A revised method for estimating hepatitis B virus transfusion residual risk based on antibody to hepatitis B core antigen incident cases

Syria Laperche, Michèle Maniez, Valérie Barlet, Marie-Hélène El Ghouzzi, Françoise Le Vacon, Thierry Levayer, Françoise Lunel, Pascal Morel, Laurence Mouillot, Yves Piquet, and Josiane Pillonel for the Transfusion-Transmissible Agents Working Group of the French National Society of Blood Transfusion

BACKGROUND: To take into account the transient nature of hepatitis B virus (HBV) antigenemia, the calculation of HBV residual risk (RR), based on the incidence/window period model, is adjusted by a correction factor that adds uncertainty to the RR estimates.
STUDY DESIGN AND METHODS: This new method to estimate the RR for HBV is a weighted sum of the RR derived from hepatitis B surface antigen (HBsAg) incident cases and the one derived from antibody hepatitis B core antigen (HBc) incident cases. An anti-HBc incident case was defined as a donation from a blood donor who had made at least one anti-HBc–negative donation followed by a donation that was found positive with two different assays within a 3-year period and positive for at least one of the following markers: 1) antibody to hepatitis B e antigen or hepatitis B e antigen, 2) anti-HBc immunoglobulin M, 3) HBV DNA, 4) hepatitis B surface antibody without HBV vaccination history, or 5) HBV DNA retrospectively found in the previous donation. Five overlapping 3-year study periods between 2000 and 2006 were analyzed.
RESULTS: The HBV RR estimated with the classical method ranged from 1.51 (2000-2002) to 0.69 per million donations in 2004 through 2006 with a decrease in 2002 through 2004 due to only two HBsAg incident cases reported in this period. By applying the revised model, the HBV RR ranged from 1.06 (2000-2002) to 0.49 per million donations (2004-2006), with a regular decrease.
CONCLUSION: The new presented model provides HBV RR estimates that do not statistically differ from those obtained with the classical model; however, it provides more accurate data, especially in low endemic areas where the HBsAg incidence is low.

The method widely used for estimating the residual risk (RR) of infectious disease transmission by blood transfusion is based on the classical incidence/window period (WP) model.[1,2] In this model, incidence is derived from the seroconversion rates observed in repeat donors, and the RR estimates on

ABBREVIATIONS: anti-HBe = antibody to hepatitis B e antigen; anti-HBs = hepatitis B surface antibody; HBeAg = hepatitis B e antigen; RR(s) = residual risk(s); RR1 = RR derived from donors who have transient or chronic antigenemia; RR2 = RR derived from donors without antigenemia; WP = window period

From the Centre National de Référence pour les hépatites B et C en transfusion, Département des Agents Transmissibles par le Sang, Institut National de la Transfusion Sanguine, Paris; Etablissement Français du Sang Nord de France, Lille; Etablissement Français du Sang Rhône Alpes, Metz Tessy; Etablissement Français du Sang Ile de France, Rungis; Etablissement Français du Sang Bretagne, Rennes; Etablissement Français du Sang Pyrénées Méditerranée, Montpellier; Laboratoire de Virologie, Centre Hospitalo-Universitaire, Angers; Etablissement Français du Sang Bourgogne Franche-Comté, Dijon; Agence Française de sécurité sanitaire des produits de santé, Saint Denis; Etablissement Français du Sang Aquitaine Limousin, Bordeaux; and Institut de veille sanitaire, Saint Maurice, France.

Address reprint requests to: Syria Laperche, Centre National de Référence pour les hépatites B et C en transfusion, Département des Agents Transmissibles par le Sang, Institut National de la Transfusion Sanguine, Paris 75015, France; e-mail: slaperche@ints.fr.

This work was realized with the institutional support of the Etablissement Français du Sang, the Institut National de la Transfusion Sanguine, and the Institut de Veille Sanitaire.

Received for publication December 10, 2007; revision received April 2, 2008; and accepted June 8, 2008.

doi: 10.1111/j.1537-2995.2008.01873.x

TRANSFUSION 2008;48:2308-2314.

the overall donor population requires hypotheses that take into account incidence among first-time donors. After the recent introduction of nucleic acid testing (NAT) in several countries, a new method for estimating the RR of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) based on NAT yield cases has been developed.[3] The main advantage of this method is to include incident cases observed in repeat and new blood donors. However, there are only a few reports using this method.[3,4] In addition this method requires large donor populations. Furthermore, NAT is not currently performed worldwide; thus this new approach cannot be widely used.

