 1.8 for syphilis. In 2003 the prevalence/100,000 donors was 8.2 for HIV, 99.3 for HCV, 158.9 for HBV, and 34.4 for syphilis. The rate of seroconversions/100,000 donations in that year was 0.8 for HIV, 1.2 for HCV, 1.0 for HBV, and 1.5 for syphilis. In comparison to data from previous years [8–10], HCV, HBV and syphilis prevalence among first-time donors did not change significantly, whereas the HIV prevalence increased significantly from 3.5/100,000 donors in 1999 to 8.2/100,000 donors in 2003 (fig. 1).

In the same time period HCV seroconversions among repeat blood donors fell significantly from 2.7/100,000 to 1.2/100,000 donations whilst the rate of new HBV and syphilis infections remained relatively stable. Also among repeat blood donors an increasing trend of HIV seroconversions since 2001 from 0.5/100,000 donations to 0.8/100,000 donations in 2003 was observed (fig. 2).

Applying the residual risk model for the 2-year period of 2002/2003, the risk of an undetected window period donation could be estimated: With HIV-1 NAT, HCV NAT, and HBsAg used as screening tests the risk was calculated to be 1 in 4.6 million donations for HIV infections, 1 in 4.2 million for HCV infections, and 1 in 260,000 for HBV infections. The residual risk calculations for all three virus infections tested with different test methods such as enzyme immunoassay (EIA), minipool NAT or single-donation NAT is shown in table 1.

Discussion

Prevalence and incidence of relevant infections are low in the blood donor population in Germany. Comparing the prevalence data of hepatitis infections among blood donors with those of a representative random sample from the Health Survey of the Federal Republic of Germany of 1998 it could be seen that, in 2003, blood donors revealed an HCV prevalence which was 4 times lower than that of the random sam-

ple taken from the population as a whole [11]. For HBV infections, a direct comparison of these data is more difficult due to deviating diagnostic criteria used in the survey. However, it can still be stated that the prevalence of HBV infections in the total group of blood donors is also approximately 4 times lower than that in the examined random sample of the total population.

There are no studies on the nationwide prevalence of HIV in Germany. For comparison the data from the unlinked anonymous testing of newborns performed in Berlin and Lower Saxony from 1993 to 1997 were available. In this study the blood of more than 95% of all newborns was tested for HIV infection, reflecting HIV infections in the mothers since HIV antibodies cross the placental barrier. The so obtained data can be regarded as an approximate value for HIV prevalence among the female, sexually active population [12]. The prevalence in this group was also 2–15 times higher (depending on the residence) than in the group of blood donors. These results confirm the effectiveness of donor selection of the individual blood donor services.

Comprehensive studies on infectious disease epidemiology in blood donors in Germany have been carried out especially in view of HIV infections since 1985 [13–15]. Since 1994, data for HIV, HCV and HBV infections in blood donors have been collected and evaluated within a joint study of the Association of Transfusion Professionals (Berufsverband der Transfusionsmediziner) and the RKI [16–18]. These notifications were laid down in the law when article 22 of the Transfusion Act came into effect in 1999. Since then the RKI has the sole responsibility for the nationwide assessment of epidemiological data from blood donors. Type and scope of the notifications were defined in more detail in the regulations on the reporting system of December 2001 and in Vote 22 of the National Advisory Committee Blood (Arbeitskreis Blut) [19]. Comparing the results of data collections on infectious disease markers in Germany from 1999 to 2003 for all donor types, relatively unchanged and low prevalences of HCV, HBV and syphilis infections are revealed. In the same time period HIV prevalence increased significantly from 3.5 to 8.2 infections/100,000 first-time donors.

