Estimated risk of transfusion-transmitted viral infections in Spain

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BACKGROUND: Estimates of the risk of transfusion-transmitted viral infections are essential for monitoring the safety of the blood supply. The aim of the present study was to estimate the residual risk of blood-borne viral infections in Spain.

STUDY DESIGN AND METHODS: Incidence rates of seroconversion for HIV, HBV, and HCV were calculated among 673,018 persons who donated blood more than once (repeat donors), from 1997 through 1999 at 22 blood donation centers (for a total of 2,464,964 allogeneic blood donations and 1,052,752 person-years).

RESULTS: Incidence rates per 100,000 person-years and their 95-percent CIs were as follows: for HBV, 8.36 (5.24-12.62); for HIV, 3.23 (2.24-4.52); and for HCV, 3.70 (2.63-5.07). After adjusting incidence rates for the estimated duration of the infectious window period for each virus, the residual risk per unit transfused was estimated at 1 in 513,000 for HIV, 1 in 74,000 for HBV, and 1 in 149,000 for HCV. The introduction of new screening test based on NAT would have reduced these risks by 27 to 50 percent for HIV, by 42 percent for HBV, and by 62 to 65 percent for HCV.

CONCLUSION: The residual risks of transmission of HIV, HBV, and HCV in Spain are similar to those reported in other countries and should be further reduced in the future.

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Despite the continuous efforts made during the past 20 years to prevent the transmission of viral infections by blood and blood components with the use of more sensitive screening tests and rigorous selection of donors, there still exists a transmission risk (residual risk)[1,2] for these infections in the transfusion setting.

The transfusion-transmitted agents that have required the most attention are HBV, HCV, and HIV. The vast majority of residual cases of infection with these viruses occur through donations made during the serologic window period. Other potential causes include chronic seronegative infection, mutations in epitopes rendering diagnostic tests useless, and technical errors during laboratory processing.[2,3] The continuous decrease in the number of cases of transmission of these infections by blood implies a proportional increase in the difficulty of calculating the residual risk.[3,4] To overcome this difficulty, in recent years various models have been developed to obviate the need for huge prospective studies. One of the most accepted such models is that of the Retrovirus Epidemiology Donors Study,[1,2,5-7] which we have followed to estimate the residual risk of infection with these viruses in Spain.

MATERIALS AND METHODS

Electronic data files were generated at 22 blood donation centers in Spain (see Appendix 1), which included information on donor identification number; dates, number, and types of donations; and results of serologic screening and confirmatory tests. Data were collected at each center between January 1, 1997, and December 31, 1999, and submitted to the coordinating center (Blood Transfusion Center of Granada-Almería, Granada, Spain). All donations made during the study period were tested for viral infections, as required by Spanish Ministry of Health. The tests performed included those for HBsAg, anti-HIV type 1 and anti-HIV-2, and anti-HCV, as well as a test for syphilis. HBsAg, anti-HIV-1 and anti-HIV-2, and anti-HCV were performed by third-generation ELISAs or chemiluminescence immunoassays. Data from these files were integrated in a central database and used to calcu-

late the number of donors who made at least two allogeneic donations during that period, their total number of donations, the number of person-years at risk (calculated by totaling the intervals between the first and the last donation for all repeat donors), and the number of donors seroconverting for each virus. The dates and results of screening and confirmatory tests (Western blot for HIV-1/HIV-2 antibodies, RIBA-3 [Chiron Corporation, Emeryville, CA] or Matrix HCV 2.0 [Abbott GmbH Diagnostics, Wiesbaden, Germany] for anti-HCV, and specific neutralization test for HBsAg) in all donations, as well as any available follow-up information, were reviewed in all cases of seroconversion to exclude false-positive results or incorrect test interpretation. A donor was considered to have seroconverted for one agent if she or he had made an initial donation that was not reactive and subsequently made a donation that was confirmed to be positive for that agent.

The residual risk of transfusion-transmitted infections was estimated according to the model of Schreiber et al.[5] except that crude, rather than adjusted, incidence rates of seroconversion were used. Crude incidence rates of seroconversion for each virus, and their 95-percent CIs, were calculated as the number of seroconverting donors divided by the total number of person-years at risk and expressed as cases per 100,000 person-years.

The crude incidence rate of seroconversion for HBsAg was used to calculate a more accurate estimation of HBV seroconversion by taking into account the different patterns of antigenemia after primary infection: transient antigenemia of variable duration (which occurs in 70% of the cases), primary antibody response without detectable antigenemia (which occurs in 25% of the cases), and persistent antigenemia (which occurs in the 5% of infected adults who become chronic HBV carriers).[5,7] Since the HBsAg test may detect all chronic carriers, none of those with a primary antibody response, and some of those with transient antigenemia, the probability of detecting a recent HBV infection with this test would be 0.05 $\times$ 100 percent + 0.25 $\times$ 0 percent + 0.70 $\times$ T. The value of T; that is, the proportion of donors with transient antigenemia that would have been identified with an HBsAg test, calculated by dividing the mean duration of antigenemia in recently infected donors (63 days) by the median interval between donations of the 22 HBsAg-seroconverting donors in our study (220 days), was 29 percent. Hence, the overall probability of detecting an incident HBV infection in our study would be 0.05 $\times$ 100 percent + 0.25 $\times$ 0 percent + 0.70 $\times$ 29 percent, or 25 percent. The incidence of HBV seroconversion was calculated by multiplying the crude incidence of HBsAg seroconversion by 1/0.25, or 4.