In the incidence/WP model, incidence rates (IRs) for HIV and HCV are calculated by measuring the rate of seroconversion to antibody positivity or RNA positivity when NAT is performed. For HBV infection, the determination of incidence is more complicated due to the fact that hepatitis B surface antigen (HBsAg) might be absent. Thus, the IR of hepatitis B infection is based on the incidence of HBsAg seroconversion multiplied by an adjusted factor applied to take into account the transient nature of HBV antigenemia.[5] This correction is derived from the composite mean probability of a positive HBsAg test in the three clinical situations observed in primary HBV infection in immunocompetent subjects: 1) donors who become chronic carriers, 2) donor with a primary antibody response without detectable antigenemia, and 3) donors who develop a transient antigenemia. By applying this model, important variations in the estimates of HBV RR especially due to the weak number of HBsAg incidence cases could be observed. To better estimate the HBV RR in France, in the absence of NAT for HBV, we developed an approach that combines rates of seroconversions to HBsAg and to antibody to hepatitis B core antigen (anti-HBc). The results obtained with this new approach were compared to the classical model.

MATERIALS AND METHODS

Data sources and incident case definition

All data necessary for the incidence calculation were retrieved from the National Epidemiological Donor database, which contains donation and demographic data on French blood donors. Each donor who presents a seroconversion for HBsAg or anti-HBc is invited to come back to be informed and controlled for HBV infection markers.

IRs were calculated including donations from donors who had made at least two donations within a 3-year period. Person-years were calculated as the sum of all interdonation intervals during the study period divided by 365. Five overlapping 3-year study periods were analyzed: 2000 through 2002, 2001 through 2003, 2002 through 2004, 2003 through 2005 and 2004 through 2006. The anti-HBc seroconversion data were collected retrospectively from 2000 to 2003 and prospectively on the basis of a specific dedicated questionnaire from 2004.

A blood donation was included in HBsAg incident cases if the donor had made at least a negative donation followed by a confirmed positive donation for this marker within the 3-year period. The screening of HBsAg was performed by Prism HBsAg (Abbott, Rungis, France), Monolisa HBsAg Plus (Biorad, Marnes la Coquette, France), or Monolisa HBsAg Ultra (Biorad, Marnes la Coquette, France) and confirmed by a neutralization reaction with hepatitis B surface antibody (anti-HBs).

An anti-HBc incident case was defined as a donation from a blood donor who had made at least one anti-HBc–negative donation followed by an anti-HBc positive donation within the 3-year period. A donation was considered as positive for the presence of anti-HBc when positive with two different assays (including Prism anti-HBc, Abbott) and fulfilling at least one of the five following criteria: 1) positive for the presence of antibody to hepatitis B e antigen (anti-HBe) or hepatitis B antigen (HBeAg), 2) positive for the presence of anti-HBc immunoglobulin M (IgM), 3) positive for the presence of HBV DNA, 4) positive for the presence of anti-HBs without HBV vaccination history, or 5) positive for the presence of HBV DNA in a previous donation. Excluded from the anti-HBc incident cases were 1) the donations positive for the presence of HBsAg (because HBsAg-positive donors were already included in HBsAg incident cases), 2) without HBe markers, 3) from a donor who was vaccinated for HBV, or 4) when the previous donation was found positive for the presence of anti-HBs. As only HBsAg and anti-HBc are currently systematically performed for detecting HBV infections in France, HBeAg, anti-HBe, anti-HBc IgM, anti-HBs, and HBV DNA were investigated retrospectively in repository samples when available. According to the results of investigations, the reported anti-HBc incident case was classified in three categories: "excluded" (1) donation that did not fulfill the inclusion criteria, 2) when anti-HBc was subsequently found negative on the follow-up sample, 3) when the anti-HBc sample/cutoff value was between 1 and 2 and when the ratio anti-HBc sample/cutoff value of the index donation/anti-HBc sample/cutoff value value of the previous donation was less than 1.5), "confirmed" (when at least one of the inclusion criteria were fulfilled), or "unclassified" (in the absence of informative data). Moreover, the proportion of unclassified cases that would be confirmed have been estimated by multiplying the total of anti-HBc unclassified cases by the proportion of confirmed cases among the total of excluded and confirmed cases.

