Health and economic impact of posttransfusion hepatitis B and cost-effectiveness analysis of expanded HBV testing protocols of blood donors: a study focused on the European Union

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BACKGROUND: Residual risk of posttransfusion hepatitis B (PT-HB) may be reduced through implementation of HBV NAT or the new, enhanced-sensitivity HBsAg assays in routine donor testing. However, there are some doubts about the cost-effectiveness of these new safety measures, because hepatitis B acquired in adulthood is not regarded as a severe disease in western countries.

STUDY DESIGN AND METHODS: A computer model was designed to estimate the health outcomes and associated costs of patients with PT-HB. Results from this model and estimations of the residual risk of HBV transmission, the risk reduction yielded by the new assays, and their cost were used to calculate the cost-effectiveness of including the new HBsAg assays or single-sample HBV NAT in the routine screening of blood donors.

RESULTS: The model predicts that 0.97 percent of patients with PT-HB die of liver disease (54% of them due to fulminant hepatitis). The mean loss of life expectancy was 0.178 years per patient, and the present value of the lifetime costs of treating PT-HB was 4160 euros per patient. Single-donor HBV NAT or the new HBsAg assays would increase the life expectancy of blood recipients by 16 (95% CI, 8-40) or 14 (95% CI, 7-28) years, respectively, per every 10 million donations tested. The projected cost per life-year gained was 0.79 (95% CI, 0.15-1.85) million euros for the enhanced-sensitivity HBsAg assays and 5.8 (95% CI, 1.9-13.1) million euros for single-donation HBV NAT, both compared with current HBsAg assays. If single-donation HBV NAT is compared with the new HBsAg assays, its cost-effectiveness ratio increases to 53 (95% CI, 16-127) million euros.

CONCLUSION: PT-HB has few health or economic repercussions. Single-donation HBV NAT would provide a small health benefit at a very high cost. Instead, in some circumstances, the cost-effectiveness of enhanced-sensitivity HBsAg assays would be within acceptable ranges for new public health interventions.

Continuous improvements of blood donor selection and testing protocols have nearly eliminated the risk of HIV or HCV transmission through screened blood. This achievement has turned attention back to posttransfusion hepatitis B (PT-HB) since, albeit infrequent, it remains as a significant transfusion-transmitted infection.[1] Reasons for the persistence of a residual risk of HBV transmission include blood collected within the HBsAg-negative window period of early infection[2] and the existence of chronic carriers with either very low levels of HBsAg[3] or mutant forms of HBV,[4] both escaping detection by the currently available HBsAg assays. Testing blood donors for HBc antibody is thought to detect most surface antigen-negative chronic carriers,[5,6] and such testing is mandatory in the United States, Japan, and other countries. However, studies conducted in Europe, including areas of low[7,8] and moderate[9,10] HBV endemicity, have shown that routine screening of blood donors for anti-HBc would produce a very low yield of HBsAg-negative, infectious donations at the cost of rejecting many safe donors. Consequently, the most suitable way to further improve the detection of HBV infectious blood donated in Europe may be through the implementation of either HBV NAT or the new HBsAg assays with subnanogram sensitivity that are under development.[11]

ABBREVIATIONS: HCC = hepatocellular cancer; LY(s) = life expectancy year(s); PT-HB = posttransfusion hepatitis B; QALY(s) = quality-adjusted, discounted year(s).

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In fact, within the past 3 years, some European source plasma manufacturers have already implemented pooled HBV NAT, and such testing of whole blood donations has begun in Japan and Germany.[12] Implementation of HBV NAT for donated blood is being considered in other European countries, especially if more suitable screening assays become available or if such policy is taken by neighboring countries or endorsed by the European Union.[12] The requirement of HBV NAT on the recovered plasma that is sent to industrial fractionators may be another force driving blood banks to implement this assay for all donated blood. However, given the already low risk of HBV transmission and the relative benignity of this infection in adulthood,[13] the benefits that may be accrued by further expansion of the donor testing protocols must be balanced against other health priorities, especially if it involves the implementation of costly technologies. This is particularly true for European countries, where the predominant model of socialized health care services implies that resources allocated to marginally increasing the safety of the blood supply have necessarily to be diverted from other areas of the health care system.

The purpose of this work is to investigate the costs and benefits that may derive from expansion of the current HBV testing protocols of blood donors. First, the health and economic impact of PT-HB was estimated, and then these results were used to predict the cost-effectiveness of new technologies aimed at increasing the detection rate of HBV infectious donations. Because the health impact of HBV infection and the cost-effectiveness estimates may vary across geographic areas, the present analysis was focused on the European Union.