The residual risk of infection and its 95-percent CI were calculated for each virus as the product of the crude incidence rate of seroconversion by the accepted duration of the serologic window period for the agent expressed as a fraction of a year.[5,8] Since all participating centers used a third-generation screening test for anti-HCV, the window period for HCV infection was considered to be 66 days (95% CI, 38-94 days).[6,8,9]

These risks indicate the probability that a recently infected donor gave blood during the seronegative window period and was not detected with the available screening test. The yield of new screening tests was calculated by multiplying the incidence rate of seroconversion by the decrease in the window period (expressed as fraction of year). The annual yield of an additional test was obtained by multiplying this last quantity by the number of units screened annually.[2]

RESULTS

From January 1, 1997, through December 31, 1999, in the 22 participant centers, corresponding to 12 different regions, a total of 1,222,583 donors made 3,014,530 allogeneic donations of whole blood or blood components obtained by apheresis. This number represents 70.6 percent of the total donations of blood and blood components made in Spain during that period (4,269,108). The number of repeat donors who made two or more donations during this interval was 673,018, and they contributed a total of 2,464,964 donations (82% of the total in this period and these regions). The number of person-years at risk (the sum of the intervals between donations) was used as the denominator to calculate crude incidence rates; the number of person-years at risk was 1,052,752 person-years. Seroconversions were assumed to occur at the midpoint between a donor's last seronegative donation and the first seropositive donation.[2,5]

Table 1 shows the number of seroconversions and the calculated crude incidence rates for each infection. In Table 2, the crude incidence rate for each virus is multiplied by the duration of the serologic window period to

TABLE 1. Rate of incidence of infection by HBV, HIV, and HCV among repeat blood donors during the period from 1997 through 1999

Virus	Number of seroconversions	Number of person-years at risk	Crude incidence rate per 100,000 donor year (95% CI)
HBV			
HBsAg	22	1,052,744	2.09 (1.31-3.16)
Total HBV*			8.36 (5.24-12.62)
HIV	34	1,052,741	3.23 (2.24-4.52)
HCV	39	1,052,734	3.70 (2.63-5.07)

* Because only 25 percent of HBV infections were considered likely to be identified by the screening test (see text), the incidence rate of seroconversion for HBsAg was multiplied by 1/0.25 to obtain the incidence rate of HBV infection.

TABLE 2. Residual risk of transmission of viral infections by transfusion of seronegative units donated during the serologic window period

Virus	Length of window period (days)		Residual risk per million donations	
	Estimated	Range	Estimated	Range
HBV				
HBsAg	59*	37-87	3.38	1.33-7.53
Total HBV			13.51†	5.31-30.08†
HIV	22*	6-38	1.95	0.37-4.71
HCV	66‡	38-94	6.69	2.74-13.06

* Data were taken from Schreiber et al.[5]
† Data were adjusted for transient antigenemia by multiplying the residual risk of HBsAg seroconversion and its range by 4.0, on the assumption that only 25 percent of HBV infections were detected with the HBsAg test.
‡ Data were taken from Couroucé et al.[6]

calculate the residual risk of infection. In fact, the residual risk of transmission of HBV in the different transfusion centers varied between 0 and 51 per million donations and in the different regions between 0 and 37 per million donations, with a mean of 14 per million donations (1 case/74,000 units transfused). Similarly, the residual risk of transmission of HIV in the different centers varied between 0 and 7 per million donations, and between 0 and 4 per million donations in the different regions, with a mean of 2 cases per million donations (1 case/513,000 units transfused). Finally, for HCV the residual risk varied between 0 and 19 per million donations in different centers and between 0 and 14 cases per million donations in the different regions, with a mean of 7 cases per million donations (1 case/149,000 units transfused).

Table 3 shows the estimated yield of new screening tests as the number of infectious seronegative units detected per 1,420,000 units (the number of units screened annually in Spain during the study period), as well as the effect of their implementation on the estimates of residual risks. Viral antigen tests and NAT might have detected six HCV-infected seronegative donations but no more than one HIV infection per year. NAT for HBV might have detected eight infected units per year.