IRs were calculated as the number of positive donations divided by the number of person-years.

HBV RR

The classical method

The RR of transfusion-transmitted HBV infection per million donations was calculated as the product of 1) the HBsAg IR adjusted according to the method of Korelitz and colleagues[5] and 2) the HBsAg WP estimate.[1] However, the duration of HBsAg detection in acute infection was modified by adding 14 days to the delay of 63 days adopted by Korelitz and colleagues,[5] to take into account the better sensitivity of current HBsAg assays,[6] resulting in a 77-day interval. Moreover, based on the HBV infectious WP model established by Kleinman and Busch,[7] the HBsAg WP delay used in our calculation was 38 days (range, 33-44 days).

The revised method

The basis of estimating RR with the new approach is the same as that used for the classical method, that is, the IR/WP model. The revised HBV RR is a composite sum of RR derived from donors who have transient or chronic antigenemia (RR1) and RR derived from donors without antigenemia (RR2). The weights are the proportion of the occurrence of markers during HBV infection: 75% for RR1 (70% of transient HBs antigenemia plus 5% of persistence of HBsAg associated with chronicity) and 25% for RR2 (25% of undetectable HBsAg).[8,9]

RR1 and RR2 were obtained by the formulas

$$\text{RR1} = (\text{HBsAg IR} + \text{anti-HBc IR}) \times (\text{HBsAg WP}/365),$$

where the HBsAg WP was estimated at 38 days (range, 33-44 days).

$$\text{RR2} = (\text{anti-HBc IR}) \times (\text{anti-HBc WP}/365),$$

where the anti-HBc WP was estimated at 69 days (range, 55-89 days).

The HBV RR was then obtained by the formula

$$\text{RR} = 75\%\,\text{RR1} + 25\%\,\text{RR2}.$$

The anti-HBc WP was obtained by the sum of the HBsAg WP (38 days) and the mean delay observed between the first sample positive for the presence of HBsAg and the first sample positive for the presence of anti-HBc in five HBV seroconversion panels (three commercial panels: BCP 6278 and BCP 6281 from BioClinical Partners, Franklin, MA; BBi 935 A, Boston Biomedica, Inc., West Bridgewater, MA; and two "in-house" seroconversion panels), estimated at 31 days (range, 22-45 days; data not shown). The anti-HBc WP range (55-89 days) was obtained by adding the range of the HBsAg WP (33-44 days) and those of the mean delay between the first HBsAg-positive sample and the first anti-HBc–positive sample observed in the seroconversion panel (22-45 days).

Confidence intervals

We obtained 95% confidence intervals (95% CIs) for IRs by the Fleiss quadratic method, which is appropriate for proportions close to 0.[10] The lower and upper bounds of the range of the CIs for the RRs RR1 and RR2 were calculated by multiplying the lower and upper limits of the WP ranges by the lower and upper limits of the 95% CI for the IRs, respectively. The lower bound of the range of the CI for the RR total was then the minimum between the lower bounds of CIs for RR1 and RR2 and the upper bound was the maximum between the upper bounds of CIs for RR1 and RR2.

RESULTS

Table 1 summarizes the data obtained from reported anti-HBc incident cases and their classification as defined herein. The number of declared anti-HBc incident cases varied from 27 in the second study period (2001-2003) to 46 in the fourth study period (2003-2005). These incident cases could have been included in two or three consecutive study periods depending on the date of previous negative donation. A large proportion (44.5%-73%) of these cases were excluded from the study mainly due to the absence of HBe markers in the donation. The percentage of confirmed cases for the calculation of revised RR ranged from 8.1% (2004-2006) to 44.5% (2001-2003). Finally, 11% to 21.7% of declared cases could not be classified because for most of them, there was not available repository sample. For each study period, the proportions of unclassified cases that would be confirmed were 31.2, 50.0, 37.1, 27.8, and 10.0%, leading to the addition of 2, 2, 3, 3, and 1 cases to the 10, 12, 13, 10, and 3 confirmed anti-HBc incident cases, respectively.

