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COST-BENEFIT ANALYSIS OF HEPATITIS-B VACCINATION

A Computerized Decision Model for Spain

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Abstract

The availability and efficacy of recombinant deoxyribonucleic acid yeast-derived hepatitis-B vaccine, at a price much lower than the previously available plasma-derived hepatitis-B vaccines against hepatitis-B virus infections, motivate a new cost–benefit analysis of hepatitis-B vaccination. Spanish data were used to calculate direct and indirect costs of hepatitis-B infection and the costs and benefits of different vaccination strategies in defined risk groups of the Spanish population. A vaccination program will reduce direct expenditures for hepatitis B if the attack rate in the target population is higher than 4.9%. If indirect costs are included, the threshold for cost saving is reduced to 0.9%. The results are sensitive to the price of the vaccine, the duration of protection, assumptions about consequences for quality of life, and to indirect costs.

Viral hepatitis is a major public health problem. It is an acute inflammation of the liver caused by hepatitis-A, hepatitis-B, hepatitis-C, hepatitis-D, and hepatitis-E viruses. Knowledge of its etiology and epidemiology is limited, mainly because of the high incidence of asymptomatic or anicteric infections. In most countries, hepatitis is underreported. Well over 50% and perhaps as much as 75% of infections with hepatitis viruses are not diagnosed.

Viral hepatitis B is clinically the most important type, with the highest rates of complications, morbidity, and mortality. Exposure to hepatitis-B virus (HBV) usually

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results in a self-limiting infection that may be symptomatic (with jaundice) or asymptomatic (subclinical) and therefore usually goes unrecognized. The rate of resolution to age dependent (48). In the USA 5–10% of infections do not resolve within 6 months; these individuals become virus carriers.[1] A protracted course of infection may lead to cirrhosis of the liver or to hepatocellular carcinoma. According to a report of an international group of experts, it is estimated that there are 200 million carriers of HBV in the world (45).

Viral hepatitis is an occupational hazard for many health care personnel. All countries also report high rates of infection among intravenous drug abusers, prostitutes, and homosexuals. Newborns of HBsAg carrier mothers are at high risk of infection (vertical transmission). The staff of certain closed institutions, such as prisons, may also be exposed to a higher risk of infection.

Hepatitis B represents a major problem in public health, especially in countries with intermediate and high rates of prevalence of the disease. In these countries, neonatal and childhood infections are frequent, with an especially high risk for chronic sequelae. In addition to its widely recognized medical and epidemiological importance, policymakers and health economists have developed a growing awareness of the economic burden of the disease on society (16;21;39).

The first vaccine against hepatitis B was introduced in 1982. Because of its very high price, about US $100 per person vaccinated, cost became one of the most important determinants of vaccination strategies. A well-timed cost-effectiveness study was published in 1982 by Mulley et al. (31). For a summary of different cost–benefit and cost-effectiveness studies of hepatitis-B vaccination, see Jönsson (24). Recently, a new generation of vaccines, produced by recombinant deoxyribonucleic acid (DNA) technology, dramatically increased the availability and reduced the price of the vaccine. This has made it necessary to reexamine existing vaccination strategies and develop new policies. Therefore, it is timely to repeat the cost–benefit studies with new epidemiological data and new prices. At the same time, there is a need to incorporate methodological developments in the economic evaluation of health care technologies.

The purpose of this study is to present a model for cost–benefit and cost-effectiveness analysis of hepatitis-B vaccination and apply the model to the existing epidemiological and economic situation in Spain. The intention is that the study will be helpful in developing rational vaccination strategies for hepatitis-B vaccination.

COST-BENEFIT AND COST-EFFECTIVENESS OF DIFFERENT VACCINATION STRATEGIES

In a review of the literature on benefits and costs of human vaccinations in developed countries, Weisbrod and Huston (46) concluded that the most telling finding from their survey was the absence of a standardized methodology for evaluating vaccination programs. They identified a number of common methodological mistakes; for example, studies overlooked costs in the form of side effects, costs of administration of the vaccine were undervalued, and costs of pain and suffering associated with the disease were omitted from the study.

