RESIDUAL RISK OF TRANSFUSION-TRANSMITTED VIRAL INFECTIONS IN SPAIN, 1997-2002, AND IMPACT OF NUCLEIC ACID TESTING

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Estimates of the risk of bloodborne viral infections are essential for monitoring the safety of the blood supply and the impact of new screening tests. Incidence rates of seroconversion and the residual risk for HBV, HIV and HCV were calculated among Spanish repeat donors between 1997 and 1999 at 22 blood donation centres, and at 7 centres between 2000 and 2002. The residual risk per million donations was estimated to be 18.67 for HBV, 2.49 for HIV and 10.96 for HCV (between 1997 and 1999). For the 2000-2002 period, the residual risk per million donations was estimated to be 9.78 for HBV, 2.48 for HIV and 3.94 for HCV. Between 1999 and 2003, about 3.4 million donations were tested by NAT, mainly in pools of 44 donations, in 12 of the 22 Spanish blood donation centres participating in the study. Eight anti-HCV negative and HCV-RNA positive donations were found, which represent an approximate yield of 1/420 000, versus a projected yield of 1/240 000 obtained from 1995-1997 data. The residual risks of transfusion-transmitted viral infections in Spain were low, and with the implementation of NAT these risks are even lower.

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Introduction

The aims of this study are:

1. To calculate the incidence rates of hepatitis B virus (HBV), human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections in blood donors.
2. To estimate the risk of transfusion-transmitted HBV, HIV and HCV.
3. To compare changes over time in HBV, HIV and HCV infection rates in the blood donor population.
4. To estimate the national impact of nucleic acid testing (NAT) implementation in blood screening.

Methods

Twenty two blood donation centres in Spain generated electronic data files with information including donor identification numbers; dates, number and types of donations; and results of serological screening and confirmatory tests. Data were collected at each centre between 1 January 1997, and 31 December 1999. In order to compare changes over time in blood donor infection rates, 7 of these 22 centres generated electronic data files with the same information, collecting the data between 1 January 2000, and 31 December 2002. These data were integrated into a central database and used to calculate 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 totalling the intervals between the first and the last donation for all repeat donors) and the number of donors seroconverting for each virus [1]. Donors were considered to have seroconverted for one agent if they had made an initial donation that was not reactive and subsequently made a donation that was confirmed to be positive for that agent. The following supplementary tests were used: specific neutralisation test for hepatitis B surface antigen (HBsAg); western blot for HIV-1/HIV-2 antibodies; RIBA-3 (Chiron Corporation, Emeryville, CA, USA) or Matrix HCV 2.0 (Abbott GmbH Diagnostics, Wiesbaden, Germany) for anti-HCV. In order to exclude false-positive results or incorrect test interpretation, the dates and results of screening and confirmatory tests, as well as any available follow-up information, were revised in all cases of seroconversion.

Incidence rates of seroconversion for each virus, and their 95% confidence intervals (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 residual risk of transfusion-transmitted infections was estimated according to the model of Schreiber *et al* [2]. The incidence rate of seroconversion for HBsAg was multiplied by 1/0.25 to correct for the transient nature of HBsAg following HBV infection and so give a more accurate estimation of HBV incidence infection in repeat donors, according to the model referred to above [2,3].

The residual risk of infection was calculated for each virus as the product of the incidence rate of seroconversion by the accepted duration of the serologic window period for the agent, expressed as a fraction of a year [2-5]. A range for each residual risk was established by multiplying the limits of the 95% CI on the incidence by the limits of the length of the window period.

In July 1999, 12 of the 22 participant centres began blood screening for HCV by NAT, either by polymerase chain reaction (PCR) in pools, or by transcription-mediated amplification (TMA) in single samples. The pool size varied between 8 and 48 units, according to the method, the program for pooling, and the blood supply in every centre.

The yield of new screening tests was calculated by multiplying the incidence rate of seroconversion by the decrease in the window period (expressed as a fraction of a year). The annual yield of an additional test was obtained by multiplying this last quantity by the number of units screened annually [6].

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Results

Between 1 January 1997, and 31 December 1999, a total of 1 222 583 donors made 3 014 530 allogeneic donations of whole blood or blood components obtained by apheresis in the 22 participant blood donation centres. This quantity represents 70.6% 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 period was 673 018, and they contributed a total of 2 464 964 units (82% of the total in this period and in these regions). The number of person-years at risk (the sum of intervals between donations), used as the denominator to calculate crude incidence rates, was 1 052 752 person-years [1]. Seroconversions were assumed to occur at the midpoint between a donor's last seronegative donation and the first seropositive donation [2,6].