As shown in Table 2, the number of HBV incident cases obtained by the addition of HBsAg and anti-HBc incident cases varied from 12 (2004-2006) to 25 (2000-2002). In France, the HBV RR estimated with the classical method varied from 1.51 per million donations in 2000 through 2002 to 0.69 per million donations in 2004 through 2006 (Table 2). A decrease of this risk was observed between 2000 through 2002 and 2002 through 2004, followed by a slight increase from 2003 through 2005 (Fig. 1). The highest HBsAg IR was found in 2000 through 2002 (0.55 per 10^5 donations corresponding to 13 reported HBsAg incident cases) while the lowest HBsAg incident rate (0.09 per 10^5 donations corresponding to 2 reported HBsAg incident cases) was observed in 2002 through 2004. The correcting factor applied to adjust HBsAg incident rates to obtain HBV incident rates ranged from 1.84 (2003-2005) to 2.65 (2000-2002). The revised method leads to a HBV RR ranged from 1.06 per million donations (95% CI, 0.41-2.22) for 2000 through 2003 to 0.49 (95% CI, 0.08-1.16) per million donations for 2004 through 2006, with a

TABLE 1. Classification of reported anti-HBc incident cases according to the results of complementary investigations

	2000-2002	2001-2003	2002-2004	2003-2005	2004-2006
Anti-HBc incident cases declared	38	27	42	46	37
Anti-HBc incident cases excluded	22 (57.9%)	12 (44.5%)	22 (52.4%)	26 (56.6%)	27 (73.0%)
HBeAg and /or anti-HBe–negative	12	7	20	24	24
History of HBV vaccination	2	0	1	1	2
Previous donation positive for the presence of anti-HBs	6	3	0	0	1
Previous donation indeterminate for HBsAg	1	1	0	0	0
Other*	1	1	1	2	0
Anti-HBc incident cases confirmed	10 (26.3%)	12 (44.5%)	13 (30.9%)	10 (21.7%)	3 (8.1%)
Anti-HBe–positive	7	6	8	8	1
Anti-HBc IgM–positive	2	2	2	1	2
HBV DNA–positive	0	1	0	1	0
Previous donation HBV DNA–positive	1	2	2	0	0
Anti-HBs–positive without HBV vaccination	0	1	1	0	0
Anti-HBc incident cases unclassified	6 (15.8%)	3 (11.0%)	7 (16.7%)	10 (21.7%)	7 (18.9%)
Anti-HBc unclassified cases that would be confirmed†	2	2	3	3	1
Estimated anti-HBc incident cases‡	12	14	16	13	4

* Anti-HBc–negative on the follow-up sample or anti-HBc ratio value of the index donation between 1 and 2 and anti-HBc ratio value of index donation/anti-HBc ratio value of previous donation less than 1.5.
† Estimated by multiplying the number of anti-HBc unclassified cases by the proportion of confirmed cases among the total of confirmed cases plus excluded cases (31.2, 50.0, 37.1, 27.8, and 10.0% for the five periods, respectively).
‡ Sum of the number of confirmed anti-HBc incident cases and the number of unclassified cases that would be confirmed.

TABLE 2. Comparison of HBV RRs according to the method used for the calculation over the five study periods

	2000-2002	2001-2003	2002-2004	2003-2005	2004-2006
Number of HBsAg incident cases	13	8	2	5	8
Number of anti-HBc incident cases*	12	14	16	13	4
Number of person-years	2,370,000	2,276,600	2,303,250	2,319,530	2,307,715
HBsAg IR per 10^5 person-years (95% CI)	0.55 (0.31-0.97)	0.35 (0.16-0.72)	0.09 (0.02-.35)	0.22 (0.08-0.53)	0.35 (0.16-0.71)
Correcting factor†	2.65	2.49	2.63	1.84	1.91
HBV IR per 10^5 person-years (95% CI)‡	1.45 (1.01-2.03)	0.88 (0.55-1.38)	0.23 (0.09-0.55)	0.40 (0.20-0.78)	0.66 (0.37-1.09)
Anti-HBc IR per 10^5 person-years (95% CI)	0.51 (0.27-0.91)	0.61 (0.35-1.06)	0.69 (0.41-1.16)	0.56 (0.31-0.99)	0.17 (0.06-0.48)
HBV RR					
Classical method per million donations (95% CI)§	1.51 (0.91-2.45)	0.91 (0.50-1.66)	0.24 (0.08-0.67)	0.41 (0.18-0.94)	0.69 (0.34-1.31)
Revised method per million donations (95% CI)‖	1.06 (0.41-2.22)	1.05 (0.53-2.58)	0.94 (0.43-2.82)	0.87 (0.43-2.40)	0.49 (0.08-1.16)