MATERIALS AND METHODS

Modeling PT-HB

A Monte Carlo simulation of a Markov model was designed to represent the more relevant health states and outcomes, and the associated costs, of patients who received transfusion of HBV-infectious blood and controls without hepatitis. Details on how such a simulation allows representation of the patients' course of disease have been published elsewhere.[14,15] Survival curves were derived from the simulation of 100,000 patients and controls, whereas 10 million cases and controls were simulated for estimating the aggregated health outcomes and costs. The model was written in PowerBASIC Console Compiler language (PowerBasic, Carmel, CA), and outputs were analyzed with computer software (Statistical Package for Social Science [SPSS] v10, SPSS Inc. Chicago, IL). Graphic plots and regression curves were drawn with computer software (Prism v3.0, GraphPad Software Inc., San Diego, CA).

Probability distributions for the age of blood recipients at the time of transfusion were derived from a population of 11,252 patients who received transfusion in our hospital from 1996 to 1999. Median age was 67 years, with first and third quartiles being 52 and 76 years, respectively. Age-adjusted mortality rates were calculated from life tables corresponding to the population of Spain in 1996[16] and were further adjusted to represent the mean mortality rate across the European Union.[17] Mortality rates due to the underlying disease(s) that triggered the transfusion were stratified by the recipient's age according to Vamvakas and Taswell[18] (Table 1). Probabilities for acute and chronic events related to PT-HB are summarized in Table 1 and Fig. 1. It was assumed that all recipients of HBV-infectious blood develop acute hepatitis, which is symptomatic in 70 percent cases. In the baseline analysis, 1 percent of acute infections were assumed to progress to fulminant hepatitis.[19] Patients with fulminant hepatitis who are younger than 60 years are considered for liver transplant, and 50 percent of them will actually receive a liver graft. Patients who do not receive transplantation face an 80 percent mortality risk, but survivors have a five times lower probability of becoming chronic carriers, compared with those without fulminant hepatitis.[19,20] Transplant-related mortality and recurrence of HBV infection were modeled according to Samuel et al.[21]

In the baseline analysis, it was assumed that 5 percent of adult patients become chronic HBV carriers.[22] This percentage was adjusted for age at the time of transfusion, so it was 19 times higher for newborns, decreasing progressively until achieving the adult rate at the age of 12. Progression of HBV infection in chronic carriers was modeled according to Fig. 1. Patients begin at the state of HBsAg-positive chronic hepatitis and HBV replication (HBV DNA detectable in serum). From here they can evolve to a nonreplicative state and even lose the HBsAg and/or progress through compensated to decompensated cirrhosis and hepatocellular cancer (HCC) according to the transition probabilities showed in Fig. 1. At each 3-month cycle in the simulation, the hypothetical patient faces the risk of dying before further progression of liver disease, according to his or her age-adjusted mortality rate. Transition probabilities between health states were derived from the studies referred to in Fig. 1. Criteria for selecting source studies included: (1) conducted in Western Europe; (2) lack of antiviral therapy, so study results represent the infection's natural history; (3) HBV replication based on detectable serum DNA rather than on the HBeAg and anti-HBe system, as the latter is not an accurate marker for HBV replication in Southern Europe;[23] and (4) enough information provided for calculating progression rates. The annual hazard rates for the analyzed events were calculated per patient-year of follow-up when enough data were provided in the article. In other cases, the DEALE method was used to derive annual rates from Kaplan-Meyer or cumulative probability plots.[24] An-

TABLE 1. Transition probabilities between health states, health-related quality of life factors, and costs used in the computer model of PT-HB

	Baseline estimate	Range used in sensitivity analyses
Short-term mortality because of underlying disease(s)[18] (first/second year after transfusion)*		
Age (years)		
<41	8/2	×0.5 to ×2.0
41-65	22/6	×0.5 to ×2.0
>65	30/20	×0.5 to ×2.0
Probability of HBV-related events[19-22]*		
Acute symptomatic infection	70	
Acute fulminant hepatitis	1	0-10
Probability of receiving a liver graft (age <60 years)	50	0-100
Outcome after liver transplant	See text	
Mortality if not liver transplant	80	
Probability of becoming chronic carrier	5	0-50
Progression of chronic hepatitis	(see text and Fig. 1)	
Quality of life factors assigned to health states[14,27,28]		
Baseline health	1.00	
Acute symptomatic hepatitis	0.70	
Acute fulminant hepatitis	0.20	
Asymptomatic chronic carrier	1.00	
Chronic hepatitis or compensated cirrhosis	0.90	
Decompensated cirrhosis or HCC	0.50	
Liver transplant		
First quarter	0.50	
Second to fourth quarter	0.75	
Second and subsequent years	0.85	
Cost associated with PT-HB complications (in year 2001 euros)[29,30]		(see text)
Acute infection	844€	
Acute fulminant hepatitis	10,488€	
Liver transplant for acute fulminant hepatitis	87,267€	
Follow-up chronic hepatitis or compensated cirrhosis (per year)	417€	
Lamivudine treatment (100 mg/day × 52 weeks)	1154€	
Conventional treatment of decompensated cirrhosis or HCC (per year)	4903€	
Liver transplant for decompensated cirrhosis or HCC	113,152€	