In this study, we incorporated the methodological standards of Weisbrod et al. as far as available data allowed. We included reduction in health care expenditures, reduction in indirect costs, and improved health as benefits from vaccination. We also included the costs of patients' time even when it was difficult to give an exact price. A general model was used for the cost–benefit estimates and applied to a major risk group, health care personnel. The costs of screening and vaccination were identified,

quantified, and valued. Benefits in terms of a reduction in health care costs, reduced indirect costs, and improved health were introduced successively. Estimates of costs and benefits were undertaken using a computerized decision model, and sensitivity analysis was performed.

EPIDEMIOLOGY OF HBV INFECTION AND THE EFFICACY OF VACCINATION

The prevalence of HBV markers in the unselected Spanish population has been estimated between 7% and 22% (average 17%), or 2.7–8.6 (average 6.5) million people (9;10;12;13;18;27;38). According to data from newly recruited blood donors and pregnant women, the prevalence of HBsAg is 0.5–2.2% (average 1.5%), a number that corresponds to between 200,000 and 860,000 (average 585,000) people nationwide (8;10;12;13;18;27;38). This fraction of the population includes recent as well as chronic infections. About 32.5 million of the Spanish population are therefore susceptible to HBV infection.

The incidence of HBV infection in the unselected Spanish population has been estimated at about 0.2%, or 65,000 new infections per year (8;42). One fifth, or 13,000, of these are expected to present with jaundice. About half of all new cases occur in under-25-year-olds, and two-thirds are encountered in the economically active strata of the population. More precise information is obtained by estimating the incidence of HBV infection in risk groups that have been studied in detail (9;10;11;12;13;17;18; 27;28;38).

A synopsis of the estimated size of some segments of the Spanish population at increased risk of HBV infection is shown in Table 1. The annual attack rate, that is, the percentage of newly infected persons in a segment of the population per year, and the prevalence of any marker for HBV infection are the bases for this estimate. The attack rate is only rarely obtainable from studies in Spain; therefore, published data from comparable populations in other countries have to be taken into account in accordance with the available information on HBV markers in the corresponding Spanish populations. It is evident that a certain prevalence of positive markers may be attained slowly with a relatively low annual attack rate (e.g., hemodialysis patients) or more rapidly with a higher attack rate (e.g., hemophiliacs, drug addicts).

For health care workers (HCWs), the risk of acquiring an HBV infection depends on their area and type of work. Only very small segments of this group may have an annual attack rate above 2% (9). For about 30% of HCWs, an annual incidence of 1–1.5%, or around five times that of the general population, can be anticipated (8;38), but the majority, 60% of HCWs, has an annual incidence below 1% (38).

Therefore, an average estimate of the attack rate for all HCWs in Spain should not exceed 1%. Vaccination of subgroups of HCWs in special high-risk departments is, however, questionable because frequent changes of personnel between departments make such an approach complicated and inefficient. Young HCWs who are in contact with patients or bodily fluids should be offered the vaccine irrespective of the service on which they are working at a certain time. In order to economize on an immunization program for HCWs, those with less than 4 years of professional activity should not be screened before vaccination, because such a screening strategy would not be cost-effective (9;38).

In many studies of hepatitis B in HCWs, specialized services such as hemodialysis, surgery, or obstetrics may comprise a larger than average proportion of persons with long professional experience (38) who are not readily comparable to younger control

Table 1. Estimates of HBV Infection in Spain (Selected Risk Groups)