* Sum of the number of confirmed anti-HBc incident cases and the number of unclassified cases that would be confirmed (see Table 1).
† Adapted from Korelitz et al.[5] with a longer interval of HBsAg detection at 63 + 14 = 77 days.
‡ Adjusted from HBsAg IR with the correcting factor.
§ Equal to HBsAg incident rate × (correction factor × HBsAg WP (38 days)/365 × 10).
‖ Equal to 75% RR1 + 25% RR2 with RR1 = ((HBsAg incident rate) + (anti-HBc incident rate)) × HBsAg WP (38 days)/365 × 10 and RR2 = anti-HBc incident rate × anti-HBc WP (69 days))/365 × 10.

regular decrease (Fig. 1). However, the difference between the first and the last periods was not statistically significant.

DISCUSSION

This report presents the current HBV RR and its trend over time in France, a low endemic country for HBV (0.65% HBsAg chronic carriers in general population). Based on the classical method,[1] and by use of the last estimates of HBsAg WP (38 days),[4] the current HBV RR (2004-2006) was estimated at 0.69 per million donations (1 in 1,450,000 donations representing less than 2 infected donations per year on the basis of 2.5 million collected donations per year in France). However, this risk fluctuates according to the study period as shown in Fig. 1. Two variables included in the mathematical formula used to estimate the risk widely contribute to these fluctuations. First, the number of HBsAg incident cases, which were very limited in France, as depicted in Table 2, and second the adjustment factor used to account for the transient presence of HBsAg. The latter factor depends on the number of HBsAg donors who had seroconverted during the study period, but, above all, on the interdonation delay calculated between the last HBsAg-negative donation and the first HBsAg-positive donation of each incident case.[5] This factor, which is different according to the study period, adds uncertainty into the risk estimate for HBV.

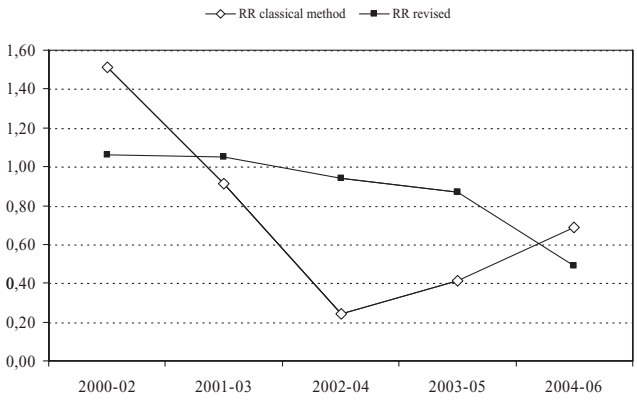

Fig. 1. Trends of HBV RR expressed per million donations calculated with classical (◇) and revised (■) methods. The HBsAg IR was expressed per 10^5 donations. Y-axis = rate of donations; X-axis = study period.

Due to these limitations, we propose to eliminate the adjustment factor in the calculation of the HBV RR in the revised method. To this end, we have associated rates of HBsAg seroconversion and those of anti-HBc seroconversion to identify all donors who underwent HBV infection during the study period. This procedure could easily be implemented, the anti-HBc screening for blood donations being mandatory in France since 1988, and because a dedicated questionnaire recording all anti-HBc incident cases was introduced in 2004. With this approach, the current HBV RR (2004-2006) was estimated at 0.49 per million donations (1 in 2,000,000 donations representing one infected donation per year. This risk is not different from the one calculated with the classical method; nevertheless, over the period 2000-2006, it demonstrates a lesser fluctuation than those obtained with the classical model (Fig. 1), especially in the third study period (2002-2004) when the RR was four times higher with the new method (1 in 1,060,000 donations) than with the classical method (1 in 4,170,000 donations). Another advantage of this method is a more accurate estimation of the number of new HBV infections in our blood donor population.