* Data presented as percentages.

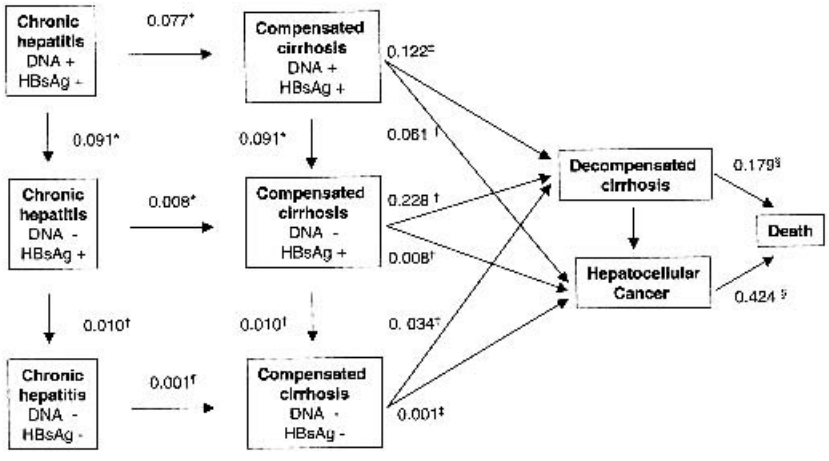

Fig. 1. Markov model of chronic PT-HB progression. Figures indicate the annual probability of transition between health states. *Derived from the work by Fattovich et al.[48] †Calculated from the results by Bortolotti et al.[49] and Moreno-Otero et al.[50] ‡Derived from Fattovich et al.[51] §Estimated from the results by Fattovich et al.[52] and Llovet et al.[53] ¶Taken from Wong et al.[28] In sensitivity analysis, the probabilities of seroconversion and clinical progression were multiplied by factors ranging from × 0.5 to × 2.0.

nual rates were then transformed into quarterly transition probabilities according to the equation $p = 1 - \exp(-\text{rate}/4)$.[25]

We assumed that a 52-week course of lamivudine (100 mg/day) was the standard therapy for patients with chronic hepatitis and HBV replication and that such treatment would increase by fourfold the transition rate to the nonreplicative state.[23] This response will be sustained in 80 percent of cases, but in half of them HBV replication will recur within 2 years after stopping lamivudine.[23] Because lamivudine has few adverse effects and is usually well tolerated by patients, it was assumed that 90 percent of the eligible individuals would actually complete the antiviral treatment. It was also assumed that 20 percent of patients with decompensated cirrhosis or HCC and nonreplicative status would be eligible for liver transplant. Outcomes after liver transplant

in these patients were modeled according to Teo et al.[26] Persons who clear the HBV, either spontaneously or after treatment, have a remaining life expectancy that is similar to that of controls without hepatitis. At each clinical state, survival was adjusted by quality of life weights that represent the most common estimates used in the specialized bibliography[15,27,28] (see Table 1).

The costs of treating the hepatic complications of HBV infection were derived from studies conducted in Germany[29] and the Netherlands,[30] and they were actualized to year 2001 euros by the medical component of the harmonized consumer price index for the European Union.[31] (*Note:* One euro (€) exchanges for one US dollar, approximately. However, the cost figures used in this study may not be fully applicable to the United States because of differences in the purchasing power of money, costs of labor and capital, and structure of health care services between the European Union and the United States.) Costs were assessed from the perspective of a national health service and included only direct medical costs. Indirect costs, such as those related to loss of productivity or other social expenses incurred by patients with PT-HB, were not accounted for. Survival was calculated in unadjusted, undiscounted life expectancy years (LYs) and also in quality-adjusted, discounted years (QALYs). Costs and QALYs were discounted at a 3 percent annual rate.

