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

J Pillonel, S Laperche et l’Etablissement Français du sang

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.

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. Furthermore, 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

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>HIV</td>
<td>866,268</td>
<td>1,100,928</td>
<td>1,406,465</td>
<td>2,276,600</td>
<td>-</td>
</tr>
<tr>
<td>HBV</td>
<td>908,258</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>432,501</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>24</td>
<td>15</td>
<td>17</td>
<td>22</td>
<td>-</td>
</tr>
<tr>
<td>HCV</td>
<td>11</td>
<td>22</td>
<td>9</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>HBV</td>
<td>87</td>
<td>96,7</td>
<td>600</td>
<td>77,4</td>
<td>-</td>
</tr>
</tbody>
</table>

With NAT for HIV-1 and HCV

*Data were adjusted for transient antigenemia

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

<table>
<thead>
<tr>
<th>Period</th>
<th>HIV</th>
<th>HCV</th>
<th>HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992-1994</td>
<td>1.68</td>
<td>0.82</td>
<td>4.59</td>
</tr>
<tr>
<td>1995-1997</td>
<td>0.82</td>
<td>4.59</td>
<td></td>
</tr>
<tr>
<td>1998-2000</td>
<td>0.73</td>
<td>3.61</td>
<td></td>
</tr>
<tr>
<td>2001-2003</td>
<td>0.32</td>
<td>1.16</td>
<td></td>
</tr>
</tbody>
</table>

*With NAT for HIV-1 and HCV

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, 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

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAT positive and antibody positive</td>
<td>8%</td>
<td>96.7</td>
</tr>
<tr>
<td>NAT positive and antibody negative</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>NAT negative and antibody positive</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted* yield of NAT per 1 million donations [CI 95%]</td>
<td>0.27 (0.0 - 1.1)</td>
<td>0.54 (0.2 - 1.5)</td>
</tr>
<tr>
<td>Observed yield of NAT between July 2001 and December 2003</td>
<td>Number of donations</td>
<td>Per 1 million donations**</td>
</tr>
<tr>
<td>HIV</td>
<td>2</td>
<td>0.33 / 10^10 donations</td>
</tr>
<tr>
<td>HCV</td>
<td>3</td>
<td>0.49 / 10^9 donations</td>
</tr>
</tbody>
</table>

* 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...
an underestimate 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 sensitivity 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 7 700 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.

Acknowledgements


References

4. Piloux X. Tinard, P. Volle, C. Waller.

Viral safety of blood
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Department for Infectious Disease Epidemiology, Robert Koch Institute.

blood supply.

reduce the already very small risk of infectious donations entering the minipool NAT testing. This demonstrates that NAT testing can further

1 in 230,000 for HBV in 2001/2002. This contrasts with 1 in 5,540 was estimated to be 1 in 2,770,000 for HIV, 1 in 670,000 for HCV and

window period. The risk of an undetected infection without NAT testing

an infection may be present but not detectable, i.e. the length of the

which multiplies the incidence rate by the number of days during which

entering the blood supply can be estimated using a mathematic model

chronic HBV carriers with very low virus levels might donate unidentified.

hepatitis C virus (HCV) in 1999 has markedly improved transfusion infections in new and repeat donors since 1997. The implementation

of mandatory nucleic acid amplification technique (NAT) testing for

infections in new and repeat donors since 1997. The implementation

required to report quarterly data on infection markers to the Robert Koch

based blood services, private blood centres, commercial plasma donation institutions, namely the German Red Cross, community and hospital-

German blood donations.

to 2002, including residual risk estimates which are representative for all

donations per year. In this report we present data collected from 2000

analyses nationwide data. In Germany, more than 100 individual blood

Transfusion Act in July 1999. The Robert Koch-Institute (RKI) collects and

Epidemiological data on HIV, HCV and hepatitis B virus (HBV) infections

mandatory for hepatitis C virus (HCV) and human immunodeficiency

screening, nucleic acid amplification technique (NAT) testing, has become

the late 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