This rise in HIV infections has to be monitored carefully, and possible causes need to be evaluated. Donor selection criteria which aim to identify donors with risk factors for acquiring an HIV infection on the predonation questionnaire or in the predonation interview did not change recently [20]. Since 2001, a rise in newly diagnosed HIV infections in the general population was observed, but this trend was most evident among men who have sex with men who are excluded from donating according to the current German guidelines [21]. There has been concern that some donors might want to donate in order to be tested for an infectious agent such as HIV. Seeking an HIV test has been recognized in previous studies as a possible motivation to donate blood [22, 23]. If a donor is seeking a test result, he or she might not admit to risk behavior because it would prevent him or her from being accepted as blood donors. The question to which extent HIV test seeking is present in the German blood donor population and whether or not these donors pose a risk to transfusion safety will be addressed by a nationwide case control study performed by the RKI in the near future. In the UK the rate of HIV infections has also increased since 2001 [24] whilst prevalence and incidence of HIV infections among French blood donors did not change over this specific time period [25].

A significant decrease of HCV seroconversions from 2.7 to 1.2 infections per 100,000 donations could be observed from 1999 to 2003. Comparable trends were observed in studies done in the UK, France and the USA [24–27]. Since the donor selection criteria have not changed in the observation period, the reason for the decrease in HCV infections in the blood donor group remains elusive. Whether or not this trend is based on a decrease of HCV infections in the total population is unclear as data on HCV incidence are not available. New HBV and syphilis infections among repeat donors remained relatively unchanged between 1999 and 2003 but the moderate increase in HIV seroconversions from 2001 (0.5/100,000 donations) to 2003 (0.8/100,000 donations) will also need careful monitoring.

It is important both for the patient and for the treating physician to estimate the risks of infections related to the use of blood products. The residual risk mainly results from donations given in the so-called diagnostic window period. This means that an infection was not yet detected in its early stage by the test procedures but that the donor was already infectious. Since the infection probability with ‘classical’ transfusion-relevant pathogens (HIV, HCV, HBV, and *Treponema pallidum*) by blood transfusions is currently very low, direct prospective data collections on the occurrence of infections among transfusion recipients are not suitable for performing a risk assessment. The very small number of infections would require an extremely high number of blood product recipients to be examined in order to obtain a statistically significant result. For this reason, mathematical models are used for the risk assessment, allowing an estimation of the probability that an unrecognized infectious donation has occurred. The most

common model includes the incidence of the infection in the donor population as well as the time interval of the diagnostic window period into the calculation. [3, 4]. For Germany, the residual risk was estimated to be 1:1,000,000 for HIV infections, 1:100,000 for HCV infections and 1:200,000 for HBV infections in 1998 [18]. Thanks to the introduction of NAT into blood donor screening, the diagnostic window period was closed further, reducing noticeably the risk of transfusion-associated HCV infections. It is now below 1:4,000,000. The additional gain in safety by the introduction of the compulsory HIV-1 genome detection for the purpose of blood screening and the voluntary HBV genome test is not quite so marked due to the smaller reduction in the diagnostic window period as compared with HCV infections. It might, however, identify other previously undetected infectious donors. The high standard of the procedures presently used results in high costs related to each additional reduction of the already low residual risk. Therefore, the assessment of the residual risk and of the necessity of new as well as already introduced test procedures should also take into account a careful cost-benefit analysis. Studies in the USA revealed that the cost-effectiveness of NAT testing of blood donors is outside the typical range for most other healthcare interventions [28].

It is difficult to compare risk estimates for transfusion-associated infections between countries because the mathematical models used are often adapted to the specific national data characteristics. Therefore, the evaluation of prevalence and incidence of relevant infections among blood donors might be more suitable for international comparisons.

Residual risk estimations have limitations. The determining factor in the equation is the length of the window period which may vary considerably depending on the specificity and sensitivity of the test used. Since in Germany different NAT tests and different pool sizes or individual donation NAT are used for donor screening, the window period used in the model reflecting the average sensitivity of minipool NAT might be inaccurate. Moreover, in the model all window period donations were considered to be infectious although during the early ramp-up phase of viral replication, this might not be the case [29]. Recently a new model for the determination of the residual risk was published [30]. This model used novel approaches: window periods were estimated by back-extrapolation of acute viral replication dynamics leading to significantly shorter window periods compared to the previously used model. The incidence was determined by the yield of viremic, antibody-negative donations detected by minipool NAT. This new model could not be applied to the German data because the notification of a NAT-only positive donor was not yet mandatory.