Variables included in the model of the clinical progression of PT-HB were highly interrelated, as occurs in real-life patients. For instance, younger patients have longer theoretical life expectancy and lower short-term mortality because of underlying diseases. However, they also have a higher probability of becoming long-term carriers and therefore of eventually progressing to end-stage liver disease. The probability of receiving a liver transplant was also related to age at the time of liver failure, which in turn was highly dependent on patient's age at transfusion. Such interrelations make univariate sensitivity analysis of the factors influencing on the health an economic impact of PT-HB to be somewhat meaningless. Therefore, a multivariate sensitivity analysis was conducted in which variables were allowed to change randomly between the bonds shown in Table 1 and Fig. 1. Outputs from 1000 iterations of 100,000 cases each were then analyzed by multivariate linear regression to identify their independent association with input covariates. The applicability conditions of this kind of regression analysis were met by taking the natural logarithms of the dependent variables.

Modeling the cost-effectiveness of screening blood donors for HBV

Outputs from the above model on the health and economic impact of PT-HB were used to calculate the cost-effectiveness of further expanding the HBV testing protocols. Cost-effectiveness calculations were carried out on a spreadsheet program (@Risk v4.0, Palisade Co., Newfield, NY; add-in to Excel, Microsoft Corporation, Redmond, WA). This Excel add-in allows Monte Carlo simulations to be performed by randomly drawing values from user-defined probability distributions at each iteration. This allows those inputs that are estimated with uncertainty to be represented in the cost-effectiveness model by probability distributions. Most variables were modeled as a triangular probability distribution. Such distribution is defined by three parameters, minimum, most likely, and maximum value, and allows uncertainty to be modeled when there is not enough information about the shape of data distribution.[32] Variables for which there was enough data were represented by the probability distribution that best fitted the data. Probability distribution fitting was carried out with computer software (BestFit for Windows 4.0, Palisade Co.).

Variables included in the cost-effectiveness calculations were those having the highest influence on the health and economic impact of PT-HB, as well as the best estimates for the current residual risk of HBV transmission, the risk reduction that the newer HBsAg assays or single-donation HBV NAT can yield, and the incremental cost of these assays. In performing these calculations, it was assumed that 1.65 blood components are transfused on average from every donated unit of whole blood.[15]

Since the probabilities of developing acute fulminant hepatitis or becoming chronic HBV carrier may be higher among blood recipients than in general population (see discussion), they were modeled as triangular distributions ranging from 1 percent to 10 percent (most likely, 5%) and from 5 percent to 15 percent (most likely, 10%), respectively. This biased the calculations in favor of further expansion of HBV testing protocols.

The residual risk for HBV transmission through HBsAg-negative blood varies from country to country within the European Union. By use of the incidence-window period model, it has been estimated at 1 in 63,000 blood donations in Italy,[33] 1 in 74,000 in Spain,[34] 1 in 180,000 in France,[35] and 1 in 250,000 in Denmark,[36] with large CIs. In the United Kingdom, a database review of acute hepatitis B cases that were reported from 1991 to 1997 found only 24 in which transfusion was the most probable route of infection,[37] which means 1 case every 730,000 blood donations, approximately. In some German blood banks, where HBV DNA testing is performed on every blood donation, HBV DNA-positive, HBsAg-negative donors are found at a rate of 1 in 214,000.[38] In Finland, it has been said that residual risk of transfusion-transmitted HBV infection would be around 1 in one million.[12] Therefore, after taking into account the relative number of units collected at each country,[39] the weighted mean residual risk of HBV transmission through HBsAg-screened blood was conservatively estimated at 1 in

100,000 (range, 1 in 50,000 to 1 in 300,000) donations for the whole European Union.

By analyzing seroconversion panels, it has been estimated that single-donation HBV NAT would reduce the window period of current serologic assays by 25 to 36 days. For minipool NAT and the newer HBsAg assays, the window period reduction has been estimated to range from 9 to 11 days and 11 to 13 days, respectively.[11] Based on these data and the Retrovirus Epidemiology Donor Study adjusted incidence of HBV infection in repeat donors (9.54 cases per 100,000 donor-years),[2] the risk reduction afforded by the new HBV screening methods was calculated. However, since the above calculations accounted only for the window period closing, and did not consider the possible detection of HBsAg-negative chronic carriers, the yield provided by each one of the new HBV assays was increased by 3-fold, with this adjustment biasing the model in favor of implementing the new technologies. The resulting risk reduction estimates fitted inverse Gauss probability distributions defined by the following parameters: $\mu = 5.3$ and $\lambda = 3.8$ for single-donor NAT, $\mu = 3.8$ and $\lambda = 2.9$ for the new HBsAg assays (both compared with the current HBsAg assays), and $\mu = 1.4$ and $\lambda = 0.75$ for single-donor NAT compared with the newer HBsAg assays. In this kind of probability density distribution μ is the mean and λ is a scale parameter that determines the variance and shape of the distribution.[40] This means, for instance, that single-donor NAT would reduce by 5.3-fold (95% CI, 3.5- to 4.2-fold) the current risk of HBV transmission (i.e., from 1 in 100,000 to 1 in 530,000, on average).