Population groups	Size of population	HBsAg (%)	Positive markers (%)	Annual attack rate (%)	Size of susceptible population (marker negative)	New cases of icteric hepatitis B per year (20% of infections)
Health care workers						
In hospitals (10;11;16;31;43)	340,000	1.5–3.5	17–45	0.5–2.5	187,000–282,000	282–935
Nonhospital	34,500	1.5–3.5	17–45	0.5–2.5	14,000–28,000	28–95
Total	374,500	1.5–3.5	17–45	0.5–2.5	206,000–311,000	310–1,030
High-risk patients						
Hemodialysis	9,800	6–10	60–75	2.5–3	2,450–4,000	15–20
Hemophiliacs (44)	2,500	6–15	70–80	13	500–750	13–20
Mentally retarded (13)	40,000	10–20	40–90	5–10	4,000–24,000	80–240
Drug addicts (45)	100,000	5–15	65–84	33–48	16,000–35,000	1,500–2,300
Total	152,300				23,000–63,750	1,608–2,580
Persons in intimate contact						
Family (8;9)	0.70–1.8 mi	3.4–21	13–51	2	0.343–1.500 mi	1,300–6,000
Nonfamily	0.05–0.2 mi	4–6	19–46	1	0.027–0.162 mi	55–325
Total	0.75–2.0 mi				0.370–1.660 mi	1,355–6,325
All risk groups	2.50–3.0 mi		35–40	2–4	0.6–2.0 mi	4,800–10,000

Abbreviation: mi = million.

groups because their exposure to HBV may have been unrelated to the profession and due rather to an increased incidence of infection in earlier decades (cohort effect).

This aspect pertains to estimates of the current incidence of HBV infections in other risk groups as well as the general population (7). Thus, recent campaigns against the spread of HIV promoting the safe handling of patients' bodily fluids (14), rigorous testing and processing of all blood products for safety with respect to viral transmission, advice against sharing of needles by drug addicts, and the promotion of "safer sex" should have an impact on the incidence of HBV infections. But since all available data on hepatitis B originate from studies performed several years ago, the estimates tend to be too high. This aspect must be taken into account by cost–benefit analyses.

Large-scale protection of the intimates or family members of patients with hepatitis B is rather cumbersome because of the need to trace and test individuals who might have been exposed, some of whom may already be in the incubation period of the infection. The addition of hyperimmune gamma globulin to vaccination adds considerably to the cost of such preventive action. Furthermore, active immunization is only needed for contacts of patients with chronic infection; the evaluation of the indication for active and/or passive immunization has to be judged individually by the physician of the index case. The impact of such measures on the overall incidence of hepatitis B nationwide is questionable. Cost–benefit analyses in this group have to take into account the high costs for administration and work time lost. As with other sexually transmitted diseases, attempts at control are fraught with difficulties.

An important group of new cases of HBV infections are newborns of HBsAg-positive mothers. Intrauterine infections are extremely rare. The rate of perinatal transmission depends on the infectivity of the mother, which is highest in HBeAg-positive mothers. In Spain, only about 7% of carrier mothers are HBeAg positive (18). An estimated average risk of perinatal transmission of 25% results in about 1,000 infected newborns per year. Carriers in Southeast Asia or Africa or drug addicts with HBV infection have a higher rate of HBe antigenemia (50–70%) (32). A target population of special interest in Spain are newborns of gypsy families (3;17). These estimates are consistent with data on the prevalence of HBV markers (31%) in children of HBsAg-positive mothers (18). The importance of HBV infections in this age group lies mainly in the high rate of chronic infection, which helps to perpetuate endemicity (15;26;40).

A nationwide vaccination program for these newborns seems feasible, because screening for HBsAg during pregnancy or at term could be organized in accordance with testing of blood donors, thus reducing the costs. In addition, pre- and postnatal care of mothers as well as ongoing vaccination programs for infants will facilitate access to this risk group. Adding hyperimmune gamma globulin to active immunization, although not required, does improve protection of perinatally exposed newborns (26).

Immunogenicity and Protection of HBV Vaccine

The immunogenicity of plasma-derived as well as recombinant HBV vaccines depends on the age and underlying diseases of the vaccinee as well as the vaccination schedule (41;43). After complete courses of HBV vaccination in healthy young adults, antibody concentrations above 10 IU/L can be expected in at least 95% of the vaccinees. The persistence of antibody levels above this threshold depends on the initial antibody titer achieved (19). Side effects are minimal, and it is even difficult to find statistically significant differences between vaccinated persons and those treated with placebo (41;43).

