ORIGINAL ARTICLES

Surveillance report

TRENDS IN RISK OF TRANSFUSION-TRANSMITTED VIRAL INFECTIONS (HIV, HCV, HBV) IN FRANCE BETWEEN 1992 AND 2003 AND IMPACT OF NUCLEIC ACID TESTING (NAT)

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Monitoring trends in residual risk of transfusion-transmitted viral infections is important to assess improvements in blood safety and to adapt the reduction risk policies. These trends were analysed in France over 4 periods of 3 years (1992-1994, 1995-1997, 1998-2000 and 2001-2003). The 2001-2003 estimates were compared to the results of HIV-1 and HCV NAT implemented on all blood donations in July 2001.

Due to improvements in donor recruitment and selection, continuing progress in screening assays, and preventive measures taken in the community to control infections, a significant decrease was observed in residual risks for HIV, HCV and HBV between 1992 and 2003. The residual risk is currently extremely low: for the 2001-2003 period, this risk was estimated at 1 in 3.15 million donations for HIV, at 1 in 10 million for HCV and at 1 in 640 000 for HBV. Of the 6.14 million donations screened with NAT between July 2001 and December 2003 in France, 2 HIV-positive and 3 HCV-positive donations were discarded thanks to NAT, representing a yield of 1 in 3.07 million for HIV and 1 in 2.05 million for HCV. These results show the limited benefit of NAT and suggest that its cost-effectiveness is poor.

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Key words: blood donation, France, HBV, HCV, HIV, NAT, residual risk

Introduction

Over the past twenty years, there has been a remarkable increase in the viral safety of the blood supply thanks to improvements in donor recruitment and selection and continuing progress in screening assays. Despite these measures, there is still a residual risk of transmitting viral infections during the transfusion of blood components. This residual risk is mainly linked to the 'window period', which occurs shortly after the donor is infected and before the markers for the infection can be detected.

This risk is now so low that it is impractical for prospective studies of transfusion recipients to give accurate estimates. One of the few methods currently available relies on a simple mathematical model called the incidence/window period model, and this has been used in our study [1].

We present here incidence rates and residual risks of transfusion-transmitted viral infections (human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV)) over ten overlapping periods of three years from 1992-1994 to 2001-2003. These data have been previously Published until the 1998-2000 period, in 2002 [2] and until the 2000-2002 period, in 2004 [3].

The 2001-2003 risk estimates were compared to the results of HIV-1 and HCV nucleic acid testing (NAT) implemented in France on all blood donations in July 2001.

Method

For the first seven periods, residual risk was estimated from data collected by 15 blood donation centres belonging to the Transfusion-Transmissible Agents Working Group (TTAG) of the French Blood Transfusion Society which collect more than 50% of blood donations in France, and for the three last periods, on the overall blood supply.

The residual risk of transfusion-transmitted infection per million donations was calculated for each virus as the product of the incidence rate and the length of the window period (in years) [1].

Incidence rate (IR) is the number of repeat donors who underwent seroconversion during a 3-year period divided by the number of person-years (P-Y) calculated by summing time intervals between the first and the last donation of each donor during the study period. If the previous seronegative donation was not transfused due to a positive result for another marker (e.g. elevated ALT, anti-HBc), the incident case was excluded from the analysis. Because of the transient presence of HBsAg, an adjustment was made to estimate the incidence rate for HBV according to Korelitz et al. [4].

For each virus, the length of the window period was derived from Published data: 22 days for anti-HIV, 66 days for anti-HCV and 56 days for HBsAg [5]. After the minipool NAT implementation, window periods were estimated at 12 days for HIV and 10 days for HCV [5].

In continental France, NAT screening is performed in pool format by using either Chiron Procleix TMA HIV-1/HCV in pools of 8 or Roche Cobas Ampliscreen HIV-1 and HCV in pools of 24, combined with the Organon Nuclisens extractor [6]. Because of the small amount of donations collected per day in the overseas territories and in the blood donation centre of the military, NAT is performed on single donations using the Chiron Procleix system.

The 95% confidence intervals (95% CI) of the incidence rates were obtained by the Fleiss quadratic method, which is adapted when proportions are near to zero [7]. To determine whether there was a temporal trend in residual risks, we used Armitage's chi-square test for linear trends [7]. As this test requires independent categories, trends were tested over four independent periods: 1992-1994, 1995-1997, 1998-2000 and 2001-2003. Futhermore, Fisher's exact test was used to compare residual risk with and without NAT.

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Results

Incidence rates

The incidence rates of HIV, HBV and HCV seropositivity decreased significantly over time [Table 1]. The most important decrease was for HCV: the incidence rate for the last period was 7 times lower than that of the first period. For HBV, the incidence rate for the last period was nearly 6 times lower than that of the first period. For HIV, there was a marked decrease until the 1995-1997 period, after which time the decrease was slower.