The incremental cost of the newer HBsAg assays was estimated to range from 0 to 3 (most likely, 1.5) euros per donation tested, as it was assumed that they will merely replace the current assays. In estimating the cost of HBV NAT, it was assumed that this assay will be performed on automated platforms already testing donations for HCV (and perhaps HIV too), so it will imply only the addition of another marker to an already operational multiplex system. However, since HCV NAT is not routinely performed in all blood banks within the European Union, regulations compelling the use of HBV NAT would trigger the acquisition or leasing of very expensive equipment in some cases. Taking all this into account, the incremental cost of single-sample HBV NAT was modeled as a triangular probability distribution ranging from 3 to 15 (most likely, 6) euros per donation tested.

RESULTS

Health and economic impact of PT-HB

The predicted median survival for patients with PT-HB and controls without hepatitis was 10.50 and 10.75 years, respectively, with a 30-year projected survival rate of 21.9 and 22.2 percent, respectively. Survival curves for PT-HB patients and controls nearly overlapped to one another. The model predicts that 0.97 percent of patients given HBV-infective blood will die of liver disease, 54 percent of them because of fulminant hepatitis following acute infection (Tables 2, 3). Patients who received transfusion with HBV-infective blood will lose a mean of 0.178 years of life expectancy (0.174 QALYs) to complications of hepatitis B. Tables 2 and 3 also show the frequency of adverse outcomes in patients with PT-HB and the mean present value of the lifetime costs of treating such outcomes. As can be seen, treatment of acute hepatitis amounts to 90 percent of total lifetime costs.

Results of multivariate sensitivity analyses aimed at identifying the factors and assumptions influencing PT-HB outcomes and associated costs are shown in Table 4. Covariates with the largest independent influence on the health and economic repercussions of PT-HB were the patient's age at the time of transfusion, the probability of fulminant hepatitis, and the probability of becoming chronic carrier. Figure 2 illustrates the effect that these factors had on either the life expectancy lost by patients with PT-HB or the lifetime costs of treating HBV-related complications. Factors related to the therapeutics of hepatitis B, such as the assumed efficacy of antiviral treatments or the availability of liver transplant for either acute or late liver failure, had less influence on the aggregated outcomes (see Table 4).

Cost-effectiveness of further expansion of HBV screening protocols

We analyzed the cost-effectiveness of three strategies aimed at further reducing the residual risk of transfusion-transmitted HBV infection. The first consists of implementing the newer, enhanced-sensitivity HBsAg assays. The second and third were based on single-donation HBV NAT, implemented either before or after the above HBsAg assays.

Table 5 shows the main health and economic repercussions projected for the three strategies. As can be seen, substituting the new, more sensitive HBsAg assays

TABLE 2. Probability of adverse effects after PT-HB

Adverse effect	Percentage of patients transfused with HBV-infective blood
Fulminant hepatitis	0.87
Chronic hepatitis	4.00
Antiviral treatment	2.62
Decompensated cirrhosis	0.29
Hepatocellular cancer	0.17
Liver transplant	0.17
Death from HBV-related liver disease	0.97
Fulminant hepatitis	0.56
Decompensated cirrhosis or HCC	0.36
Complications of liver transplant	0.05

TABLE 3. Outcomes of PT-HB

Outcome	Average per patient transfused with HBV-infective blood
Life expectancy lost to PT-HB	
LYs	0.178
QALYs	0.174
Lifetime cost of treating HBV complications (in euros)*	
Acute hepatitis	3780
Fulminant hepatitis	90
Follow-up chronic hepatitis and compensated cirrhosis	130
Conventional treatment of decompensated cirrhosis or HCC	120
Liver transplant	40
Total lifetime cost	4160

* Future costs were discounted at a 3% annual rate and are rounded to the second significant figure.