Protection from all HBV-related events, including asymptomatic seroconversion, has been reported to be between 75% and 86% in healthy persons, depending on the

initial antibody response (range 21–97%) (19;41;43). Some protection has even been observed in nonresponders. HBV infections occurring in spite of vaccination take a more benign course than those in nonvaccinated persons. Thus, the average protection from becoming a chronic carrier has been estimated at about 90% (25–100%) (19).

The duration of protection depends on the immune response to the vaccination. In general, immunocompetent vaccinees can expect protection from HBV infection for at least 5 years. This is certainly a reasonable time span to work with in cost-effectiveness analyses. For hemodialysis patients, the protection is only about half that of normal adults.

OUTLINE OF THE MODEL

Main Assumptions

The general model includes opportunities for screening, postexposure prophylaxis, and variations in compliance with the vaccination schedule. Because screening is mandatory in public vaccination programs for hepatitis B in Spain, the model starts with a decision node for the alternatives "screen" and "not screen." The costs of a possible infection with HBV vary according to the patient's history (not screened vs. screened, not vaccinated vs. vaccinated, etc.), and according to the degree of severity of the clinical consequences of infection.

Postexposure Prophylaxis

For unvaccinated persons, hepatitis-B vaccine series are initiated after accidental exposure. If the source is positive, one dose of hepatitis-B immune globulin is also given (1). Instead of vaccination, it is common to give one dose of HBIG immediately and a *second* dose of HBIG if screening confirms that the source was positive and the victim negative.

Saenz Gonzalez et al. (37) reported 1,980 cases of accidental exposure per 100,000 hospital employees. Screening of both source (HBsAg) and victim (HBsAg, anti-HBs, and HBc) was undertaken, and HBIG was injected. The result of testing was that 80% of victims and 50% of sources were negative. For zero-negative victims and positive source, a second dose of HBIG was injected; approximately 40% of the victims fit this scenario.

Postexposure prophylaxis with vaccination reduces the costs of screening, as only the source is screened. It also reduces the costs for HBIG. Because the costs of one series of vaccinations are less than one dose of HBIG, the total cost of this strategy is lower. The expected costs for postexposure prophylaxis are 11,650 pesetas for vaccination and 16,500 for prophylaxis in the screening/vaccination strategy. But discussion of this method will only complicate the model and not significantly affect the result of the analysis.

Postexposure prophylaxis is only relevant for hospital staff or other personnel in contact with contaminated material (syringes, needles, blood, etc.).

Compliance with the Vaccination Program

Compliance with a vaccination program is dependent on the target group, the efforts made, and the resources used to produce a high compliance. Studies of compliance have shown that not more than 50% of the hospital staff who were screened and found negative accepted vaccination. One reason for this could have been fear of AIDS. Now that a genetically produced vaccine is available, there should be less fear. Therefore, we will assume a 90% compliance for the first dose, 85% for the second, and 80%

for the third. Sensitivity analysis will be performed with a lower rate of compliance. For vaccination of newborns of carrier mothers, we can probably assume an even higher compliance, close to 100%, because of the special situation in which such a program is implemented. For high-risk patients we can also assume a high compliance rate, while other risk groups, for example, drug addicts, can be assumed to have a rather low compliance rate. Because low compliance means that there are costs without (or with reduced) benefits, the level of compliance is important for the cost-effectiveness of a vaccination strategy.

We assumed that the probability of infection is reduced 20% after the first dose, 50% after a second dose, and 90% after a third dose. For persons receiving only one dose, this is equivalent to the assumption that they, on average, have received protection for 1 year. Sensitivity analyses will be undertaken with the values 33%, 67%, and 98%, respectively.

Side Effects

When Mulley et al. (31) undertook their study, about 6,000 people had been vaccinated. No serious adverse effects had been reported, but they estimated that a serious reaction would occur with a frequency of 1 in 100,000 and that 10% of serious reactions would be fatal. Approximately 100 episodes of severe illness have been reported among 750,000 vaccinees (31).