DISCUSSION

In the present study, we made estimates based on crude incidence rates without adjusting for the number of repeat donors whose prior donation met all screening criteria required for transfusion, as in previous studies. In the only center in which data to calculate adjusted incidence rate was available, both values were similar for HBV and HIV, but not for HCV (crude rates for HBV, HIV, and HCV, 6.37, 5.66, and 5.66/100,000 person-years, respectively; adjusted rates for HBV, HIV, and HCV, 6.46, 5.74, and 4.30/100,000 person-years, respectively). These data correspond to the period from 1995 through 1997; for the HCV incidence rate, the difference was due to the elimination of two incident cases because the donation before seroconversion had an elevated ALT level in one case and a false-positive result for anti-HCV in the other case.

The incidence rates varied remarkably between different centers for the three viral infections. One blood center, with 12 of 39 HCV incident cases, shows an incidence rate for HCV about 10.50 per 100,000 person-years (mean of all blood centers, 3.70) and remarkable differences were also found for HIV incidence (about 11/100,000 person-years with 3.23 as mean for all blood centers). A study made following a different method also found differences between distinct regions in the US.[10]

When the results of present study were compared with the results obtained by other previous studies by use of the same method,[5,6] we found comparable values. The residual risk mean values (95% CIs) for HIV are 2.03 (0.36-4.95) in the US,[5] 1.7 (0.3-4.4) in France,[6] and 1.95 (0.37-4.71) in Spain. For HBV and HCV, the residual risk mean values are slightly different than for HIV among the three countries, despite the fact that there is overlap in their CIs. However, it must be remarked that the tests used and, so, the estimated window period, as well as the years in which the studies were conducted, are not the same.

The introduction of new screening tests would further reduce the residual risk of transmitting viral infections by transfusion. The effect would be limited for HIV because the risk of transmission of this agent is already

TABLE 3. Projected yield of the utilization of new screening tests to reduce the risk of transmission of infections by transfusion

Virus tests	Estimated reduction in window period (days)	Residual risk with additional tests		Projected yield (infected units detected/ 1,420,000 units)
		Projected (/million donations)	Reduction (%)	
HBV				
DNA PCR	25*	7.79	42.4	8
HIV				
p24 test	6*	1.42	27.3	1
DNA PCR	6*	1.42	27.3	1
RNA PCR	11*	0.97	50.0	1-2
HCV				
Core antigen	41†	2.53	62.12	6
RNA PCR	43‡	2.33	65.15	6

* Data were obtained from Schreiber et al.[5]
† Data were obtained from Couroucé et al.[11]
‡ Data were obtained from Schreiber et al.[5] and Couroucé et al.[11]

very small. Even the most sensitive NAT for HIV infection (RT-PCR for HIV RNA) would identify no more than one infectious donation among 1,420,000 units collected annually in Spain. Based on data from Couroucé et al.,[11] we considered that HCV core antigen testing would shorten the seronegative window period by 41 days, a figure similar to the 43-day reduction achieved by HCV RNA testing over third-generation antibody tests. Either test would identify 6 infectious seronegative donations every year and reduce the current residual risk by more than 60 percent. This reduction could be even higher since recent data suggest that with NAT the window period for HCV infection is shortened to 13 days[12] rather than to the 23-day figure used in our study.[8]

Between May 1999 and January 2001, a total of 803,249 donations were tested for HCV RNA (Amplicscreen HCV v2.0, Roche Diagnostics, Branchburg, NJ), by use of pools of 22 or 44 units, in five Spanish blood centers. Two anti-HCV-negative and HCV-RNA-positive units were found.[13] Both of them were made by repeat donors (A. Eiras, MD, PhD, written communication, October 2001; D. Planelles, PhD, written communication, October 2001). According to previous data concerning these five centers, the crude incidence rate for HCV was 4.9 per 10^5 donations and 83 percent of donations were made by repeat donors (666,697 units). So, the expected number of seronegative but infected units should be $(4.9/10^5) \times (43/365) \times 666{,}697 = 3.8$; that is, 4 units instead the 2 found by NAT. The number of units screened by NAT in Spain is not enough to make conclusions about the consistency between the projections derived from estimates from the model based on incidence and window-period values and the yield of minipool NAT screening.

As previously reported,[5] incidence rates and residual risks derived from the model used have several limitations. One of these limitations is that the model using incidence and window period values cannot estimate the first-time donors' contribution to the risk of the blood supply. It has been pointed out[2] that an incidence rate for first-time donors by definition is not measurable. Previous studies[5] have concluded that an adjustment to include the risk derived from first-time donors would not alter the results significantly, as first-time donors accounted only for 20 percent of the donations. In Spain, during the period of this study, such proportion was 18 percent in the participating centers.

The incidence and window period model provides a useful tool to estimate the residual risks of transfusion-transmitted viral infections, despite the limitations derived from noninclusion of first-time donors and the difficulty in calculating the incidence rate of seroconversion for HBV. Following this model, the risks in Spain are low and comparable to those obtained in other developed countries. With the routine implementation of NAT in our country, these risks will be even lower.

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