TABLE 4. Multivariate sensitivity analysis of factors and assumptions influencing the health and economic impact of PT-HB*

		Standardized β coefficients of regression to	
	Mean ± SD	ln (LY lost)	ln (costs)
Dependent variables			
LY lost to PT-HB (natural logarithm of years)	0.01 ± 1.7		
Lifetime cost due to PT-HB (natural logarithm of euros)	8.9 ± 0.5		
Covariates			
Patient age (years)	49 ± 28	–0.83	–0.78
Probability of fulminant hepatitis (%)	5 ± 3	0.25	0.23
Probability of becoming chronic carrier (%)	25 ± 15	0.14	0.21
Probability of liver transplant for fulminant hepatitis (%)	50 ± 28	–0.04	0.18
Probability of liver transplant for decompensated cirrhosis or HCC (%)	50 ± 30	–0.01	0.01
Proportion of patients on lamivudine (%)	50 ± 30	≤0.01	0.01
Probability of relapse after lamivudine (%)	50 ± 29	<0.01	–0.02
Seroconversion speed†	2.1 ± 1.1	–0.12	–0.06
Clinical progression speed†	2.1 ± 1.1	0.18	0.11
Short-term mortality due to underlying disease(s)†	1 ± 0.5	–0.09	0.12

* Standardized β coefficients indicate how many SD will increase or decrease the dependent variable when the covariate changes 1 SD so they are measuring the sensitivity of the dependent variable to changes of the covariates.[54] The higher the absolute value of the standardized β coefficient, the stronger the sensitivity of the dependent variable to changes of the covariate. For instance, a 3% increase of the probability of fulminant hepatitis will result in a 0.25 × 1.7 increase in the natural logarithm of the life years lost to PT-HB.

† Baseline values used in the model of PT-HB were multiplied by the indicated factor (see Table 1).

for those currently in use would be the most cost-effective strategy, whereas implementation of individual sample HBV NAT once these newer HBsAg assays were in place would be the least efficient one. Compared with current screening protocols, addition of single sample HBV NAT would cost 5.8 (95% CI, 1.9-13.1) million euros per LY gained. If it were implemented after the residual risk of HBV transmission had already been reduced by the new HbsAg assays, the cost-effectiveness of individual sample HBV NAT would increase to 53 (95% CI, 16-127) million euros per LY gained. Sensitivity analyses showed that cost-effectiveness estimates significantly depended on the assumptions made for the current residual risk for HBV transmission, the incremental cost of the new technologies, and the risk reduction that they would yield (see Table 5). In contrast, factors related to the health and economic impact of PT-HB, such as the probabilities of presenting fulminant hepatitis or becoming chronic carrier, had much less influence (standardized β coefficients < 0.1).

DISCUSSION

In western countries, HBV infection acquired in adult life is not regarded as a severe disease because it usually resolves spontaneously, has low chronic carrier rate, and only rarely has late progression to decompensated cirrhosis or HCC. For instance, long-term follow-up of US military recruits who were accidentally infected through vaccination in the early 1940s failed to show an excess of liver disease compared with noninfected controls.[13] Results from our model of PT-HB are consistent with this view, since less that 1 percent of patients will eventually die of liver disease, and the infection reduces the mean patient life expectancy by only 2 months. These figures are 10- and 4.5-fold smaller, respectively, than the equivalent ones that were recently estimated for post-transfusion hepatitis C.[15]

It is worth noting that, in our model, fulminant hepatitis following acute infection accounted for more than half the deaths attributable to PT-HB. Since this occurs