Table 1

Incidence rates (IR) of HIV, HCV and HBV in France, 1992-2003

		1992-1994	1995-1997	1998-2000	2001-2003	P
No of person-years (P-Y)	HIV	864 268	1 100 928	1 406 465	2 276 600	-
	HCV	432 501				
	HBV	908 258				
HIV	Incident cases	24	15	17	22	0.0006
	IR per 10^5 P-Y (CI 95 %)	**2.78** (1.8 - 4.2)	**1.36** (0.8 - 2.3)	**1.21** (0.7 - 2.0)	**0.97** (0.6 - 1.5)	
HCV	Incident cases	11	22	9	8	<10^{-4}
	IR per 10^5 P-Y (CI 95 %)	**2.54** (1.3 - 4.7)	**2.00** (1.3 - 3.1)	**0.64** (0.3 - 1.3)	**0.35** (0.2 - 1.3)	
HBV*	Incident cases	52	35	20	23	<10^{-4}
	IR per 10^5 P-Y (CI 95 %)	**5.78** (4.4 - 7.7)	**3.22** (2.3 - 4.5)	**1.39** (1.0 - 2.7)	**1.02** (0.7 - 1.6)	

*Data were adjusted for transient antigenaemia

HIV incidence rates have been higher than HCV incidence rates since the 1998-2000 period.

Residual risks

Trend analysis showed a significant decrease in residual risks for the three viruses [Table 2, figure], by a factor around 5 for HIV and HBV, and 45 for HCV.

Table 2

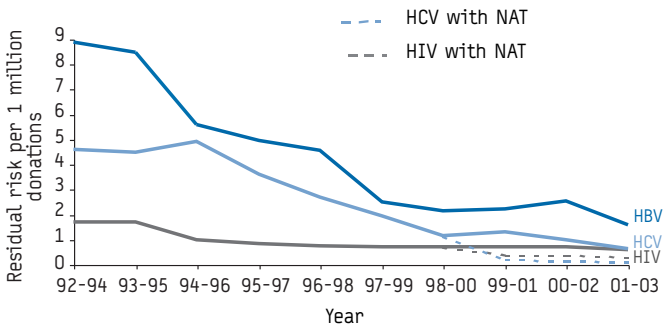
Residual risk of transfusion-transmitted viral infections in France, 1992-2003

		1992-1994	1995-1997	1998-2000	2001-2003*	P
HIV	Residual risk per 106 (CI 95 %)	**1.68** (0.3-4.4)	**0.82** (0.1-2.4)	**0.73** (0.1-2.1)	**0.32** (0.0-1.1)	0.004
HCV	Residual risk per 106 (CI 95 %)	**4.59** (1.4-12)	**3.61** (1.3-7.9)	**1.16** (0.3-3.3)	**0.10** (0.0-0.8)	<10-4
HBV*	Residual risk per 106 (CI 95 %)	**8.87** (3.0-23)	**4.94** (1.6-13)	**1.81** (0.7-7.6)	**1.57** (0.5-4.7)	<10-4

*With NAT for HIV-1 and HCV

Figure

Residual risk of transfusion-transmitted viral infections by period of time, France, 1992-2003



During the 2001-2003 period, residual risks without NAT were estimated at 1 in 1 700 000 donations for HIV, at 1 in 1 560 000 for HCV and at 1 in 640 000 for HBV. With minipool NAT, the residual risk is currently estimated at 1 in 3.15 million donations for HIV and 1 in 10 million for HCV. Nevertheless, the differences between residual risk with and without NAT were not significant either for HIV (p=0.7) or for HCV (p=0.2).

Results and impact of nucleic acid testing (NAT)

Of the 6.14 million donations collected in France between July 2001 and December 2003 in France, 90 were found to be HIV positive (0.15 per 10 000 donations) and 775 HCV positive (1.26 per 10 000 donations). Two of the 90 HIV positive and 4 of the 775 HCV positive were NAT positive and antibody negative [Table 3].

Table 3

Results of HIV and HCV screening in blood donations in France from July 2001 to December 2003

	HIV		HCV	
	N	%	N	%
NAT positive and antibody positive	87	96,7	600	77,4
NAT positive and antibody negative	2	2,2	4	0,5
NAT negative and antibody positive	1	1,1	171	22,1
Total	**90**	**100**	**775**	**100**

One of the 4 HCV-NAT positive/antibody negative donations would have been discarded anyway, because of an elevated ALT level. Finally, from July 2001 to December 2003, 2 HIV and 3 HCV positive donations were discarded thanks to NAT, that represents a yield of 1 in 3.07 million donations for HIV and 1 in 2.05 million donations for HCV.