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

Table 1

Incidence rates of HBV, HIV and HCV in repeat blood donors in 22 blood donation centres in Spain, 1997-1999

Virus	Number of seroconversions	Number of donor-years at risk	Incidence rate per 100 000 donor-years (CI 95%)
HBV			
HBsAg	22	1 052 744	2.09 (1.31-3.16)
Total HBV*			8.36 (6.76-10.36)
HIV	34	1 052 741	3.23 (2.24-4.52)
HCV	39	1 052 734	3.70 (2.63-5.07)

* Incidence rate of seroconversion for HBsAg was multiplied by 4 to obtain the incidence rate of HBV infection, assuming that only 25% of HBV infections are identified with the screening test [1,2]

Table 2

Residual risk of viral infection transmission by transfusion of seronegative units donated during the serological window period, Spain, 1997-1999

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 taken from Schreiber et al [2]

† Data adjusted for transient antigeanemia 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 taken from Couroucé et al [4]

From 1 January 2000 to 31 December 2002 in 7 of the 22 participant blood donation centres, a total of 509 380 donors made 1 221 185 allogeneic donations. The number of repeat donors who made two or more donations during this period was 270 546, and they contributed a total of 982 351 units. The number of person-years at risk (the sum of intervals between donations), used as the denominator to calculate crude incidence rates, was 413 531. The values in the same centres during the 1997-1999 period were as follows: total donors, 420 824; donations, 1 039614; repeat donors, 231 267, who made 850 052 donations; person-years at risk, 363 015. Table 3 summarises the incidence and risk results for these seven centres in both periods.

Table 3

Estimated residual risk during 1997-1999 and 2000-2002 in the seven centres, Spain, 1997-2002

Virus (period)	No of Incident cases	No of person-years	Incidence rate per 100 000 person-years (CI 95%)	Window period, days (range)	Residual risk per million donations (range)
HBV (97-99)	13	363 015	11.55* (6.14-19.75)	59 (37-87)	18.67 (6.22-47.07)
HBV (00-02)	6	413 531	6.05† (2.22-13.19)	59 (37-87)	9.78 (2.25-31.44)
HIV (97-99)	15	363 015	4.13 (2.31-6.81)	22 (6-38)	2.49 (0.38-7.09)
HIV (00-02)	17	413 531	4.11 (2.40-6.58)	22 (6-38)	2.48 (0.39-6.85)
HCV (97-99)	22	363 015	6.06 (3.80-9.15)	66 (38-94)	10.96 (3.96-23.56)
HCV (00-02)	9	413 531	2.18 (1.00-4.14)	66 (38-94)	3.94 (1.04-10.66)

* Incidence rate of seroconversion for HBsAg was multiplied by 1/0.31 to obtain the incidence rate of HBV infection

† Incidence rate of seroconversion for HBsAg was multiplied by 1/0.24 to obtain the incidence rate of HBV infection

Table 4 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 1997-1999 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 one HIV infection per year. NAT for HBV might have detected eight infected units per year.

Between July 1999 and December 2003, a total of 3 374 807 donations were tested for NAT in single samples or in pools of 8 to 48 units (the vast majority in pools from 44 or 48 donations), in 12 of the 22 Spanish blood donation centres participating in the study. Eight anti-HCV negative and HCV-RNA positive donations were found, 5 of them in 44 unit pools, 1 in a 48 unit pool, another in a 24 unit pool, and the last in an individual sample (J.M. Hernández, personal communication, March 2004).

Table 4

Projected yield of the utilisation of new screening tests to reduce the risk of transmission of infections by transfusion, Spain, 1997-1999

Virus tests	Estimated reduction of the window period in days	Residual risk with additional tests		Projected yield (infected units detected per 1 420 000 units)
		Projected (per million donations)	Reduction percentage	
HBV				
DNA VHB	25*	7.79	42.4	8
HIV				
p24test	6*	1.42	27.3	1
DNA HIV-1	6*	1.42	27.3	1
RNA HIV-1	11*	0.97	50.0	1-2
HCV				
Core Antigen	41†	2.53	62.12	6
RNA HCV	43‡	2.33	65.15	6

* Data obtained from Schreiber et al [2]

† Data obtained from Couroucé et al [7]

‡ Data obtained from Schreiber et al [2] and Couroucé et al [7]

Discussion

An excellent comparison of different works about residual risk was made by Glynn et al [8].

With regard the changes over time in blood donor HBV, HIV and HCV infection rates, we consider that the number of centres with

data from two periods (seven centres) is insufficient to make definite conclusions. The incidence rate and residual risk of HIV does not seem to have changed [Table 3], but the number of HBV incidents decreased from 13 in 1997-1999 to 6 in 2000-2002 ($p > 0.05$, chi-square test), and the number of HCV incidents decreased from 22 in 1997-1999 to 9 in 2000-2002 ($p < 0.01$, chi square test).

The 8 anti-HCV negative, HCV RNA positive cases found represent an approximate yield of 1/420 000, versus the projected yield obtained with 1995-1997 data: 6/1 420 000 or 1/240 000. With 2000-2002 data, the projected yield of HCV NAT should be (2.18/105) x (43/365) x 3 374 807 = 8.7, practically the same value as the yield actually obtained. We think that the NAT yield in Spain is higher than other countries because the prevalence of hepatitis C virus is also higher, at about 1%.

We conclude that following the incidence/window period model, the residual risks of transfusion-transmitted viral infections 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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