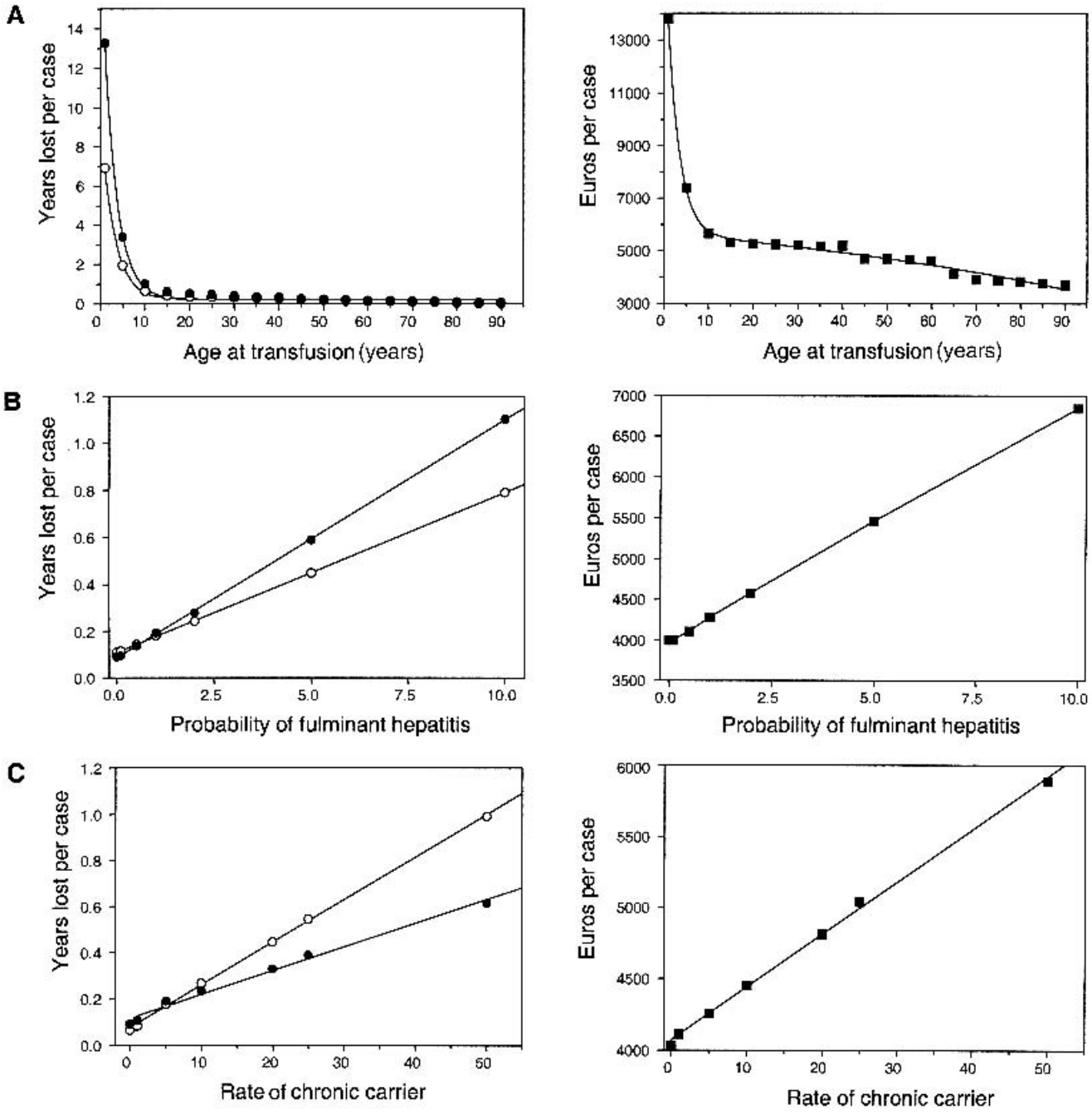

Fig. 2. LYs (●) or quality-adjusted life years (○) lost and lifetime costs (■) incurred by patients with PT-HB according to age at the time of transfusion and the assumed probabilities of fulminant hepatitis or chronic carrier.

early in the disease's course, and is independent of the typically low rate of chronic carrier or the competing risk for mortality that represents the advanced age of many blood recipients, fulminant hepatitis, albeit rare, emerges from our study as the main hazard associated with PT-HB. In addition, the risk of fulminant hepatitis among blood recipients may be higher than the 1 percent figure assumed in our baseline analysis, which was drawn from cases of hepatitis B acquired from sources other than blood transfusion.[19] Risk of acute hepatic failure after HBV infection or reactivation is increased in patients undergoing intermittent immunosuppression,[22,41] as is the case of those receiving courses of antineoplastic chemotherapy, most of whom are also under heavy transfusion support. Immunosuppressive therapies also decrease the ability of the immune system to eliminate the HBV after infection,[20,42] so the chronic carrier rate could be higher in some groups of blood recipients than in cases of com-

TABLE 5. Health gains, incremental cost, and cost-effectiveness ratio of strategies aimed at further decreasing the risk of transfusion-transmitted HBV infection

	Intervention vs. comparator		
	New HBsAg assays vs. current HBsAg assays*	Single-sample HBV NAT vs. current HBsAg assays*	Single-sample HBV NAT vs. new HBsAg assays*
Aggregated health gains and costs (per 10-million donations tested)			
Number of infections averted	56 (27-108)	61 (30-119)	7 (3-15)
LYs gained	14 (7-28)	16 (8-40)	2 (1-4)
QALYs gained	16 (8-32)	18 (9-35)	2 (1-4)
Net incremental cost (in million euros)	10 (2-17)	80 (39-133)	80 (39-133)
Cost-effectiveness ratio (in million euros)			
Cost per LY gained	0.79 (0.15-1.85)	5.8 (1.9-13.1)	53 (16-127)
Cost per QALY gained	0.70 (0.13-1.64)	5.1 (1.7-11.6)	47 (14-113)
Cost per infection averted	0.20 (0.03-0.47)	1.5 (0.5-3.4)	14 (4-33)
Standardized β coefficients for factors influencing on the cost per LY gained†			
Residual risk before intervention	0.64	0.72	0.65
Incremental cost per donation tested	0.73	0.64	0.58
Risk reduction yielded by the intervention	–0.31	–0.06	–0.35