These results are consistent with the predicted yield of NAT for both HIV and HCV [Table 4].

Table 4

Predicted versus observed yield of NAT, France, July 2001-December 2003

	Predicted* yield of NAT per 1 million donations (CI 95%)	Observed yield of NAT between July 2001 and December 2003	
		Number of donations NAT only positive	Per 1 million donations**
HIV	**0.27** (0.0 – 1.1)	2	0.33 / 10^6 donations
HCV	**0.54** (0.2 – 1.5)	3	0.49 / 10^6 donations

* obtained by difference between residual risks with and without NAT

** 6.14 million donations collected in France between July 2001 and December 2003

Discussion

A residual risk of transmitting viral infections during the transfusion of blood components persists, but it is currently extremely low. This risk can be due to factors other than those linked to the window period: technical and human errors evaluated at 0.009 for HIV and at 0.13 for HCV before NAT and at 0.11 for HBV [2], viral variants that might be not recognised by some assays, which are extremely rare and chronic virus carriers who have not developed antibodies and who are also very rare. Furthermore, NAT should detect most virus variant and testing errors, and all chronic antibody-negative carriers and so reduce or eliminate those risks for HIV and HCV. Consequently, the highest risk is that associated with the window period. The method used in this article to estimate this risk is a mathematical model that

can under- or overestimate the risk.

An underestimate can occur because the calculation does not take into account all donations but only those from donors who gave blood more than once in the three-year period. As such donors account for 83% to 85% of all donations and on the basis of an HIV incidence twofold higher in first-time donors than in repeat donors [8], the total residual risk for HIV can be estimated at 0.37 per million donations in 2001-2003, which is close to the original estimate (0.32 per million donations).

The residual risk, as estimated, depends on the length of the window periods, which were derived from the Published data. For HIV, only the infectious part of the window period was used, i.e. the part during which the donation of an infected donor is infectious, which is shorter than the entire length of the window period [5]. For HCV and HBV, the entire window period was used because the non-infectious initial period was unknown [5]. This probably overestimates the risks estimated for HCV and HBV.

In other respects, residual risks were estimated from 15 blood donation centres belonging to the TTAG for the first seven periods and on the overall French blood supply for the last three periods. Nevertheless, extrapolations have been made for these seven periods to estimate residual risks for the whole country. For each virus and each period, there were no significant differences between the residual risks obtained from the TTAG and the national extrapolations [2].

Lastly, the residual risk estimated for HBV is the most subject to discussion because the incidence of new HBV infections cannot be accurately measured and was only estimated from HBsAg incidence, which is multiplied by a correcting factor (between 2 and 3 depending on the study period [2]) to take into account the transient presence of HBsAg. In addition to HBsAg, Anti-HBc could be a relevant marker to detect all the HBV incident cases but the lack of specificity of the available anti-HBc screening tests and the absence of a confirmatory assay make it not easy to use. Furthermore, the length of the window period for HBsAg (56 days) used to estimate the HBV residual risk was obtained from assays (AUSRIA II) with a detection threshold of 0.3 ng/ml [9,10]. With the assays currently used (Prism HbsAg), the sensibility is now less than 0.1 ng/ml and then the window period has recently been estimated at 45 days [11]. These two factors show that our residual risk calculated for HBV is overestimated and needs to be re-evaluated.

After the implementation of NAT, the residual risk of transfusion-transmitted HIV infection was estimated at 1 in 3 315 000 donations for the 2001-2003 period, which represents less than one potentially infected donation per year in France. The current residual risk is more than ten times lower than it was in 1990 (1/311 000) [12]. This decrease is the consequence of the prevention policy in the community, improved donor recruitment and selection before donation and the improved sensitivity of screening tests, which have shortened the window period from an average of 45 days in 1990 [13] to 22 days in 1992 and to 12 days with the use of minipool NAT. In the United States, the risk of HIV transmission calculated with the same method was estimated with the NAT (minipool of 16 or 24) at 1 in 2 135 000 in 2000-2001 [14], which is close to the residual risk estimated in France.

The risk of HCV transmission was estimated with the NAT at 1 in 10 million donations for the 2001-2003 period, which represents one potentially infected donation every four years in France. The dramatic decrease between the early 1990s is the consequence of the prevention policy to avoid healthcare-acquired infections, and improved donor selection, but the main factor for HCV is the huge improvement in screening tests. With the first generation tests used in 1990 and 1991, the residual risk was estimated at 1 in 1 700 donations through prospective studies among recipients in the United States [15], whereas it was estimated at 1 in 276 000 donations without NAT on the 2000-2001 period, representing a decrease by a factor 160 in ten years. With the use of NAT (minipool of 16 or 24), it was estimated at 1 in 1 935 000 in the US blood donors [14], five times higher than in France. As the same length of window period was used in both countries to make these estimate, this difference is due to a higher HCV incidence rate in the US blood donors.