Despite the improvement provided by this new approach to estimate HBV RR, the mathematical model remains unchanged because based on the incidence/WP model. The major limitation of this model is the failure to measure the incidence in first-time blood donors. Indeed, it has been reported that this latter category of donor is often more at risk than repeat donors who are progressively deferred at the pre-donation stage or at the screening stage.[11-14] However, the proportion of donations collected from repeat blood donors is higher than those from first-time donors (15 and 85%, respectively, in 2006, in France), reducing the likelihood to collect blood from an infected but negative donation from a new donor. Moreover, the calculation of viral RR depends on incidence estimate, which is not easily obtained in most blood centers. In addition, the incidence of transfusion-transmissible viral infection seems not to be easily predicted from the prevalence.[15] To evaluate the potential risk represented by first-time donors, some authors have used alternative approaches. One of them consists of using a sensitive/less-sensitive enzyme immunoassay (EIA) developed to differentiate new from past infections of HIV-seropositive donors.[3,16] Another method, which allows the determination of the incident rate in all donations,[3,4] proposes the introduction of the NAT yield cases in the calculation of RR. Unfortunately, no sensitive/less-sensitive EIA is currently available for HBV to classify donations in early and chronic infection and HBV NAT is not performed in continental France.

Another limitation of our model is linked to the anti-HBc incident case definition. The reported poor specificity of anti-HBc assays, albeit improved,[17] and the absence of a confirmatory specific assay, result in a theoretical overestimation of incident cases and, consequently, an overestimation of HBV RR. Although it has been reported that samples with low anti-HBc sample/cutoff values are more often the results of false reactities,[17] we decided to not fix a value for the "true" positive results, because this threshold would have been arbitrary. It was thus decided to adopt strict inclusion criteria, including the presence of an additional marker (serologic or clinical) of HBV infection. Among HBV markers, anti-HBc IgM has a good positive predictive value, but poor negative predictive value, especially for incident cases reported in a 3-year period of time. Anti-HBs is a pertinent marker but only in the absence of vaccination. In addition, false weak-reactive samples for anti-HBc from subjects with a history of HBV vaccination may occur. Interestingly, in most situations in our study, the most pertinent marker for the classification of suspected anti-HBc incident cases was anti-HBe. Indeed, the coexistence of both anti-HBc and anti-HBe is a solid argument in favor of a real HBV infection.[17] As the number of suspected anti-HBc incident cases does not exceed 10 per year in a low endemic country such as France, the anti-HBe screening appears as an affordable and useful tool to investigate such a case. By limiting complementary investigations to this particular marker, some clinical situations could be missed in such case as the early HBV infection with a HBs mutant that could be reactive for HBeAg but not reactive for anti-HBe. However, we have to keep in mind that, due to the low frequency of undetectable HBs variants chronic carriers in blood donor population,[18] the probability of seroconversion with a HBs mutant remains exceptional. On the other hand, the exclusion of anti-HBc–only samples from anti-HBc incident cases might be disputable since some studies have shown that anti-HBc–positive samples containing or not HBV DNA did not carry detectable HBe markers.[18-20]

However, contrary to individuals described in those studies, donors included in anti-HBc incident cases as defined above were supposed to have been recently infected, since the main inclusion criteria is to have seroconverted for anti-HBc in a 3-year period of time after the previous anti-HBc–negative donation. Hence, as no recent HBV infection with an anti-HBc alone has been reported, this putative situation was excluded.

The determination of the anti-HBc WP delay used in our model (69 days) was based on only five subjects in HBV early phase. Data concerning the appearance of anti-HBc in the acute HBV infections are limited. One recent Japanese study reported an anti-HBc WP at about 80 days;[21] however, the detection of anti-HBc was performed with an in-house hemagglutination assay inhibition technique that is less sensitive than EIA currently used in blood screening in Europe.