* Data reported as mean (95% CI).
† See footnote of Table 4 for an explanation of the meaning of standardized β coefficients in sensitivity analysis.

munity-acquired hepatitis B. Both the increased risk of fulminant hepatitis and the possible higher rates of chronic carrier could confer on PT-HB a health repercussion significantly greater than that estimated in our baseline analysis. In fact, both factors ranked high, after patient's age, in sensitivity analyses aimed at identifying those variables having the greatest influence on the health and economic impact of PT-HB.

The above uncertainties about the health and economic impact of PT-HB were translated into the cost-effectiveness analysis of HBV screening protocols, where they were biased in favor of increasing both impacts. The cost-effectiveness analysis was also biased in favor of further expansion of the current screening protocols by assuming figures for both the current residual risk of transfusion-transmitted HBV infection and the projected risk reduction yielded by the new testing protocols that were higher than can be supported by current evidence. The shortcomings of the incidence-window period model for estimating the residual risk of PT-HB have been discussed elsewhere,[2] and it is probable that such model greatly overestimates the actual risk. In addition, the risk of HBV transmission through blood given by HBsAg-negative chronic carriers seems to be very low in Europe,[10,43] out of some high-risk groups that are already screened out from donating blood.[44] In contrast, the infectiousness of blood given by chronic carriers with low HBV DNA burden has not unequivocally been established,[45] so the risk reduction achieved by single-donation HBV NAT might actually be smaller than what was previously estimated.

Although the above biases favored further expansion of HBV testing protocols, the resulting cost-effectiveness estimates compared very unfavorably with those of most medical and public health interventions.[46] Only the new, more sensitive HBsAg assays would have a cost-effectiveness ratio within acceptable ranges, provided that they are marketed at prices similar or very close to those of current assays. In contrast, compared with the current HBV screening protocols, single-donation NAT is extremely costly for the expected health benefit, even after assuming that it would be performed on fully automated, multiplex platforms. The efficiency of single-donation HBV NAT would greatly worsen if it were implemented after the current residual risk of PT-HB had already been reduced by the new HBsAg assays. We did not take into account the possibility that single-donation HBV NAT would allow discontinuation of HBsAg testing. This would decrease somewhat the incremental cost of the new technology, thus improving the cost-effectiveness projection, but the existence of HBsAg-positive carriers with very low serum levels of HBV DNA[47] makes discontinuation of HBsAg testing quite improbable.

There are other factors potentially decreasing the effectiveness of the new HBV screening protocols that were not taken into account in our analysis. The fact that many patients on chronic transfusion support are actually immune to HBV because of selective vaccination was not considered. We also did not take into account the effect of blood donor vaccination on the residual risk of HBV transmission. Years ago, many European countries implemented routine vaccination of infants and adolescents against HBV, so as these people reach the age of

donating blood, a marked reduction in the risk of transfusion-transmitted HBV infection can be anticipated. In contrast, some circumstances that might increase the efficiency of the new assays were not considered either. For instance, incorporation of immigrants from high HBV endemicity areas into the pool of blood donors might increase the number of HBsAg-negative carriers who pass undetected through the current blood bank screening protocols. Also not included in the model was the possibility that patients with PT-HB may transmit the virus to other people, thereby amplifying the public health impact of this infection. Such an impact, however, is probably very low, as transfusion contributes to only a minority of the HBV infections found in the community.

It is a political goal of the European Union to achieve a greater unity between member states regarding transfusion safety standards and regulations. If a consensus decision must be taken on further expanding the HBV testing protocols of blood donors, the results from the present study support the implementation of enhanced-sensitivity HBsAg assays instead of single-donation HBV NAT. The latter would represent an unfair burden on limited health care resources that would probably be more effective if allocated to other health priorities. For instance, individual sample HBV NAT of all blood donated in the European Union, where around 14 million units are collected per year,[39] would save 22 LYs (25 QALYs) counting all European blood recipients, at an annual cost of 112 million euros. Allocating this sum of money to programs of universal vaccination against the HBV seems a wiser decision than expending it in preventing a few transfusion-transmitted cases.

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