Furthermore, all given risk estimates were derived from repeat whole blood donors only and might therefore underestimate the true risk. This is if first-time donors in Germany have incident HIV infections more frequently than repeat donors as it was shown for the American Red Cross donor population

[30]. The detailed analysis of NAT-only positive donations in Germany in the future will allow further conclusions. Infectious disease surveillance of blood donors constitutes an important contribution to the safety of blood products since it helps to identify new risks of infection and to re-assess known

ones. The analysis of these data helps to adjust donor selection criteria and can be helpful in decision making regarding the implementation of new test procedures. In addition, it enables the public health authorities to collect relevant epidemiological data from a defined subpopulation.

References

- Graul A, Heiden M, Gräf K, Keller-Stanislawski B: Hemovigilance in Germany – reports to the Paul-Ehrlich-Institute between January 1995 and December 2002 concerning suspected transfusion reactions. *Transfus Med Hemother* 2003;30(5): 232–238.
- Gesetz zur Regelung des Transfusionswesens (Transfusionsgesetz) vom 1. Juli 1998. Bundesgesetzblatt 1998; Teil I:1752.
- Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ: The risk of transfusion-transmitted viral infections. *N Engl J Med* 1996;334:685–690.
- Glynn SA, Kleinman SH, Wright DJ, Busch MP: International application of the incidence rate/window period model. *Transfusion* 2002;42:966–972.
- Dodd RY, Notari EP, Stramer SL: Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. *Transfusion* 2002;42:975–979.
- Biswas R, Tabor E, Hsia CC, Wright DJ, Laycock ME, Fiebig EW, Peddada L, Smith R, Schreiber GB, Epstein JS, Nemo GJ, Busch MP: Comparative sensitivity of HBV NATs and HBsAg assays for detection of acute HBV infection. *Transfusion* 2003; 43:788–798.
- Korelitz JJ, Busch MP, Kleinman SH, Williams AE, Gilcher RO, Ownby HE, Schreiber GB: A method for estimating hepatitis B virus incidence rates in volunteer blood donors. *Transfusion* 1997;37:634–640.
- Stark K, Werner E, Seeger E, Offergeld R, Altmann D, Kramer MH: Infections with HIV, HBV, and HCV among blood donors in Germany 1998 and 1999. *Infus Ther Transfus Med* 2002;29:305–307.
- Bekanntmachung des Robert Koch-Instituts: Bericht zur Meldung nach § 22 TFG für die Jahre 1999 und 2000. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 2004;47:156–164.
- Offergeld R, Ritter S, Faensen D, Hamouda O: Bericht des Robert Koch-Instituts zu den Meldungen nach § 22 Transfusionsgesetz für die Jahre 2001 und 2002. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 2004;47:1216–1229.
- Thierfelder W, Meisel H, Schreier E, Dortsch R: Die Prävalenz von Antikörpern gegen Hepatitis-A, Hepatitis-B- und Hepatitis-C-Viren in der deutschen Bevölkerung. *Gesundheitswesen* 1999;61(2): 110–114.
- Siedler A, Hamouda O, Schwartländer B: Anonymous unlinked testing as a sentinel approach: experience in Germany. *J Epidemiol Comm Health* 1998;52(suppl 1):25S–27S.
- Maurer C, Kiehl W, Altmann D: Zur HIV-Prävalenz und HIV-Inzidenz bei Blutspendern in Baden-Württemberg; in Kretschmer V, Stangel W, Eckstein R (Hrsg): *Transfusionsmedizin 1992/1993. Beitr Infusionsther.* Freiburg, Karger, 1993, vol 31, pp 5–9.