Therefore, it is reasonable to conclude that serious side effects of the vaccine have not been underestimated. If one assumes a frequency of 1 in 100,000 for a serious reaction, and the costs of a serious reaction to be 350,000 pesetas (US $1 = 115 pesetas), this will add only 3.5 pesetas to the cost of vaccination.

Minor side effects, such as a transient fever or a sore arm, have occurred among approximately 25% of both vaccine and placebo recipients participating in clinical trials (31). The medical costs associated with these reactions are probably negligible. However, for the sake of completeness, we calculated that 1 person in 10 with a minor side effect will make an extra visit to a physician, which will cost 6,000 pesetas. These complications will add 150 pesetas to the costs of vaccination. Rivera et al. (34) estimated the costs of complications at 132 pesetas per vaccinated person, which accounted for 0.9% of an estimated total vaccination cost of 14,108 pesetas.

Externalities: Reduction in the Probability of Secondary Infection

Vaccination reduces not only the probability of infection for the vaccinated person but also the probability of other persons being infected. This benefit is important, particularly in vaccination programs for drug addicts and for children of carrier mothers. It is also important, but to a lesser extent, for health care workers. It was too complicated to model this benefit, but it is possible to take it into account by multiplying the costs of infection with a certain factor, for example, 1.15, if we assume that the secondary effect is 15% of the primary effect. Another benefit of vaccination is the prevention of delta infection. Apart from a few exceptions, delta infections occur only in drug addicts (30).

COSTS OF VACCINATION AND SCREENING

Cost of Vaccination

Vaccination costs include three doses of vaccine, handling and administration, and travel and time costs for the patient. A problem with costs of administration, travel, and patients' time is that these depend on the design of the vaccination program and the risk groups vaccinated.

Table 2. Summary of Vaccination Costs, in Pesetas

	1st dose	2nd dose	3rd dose	Total
Vaccine	1,800	1,800	1,800	5,400
Administration	100	100	100	300
Side effects	50	50	50	150
Time costs[a]	300	300	300	300
Total	2,250	2,250	2,250	6,750

[a] For hospital personnel.

Costs of handling and administration vary considerably. For individual vaccinations, it is reasonable to assume that the costs of administration are equal to the costs of a physician visit. If it is a program of mass vaccination, costs will be lower, but not negligible. Administration costs can be reduced if the vaccine is delivered in, for example, ready-to-use syringes. This will, of course, increase the costs for the producer of the vaccine.

The vaccination costs are shown in Table 2. Costs for administration of the vaccine were calculated by Rivera et al. (34) to be 189 pesetas for personnel and 15 pesetas for material, in 1982 prices. Rivera et al. calculated direct costs of side effects at 132 pesetas.

Time and travel costs for the patient are dependent on the specific risk group. For hospital staff, we assumed travel costs were zero, and that a maximum of 30 minutes were lost from work for each injection.

Costs of Screening

Saenz Gonzalez et al. (37) give the following costs for screening tests: anti-HBc, 736 pesetas; anti-HBs, 637 pesetas; and HBsAg, 474 pesetas. Given the screening strategy used in Spain (22), the average screening cost will be 952 pesetas per person screened. Time and travel costs for patients who are screened should also be taken into account. For health care workers, we will assume the same costs as for vaccination, 300 pesetas. Total costs per person for screening, therefore, will be 1,250 pesetas for this risk group.

The Cost-Effectiveness of Screening in Relation to Vaccination

If one assumes that the problem of false test results can be ignored, the threshold between vaccination and screening is determined by the costs of screening and vaccination. When the prevalence of HBV markers is lower than the ratio of screening costs to vaccination costs, vaccination will be less costly than screening. If one assumes that the costs of vaccination are 5,850 pesetas and the costs of screening are 950 pesetas, the ratio is 0.16. If the expected prevalence of serological markers is higher than this ratio, screening is cost-effective; otherwise, it is not. For health care personnel, the ratio is $1{,}250/6{,}750 = 0.19$ when time costs are included.

COSTS OF HEPATITIS-B INFECTION

Modeling Acute Infection

The first distinction must be made between asymptomatic (subclinical) and clinical cases. Clinical cases can be divided into mild, severe (icteric), and fulminant. The boundaries between different cases are not very strict. It may, for example, be very difficult to separate asymptomatic and mild cases.