Finally, the weights of 75 and 25% used in our model to estimate HBV RR are based on the occurrence of markers during HBV infection. Seventy-five percent corresponds to 70% of transient HBs antigenemia plus 5% of persistence of HBsAg due to the evolution toward chronic carriage and 25% to undetectable HBsAg.[8,9] As the sensitivity of screening tests for HBsAg has improved since the mid-1970s, these figures have probably changed to an increased proportion of transient HBs antigenemia. Nevertheless, there are no published updated data. The sensitivity analysis (not shown in details) has demonstrated that, using the proportions of 95 and 5% instead of 75 and 25%, the point estimates of RRs would have been 1.09 per million instead of 1.06 for the 2000 through 2002 period, 1.01 instead of 1.05 for the 2001 through 2003 period, 0.84 instead of 0.94 for the 2002 through 2004 period, and 0.82 instead of 0.87 for the 2003 through 2005 period and 0.53 instead of 0.49 for the 2004 through 2006 period. Then, the proportions of transient antigenemia did not have main impact on the RR estimates.

The introduction of HBV NAT is now widely debated because the HBV RR is usually larger than that of the other viruses.[4,22-25] Thus, in many countries, especially located in moderate and high endemic areas, this technique has already been introduced in blood screening[18,26-29] with a benefit essentially linked to the detection of the late stage of the infection[18,27,29] corresponding to occult hepatitis B carriers who are viremic with undetectable HBsAg.[30] In low endemic countries, such as France, due to the systematic screening of anti-HBc, the decision for the implementation of HBV NAT is only based on the benefit expected by the detection of the HBsAg WP. It is the reason why the risk of transmitting HBV by blood transfusion needs to be estimated with accuracy. The proposed model, using the anti-HBc incident rate in association with HBsAg IR, could easily be used to provide more accurate estimates of HBV RR especially in low endemic areas where the HBsAg incident rate is low.

ACKNOWLEDGMENTS

The authors thank Annie Girault, Nadine Le Marrec, Rémi Caparros and Danielle David for their technical assistance and Azzedine Assal, Marie Lise Béolet, Claude Chuteau, Pierre Gallian, Philippe Guntz, Marcel Joussemet, Françoise Maire, Josiane Relave, and all colleagues implicated in the hemovigilance survey from the Etablissement Français du Sang and the Centre de Transfusion des Armées who participate in the national blood donor surveillance. We thank Camille Sureau for his helpful advice in the redaction of the manuscript.