- Köhler M, Mayr WR: Nebenwirkungen der Therapie mit Blut und Blutprodukten. *Hämostaseologie* 1995;15:192–196.
- Glück D, Koerner K, Caspari G, Elbert G, Gräßmann W, Hesse R, Holzberger G, Kostuch B, Sternberger J, Vornwald A, Kubanek B: Prävalenz von HIV-Antikörpern bei Blutspendern in der Bundesrepublik Deutschland und in West-Berlin. *Dtsch Med Wochenschr* 1987;112(42):1603–1610.
- Glück D, Maurer C, Kubanek B: Infektionsmarker bei Blutspenden. *Infusionsther Transfusionsmed* 1997;24:167–170.
- Glück D, Kubanek B, Maurer C, Petersen N: Seroconversion of HIV, HCV, and HBV in blood donors in 1996 – risk of virus transmission by blood products in Germany. *Infusionsther Transfusionsmed* 1998;25:82–84.
- Glück D: Risiko der HIV-, HCV- und HBV-Übertragung durch Blutpräparate. *Infusionsther Transfusionsmed* 1999;26:335–338.
- Empfehlung zum Meldewesen nach Transfusionsgesetz § 22: Votum 22 des Arbeitskreis Blut. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 2000;43(3):249–252.
- Richtlinien zur Gewinnung von Blut und Blutbestandteilen und zur Anwendung von Blutprodukten (Hämotherapie). Deutscher Ärzte-Verlag, Köln, 2000.
- Robert Koch-Institut: Stand und Entwicklung der HIV-Epidemie in Deutschland. *Epidemiol Bull* 2005;47:437–443.
- Chiavetta JA, Ennis M, Gula CA, Baker AD, Chambers TL: Test-seeking as motivation in volunteer blood donors. *Transfus Med Rev* 2000;14(3): 205–215.
- Stigum H, Bosnes V, Magnus P, Orjasaeter EH: Risk behaviour among blood donors who give blood in order to be tested for the human immunodeficiency virus. *Vox Sang* 2001;80:24–27.
- Health Protection Agency: Surveillance of viral infections in donated blood, England and Wales: 2003. *CDR Weekly* 2004;14(44).
- Pillonel J, Le Marrec N, Girault A, David D, Laperche S: Epidemiological surveillance of blood donors and residual risk of blood borne infections in France, 2001 to 2003. *Transfus Clin Biol* 2005;12: 239–246.
- Dodd RY, Notari EP, Stramer SL: Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. *Transfusion* 2002;42:975–979.
- Zou S, Notari EP 4th, Stramer SL, Wahab F, Musavi F, Dodd RY, for the ARCNET Research Group: Patterns of age- and sex-specific prevalence of major blood-borne infections in United States blood donors, 1995 to 2002: American Red Cross blood donor study. *Transfusion* 2004;44(11): 1640–1647.
- Marshall DA, Kleinman SH, Wong JB, AuBuchon JP, Grima DT, Kulin NA, Weinstein MC: Cost effectiveness of nucleic acid test screening of volunteer blood donations for hepatitis B, hepatitis C and human immunodeficiency virus in the United States. *Vox Sang* 2004;86:28–40.
- Weusten JJAM, van Drimmelen HAJ, Lelie PN: Mathematic modelling of the risk of HBV, HCV, and HIV transmission by window-phase donations not detected by NAT. *Transfusion* 2002;42:537–548.
- Busch MP, Glynn SA, Stramer SL, Strong DM, Caglioti S, Wright DJ, Pappalardo B, Kleinman SH, for the NHLBI-REDS NAT Study Group: A new strategy for estimating risks of transfusion-transmitted viral infections based on rates of detection of recently infected donors. *Transfusion* 2005;45 (2):254–264.
- Janssen RS, Satten GA, Stramer SL, Rawal BD, O'Brien DE, Weiblen BL, Hecht FM, Jack N, Cleghorn FR, Kahn JO, Chesney MA, Busch MP: New testing strategy to detect early HIV-1 infection for use in incidence estimates and for clinical and prevention purposes. *JAMA* 1998;280(1):42–48. Erratum in *JAMA* 1999;281(20):1893.