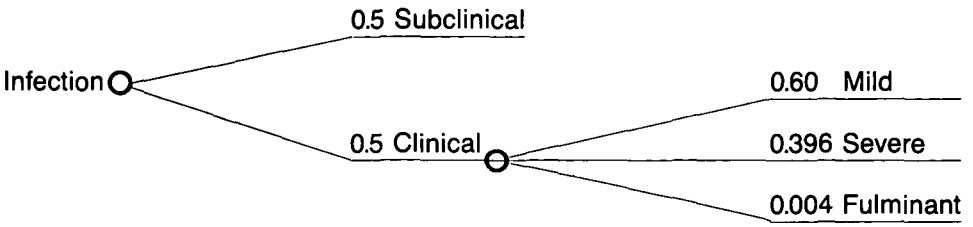

Figure 1. Model of acute outcome of infection.

Table 3. Probabilities for Different Chronic Outcomes of Hepatitis-B Infection

	Probability		
Outcome	High	Main	Low
Resolution	0.74	0.9	0.95
Carrier state	0.12	0.05	0.025
Persistent hepatitis	0.093	0.035	0.0175
Active hepatitis	0.047	0.015	0.0075

The basic probabilities are shown in Figure 1. Mild clinical hepatitis is associated with moderate pain and/or impairment and usually requires a visit to a physician. Severe symptoms can require a hospitalization. More precise assumptions about the costs of the different acute outcomes are shown in the section on costs.

Modeling Chronic Sequelae

For chronic outcomes, we distinguish between resolution, carrier, persistent, and active hepatitis. For fulminant hepatitis, we also include the probability of death. Probabilities for different chronic outcomes are based on three different assumptions. The first is based on the internationally accepted distribution used, for example, by Mulley et al. (31). We then make a sensitivity analysis using data from the Spanish study by Saenz Gonzalez et al. (37) as the high alternative for chronic outcome and newer data from Italy (6) and Greece (35) as the low alternative. Sensitivity analysis makes it possible for us to understand the importance of the severity of the chronic outcomes for the result of the cost-effectiveness analysis. Table 3 shows the model for chronic outcomes with the different probabilities used.

Direct Health Care Costs

Very few studies are published about the use of health care resources after hepatitis-B infection. This makes it necessary to calculate expected costs based on knowledge about medical management of the disease. Treatment of patients with hepatitis-B infection varies between physicians and hospitals. In addition, the great variability in the consequences of the disease for patients makes it difficult to calculate costs of hepatitis-B infection. The estimates in Tables 4 and 5 are based on the best information available and relate to other estimates, such as those by Mulley et al. (31). However, they must be viewed only as a reasonable average. We need more detailed cost studies linked to serious epidemiological investigation in order to answer questions about the consequences of hepatitis-B infection. Treatment of patients changes continuously over time because of progress in medical knowledge and treatment methods.

There is no need to discount the costs of acute hepatitis. We assume that the cost

Table 4. Direct Costs, in Pesetas, of Acute Hepatitis

Subclinical hepatitis	0
Anicteric hepatitis	
3 visits plus biochemical investigations (7,000 × 3 = 21,000)	21,000
Icteric hepatitis	63,000
Hospitalized (25%) (0.25 × 168,000)	42,000
7 hospital days at 20,000 per day	
Convalescent visits (3 × 7,000)	
Postconvalescent visit, including HBsAg/anti-HBs assay	
Nonhospitalized (75%) (0.75 × 28,000)	21,000
Initial physician visit, including HBsAg/anti-HBs assay	
Convalescent visits (3 × 7,000)	
Postconvalescent visit, including HBsAg/anti-HBs assay	
Fulminant hepatitis	300,000
Fatal (70%) (0.70 × 255,000)	180,000
7 days plus intensive care and special investigations (7 × 36,500 = 255,000)	
Nonfatal (30%) (0.30 × 400,000)	120,000
15 days of hospitalization at 20,000 = 300,000 plus special investigations and follow-up	