The risk of HBV transmission was estimated at 1 in 640 000 donations for the 2001-2003 period, which represents less than four potentially infected donations per year in France. This risk, which is the highest of the three viruses, felt by a factor of near six between the first and the last period. The decrease of the HBV incidence rate could be partly explained by the improvement in donor selection and the preventive measures taken to avoid healthcare-acquired infections but another factor is probably the use of hepatitis B vaccine. In France, 5.5% of the population was immunised with this vaccine in 1994 compared to 21.7% in 2002 [16]. In the United States, the risk of HBV transmission calculated with the same method was estimated at 1 in 205 000 in 2000-2001 [14], which is three times higher than in France.

Since 1 July 2001, it has been possible to compare the predicted yield of NAT with the observed yield in France. For both HIV and HCV, predicted and observed yield are very close, confirming the validity of the mathematical model used to estimate residual risks. In the United States, the observed NAT yield for HIV from March 1999 to April 2002 was 1 in 3.1 million [17], which is similar to the French yield (1 in 3.07 million donations) whereas for HCV it was 1 in 350 000 [17], which is six times higher than in France (1 in 2.05 million). These results show the limited benefit of NAT and suggest its poor cost-effectiveness. Jackson et al estimated the cost-effectiveness of HIV-1 and HCV minipool NAT at US$ 4.3 million in the United States [18] and it is probably even poorer in France as the NAT yield for HCV is lower than in the United States.

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ORIGINAL ARTICLES

Surveillance report

HUMAN IMMUNODEFICIENCY VIRUS, HEPATITIS C AND HEPATITIS B INFECTIONS AMONG BLOOD DONORS IN GERMANY 2000-2002: RISK OF VIRUS TRANSMISSION AND THE IMPACT OF NUCLEIC ACID AMPLIFICATION TESTING

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Blood and plasma donations in Germany are collected by several institutions, namely the German Red Cross, community and hospital-based blood services, private blood centres, commercial plasma donation sites and transfusion services of the army. All blood donation centres are required to report quarterly data on infection markers to the Robert Koch Institute, thus providing current and accurate epidemiological data. The prevalence and incidence of relevant viral infections are low in the blood donor population in Germany, with a decreasing trend for hepatitis C infections in new and repeat donors since 1997. The implementation of mandatory nucleic acid amplification technique (NAT) testing for hepatitis C virus (HCV) in 1999 has markedly improved transfusion safety. HIV-NAT became mandatory in 2004 but was done voluntarily by the majority of the blood donation services before then. The potential benefit of hepatitis B virus (HBV) minipool NAT is not as clear because chronic HBV carriers with very low virus levels might donate unidentified. The residual risk of an infectious window period donation inadvertently entering the blood supply can be estimated using a mathematic model which multiplies the incidence rate by the number of days during which an infection may be present but not detectable, i.e. the length of the window period. The risk of an undetected infection without NAT testing was estimated to be 1 in 2 770 000 for HIV, 1 in 670 000 for HCV and 1 in 230 000 for HBV in 2001/2002. This contrasts with 1 in 5 540 000 for HIV, 1 in 4 400 000 for HCV and 1 in 620 000 for HBV with minipool NAT testing. This demonstrates that NAT testing can further reduce the already very small risk of infectious donations entering the blood supply.

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Introduction

Protection of the blood supply from virus-infected donations has reached a very high level due to effective donor selection and testing with the latest techniques. The most sensitive diagnostic method suitable for donor screening, nucleic acid amplification technique (NAT) testing, has become mandatory for hepatitis C virus (HCV) and human immunodeficiency virus (HIV)-1 in Germany in 1999 and 2004, respectively. Surveillance of infectious disease markers in the blood donor population is important in recognising trends in prevalence and incidence of transfusion related infections. It also provides an opportunity to estimate the risk of an infectious donation inadvertently entering the blood supply. Mathematic models applied to surveillance data help evaluate the potential benefit of new tests, like the introduction of minipool or individual donation NAT. Epidemiological data on HIV, HCV and hepatitis B virus (HBV) infections has been systematically analysed in Germany since 1996 and reporting of detected infections has become mandatory with the enactment of the Transfusion Act in July 1999. The Robert Koch-Institute (RKI) collects and analyses nationwide data. In Germany, more than 100 individual blood donation services collect several thousand to several hundred thousand donations per year. In this report we present data collected from 2000 to 2002, including residual risk estimates which are representative for all German blood donations.

Methods

Data were obtained from the RKI nationwide blood donation infection surveillance and included more than 99% of all donations in 2000 and 100% of all donations in 2001 and 2002. Blood and plasma donation centres reported aggregated data on number and