REFERENCES

1. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor study. N Engl J Med 1996;334:1685-90.
2. Glynn SA, Kleinman SH, Wright DJ, Busch MP. International application of the incidence rate/window period model. Transfusion 2002;42:966-72.
3. 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; 45:254-64.
4. O'Brien SF, Yi QL, Fan W, Scalia V, Kleinman SH, Vamvakas EC. Current incidence and estimated residual risk of transfusion-transmitted infections in donations made to Canadian Blood Services. Transfusion 2007;47:316-25.
5. 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. National Heart, Lung, and Blood Institute Retrovirus Epidemiology Donor Study. Transfusion 1997;37:634-40.
6. Seed CR, Cheng A, Ismay SL, Bolton WV, Kiely P, Cobain TJ, Keller AJ; Virology Subcommittee of the National Donor and Product Safety Committee, Australian Red Cross Blood Service. Assessing the accuracy of three viral risk models in predicting the outcome of implementing HIV and HCV NAT donor screening in Australia and the implications for future HBV NAT. Transfusion 2002;42:1365-72.
7. Kleinman SH, Busch MP. Assessing the impact of HBV NAT on window period reduction and residual risk. J Clin Virol 2006;36 Suppl 1:S23-9.
8. Hoofnagle JH, Gerety RJ, Barker LF. Hepatitis B core antigen and antibody. Dev Biol Stand 1975;30:175-85.
9. Hoofnagle JH, Seef LB, Buskell-Bales Z. Serologic response in HB. Philadelphia (PA): Franklin Institute Press; 1978. p. 219-42.
10. Fleiss J. Statistical methods for rates and proportions. 2nd ed. New York: Wiley Press; 1981.
11. 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;42:975-9.
12. Van der Bij AK, Coutinho RA, Van der Poel CL. Surveillance of risk profiles among new and repeat blood donors with transfusion-transmissible infections from 1995 through 2003 in the Netherlands. Transfusion 2006;46:1729-36.
13. Zou S, Notari EP, Stramer SL, Wahab F, Musavi F, Dodd RY. 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;44:1640-7.
14. 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;12:239-46.
15. Wang B, Schreiber GB, Glynn SA, Kleinman S, Wright DJ, Murphy EL, Busch MP; Retrovirus Epidemiology Donor Study. Does prevalence of transfusion-transmissible viral infection reflect corresponding incidence in United States blood donors? Transfusion 2005;45:1089-96.
16. Pillonel J, Barin F, Laperche S, Bernillon P, Le Vu S, Liandier B, Desenclos JC. Human immunodeficiency virus type 1 incidence among blood donors in France, 1992 to 2006: use of an immunoassay to identify recent infections. Transfusion 2008 [Epub ahead of print].
17. Schmidt M, Nubling CM, Scheiblauer H, Chudy M, Walch LA, Seifried E, Roth WK, Hourfar MK. Anti-HBc screening of blood donors: a comparison of nine anti-HBc tests. Vox Sang 2006;91:237-43.
18. Brojer E, Grabarczyk P, Liszewski G, Mikulska M, Allain JP, Letowska M; Polish Blood Transfusion Service Viral Study Group. Characterization of HBV DNA+/HBsAg- blood donors in Poland identified by triplex NAT. Hepatology 2006;44:1666-74.
19. Grob P, Jilg W, Bornhak H, Gerken G, Gerlich W, Günther S, Hess G, Hüdig H, Kitchen A, Margolis H, Michel G, Trepo C, Will H, Zanetti A, Mushahwar I. Serological pattern "anti-HBc alone": report on a workshop. J Med Virol 2000; 62:450-5.
20. Zervou EK, Dalekos GN, Boumba DS, Tsianos EV. Value of anti-HBc screening of blood donors for prevention of HBV infection: results of a 3-year prospective study in Northwestern Greece. Transfusion 2001;41:652-8.
21. Yoshikawa A, Gotanda Y, Itabashi M, Minegishi K, Kanemitsu K, Nishioka K; Japanese Red Cross NAT Screening Research Group. HBV NAT positive [corrected] blood donors in the early and late stages of HBV infection: analyses of the window period and kinetics of HBV DNA. Vox Sang 2005;88:77-86.
22. Alvarez M, Oyonarte S, Rodriguez PM, Hernandez JM. Estimated risk of transfusion-transmitted viral infections in Spain. Transfusion 2002;42:994-8.
23. Pillonel J, Laperche S. Trends in risk of transfusion-transmitted viral infections (HIV, HCV, HBV) in France between 1992 and 2003 and impact of nucleic acid testing (NAT). Euro Surveill 2005;10:5-8.
24. Gonzalez M, Regine V, Piccinini V, Vulcano F, Giampaolo A, Hassan HJ. Residual risk of transfusion-transmitted human immunodeficiency virus, hepatitis C virus, and hepatitis B virus infections in Italy. Transfusion 2005;45: 1670-5.
25. Seed CR, Kiely P, Keller AJ. Residual risk of transfusion transmitted human immunodeficiency virus, hepatitis B virus, hepatitis C virus and human T lymphotrophic virus. Intern Med J 2005;35:592-8.
26. Gonzalez R, Echevarria JM, Avellon A, Barea L, Castro E. Acute hepatitis B virus window-period blood donations detected by individual-donation nucleic acid testing: a report on the first two cases found and interdicted in Spain. Transfusion 2006;46:1138-42.
27. Liu CJ, Chen DS, Chen PJ. Epidemiology of HBV infection in Asian blood donors: emphasis on occult HBV infection and the role of NAT. J Clin Virol 2006;36 Suppl 1:S33-44.
28. Zanetti AR, Romano L, Zappa A, Velati C. Changing patterns of hepatitis B infection in Italy and NAT testing for improving the safety of blood supply. J Clin Virol 2006;36 Suppl 1:S51-5.
29. Comanor L, Holland P. Hepatitis B virus blood screening: unfinished agendas. Vox Sang 2006;91:1-12.
30. Raimondo G, Pollicino T, Cacciola I, Squadrito G. Occult hepatitis B virus infection. J Hepatol 2007;46: 160-70.