Table 5. Direct Costs, in Pesetas, of Chronic Hepatitis

Resolution	0
Carrier	54,000
Persistent	144,000
Active	470,000

of resolution is zero. For the carrier state, we can follow Mulley et al. (31) and assume that there will be a physician visit each year plus laboratory tests with HBsAg at a total cost of 7,000 pesetas. If one assumes that the carrier state will last an average of 10 years, total costs will be 54,000 pesetas with a discount rate of 5%. Saenz Gonzalez et al. (37) estimated the annual medical costs to be 32,052 pesetas for asymptomatic carriers.

For persistent hepatitis, we assume an initial 3-day hospital visit for a liver biopsy and other tests. We assume an annual physician visit plus laboratory tests:

- 3 days of hospitalization: 3 × 20,000 — 60,000 pesetas
- Liver biopsy — 30,000 pesetas
- Total hospitalization costs — 90,000 pesetas

To this we add one follow-up visit including laboratory testing discounted at 5% for

- 5 years = 4.33 × 7,000 = 30,310 pesetas
- 10 years = 7.72 × 7,000 = 54,040 pesetas
- 20 years = 12.46 × 7,000 = 87,220 pesetas

At an average follow-up period of 10 years, the total costs for persistent hepatitis is 90,000 + 54,000 = 144,000 pesetas.

For active hepatitis, we assume the same costs as for persistent hepatitis but add that for years 2–10, 20% of the patients have a repeated episode of hospitalization and liver biopsy, and for years 11–20, this share increases to 40%. Total costs discounted at 5% amount to 470,000 pesetas.

Table 5 summarizes our estimates of the direct costs of chronic hepatitis. These estimates can be compared with Saenz Gonzalez et al.'s (37) estimates for chronic hepatitis (persistent plus active), which were 370,000 pesetas for the first year and 92,417 pesetas for years 2–5. Their figures are somewhat higher, but the order of magnitude is not too different.

Indirect Costs

Indirect costs are resources lost because of morbidity and premature mortality. Because indirect costs are calculated as lost earnings, they are dependent on the age, sex, and employment situation of each risk group. A sample of clinical cases of hepatitis B tested showed that two-thirds of the cases were in the age-group 15–45 years (22).

Because hepatitis-B infection is most common among economically active groups, the indirect costs of the disease can be very important. Earlier studies of costs of clinical (icteric) hepatitis B have also shown that indirect costs exceed direct costs, for example, Adler et al. (2) and Rivera et al. (34). The most detailed calculation has been done for the United States by Schatz et al. (39). Total annual cost in the United States is estimated at $365 million. Direct costs amount to $225 million (60%).

Total cost is equally distributed between acute and chronic costs. They assume that an acute, nonhospitalized case is associated with, on average, a loss of 21 days of work. Hospitalized patients lose 43 days of work. For hospital workers, it is particularly relevant to take indirect costs into account, because in this group, by definition, 100% are employed. The unemployment rate is also low, indicating that it is difficult to substitute time lost from work with otherwise unemployed workers.

For patients in mental health hospitals, patients on hemodialysis, drug addicts, and prisoners, the loss of productive time will probably in most cases be very low. However, for family members of HBV carriers, and for recruits in the armed forces, loss of productive time (or loss of training time) can be of importance.

The following estimates for indirect costs are for medical personnel only. Saenz Gonzalez et al. (37) estimated the following number of days of sick leave due to acute hepatitis:

- Resolution — 100.5 days ± 59.5
- Carrier — 93.7 days ± 31.8
- Chronic hepatitis — 215.2 days ± 151.5
- Average — 118.4 days ± 88.7

Rivera et al. (34) calculated indirect costs per case of hepatitis to be 631,000 pesetas, equivalent to about 96 days lost from work at 6,569 pesetas per working day. They calculated costs per day assuming 250 working days per year.

To relate these data to our model, we make a distinction between the first and subsequent years. For the first year, we assume that only the symptomatic cases lose time from work. We then assume that in subsequent years only patients with persistent and active hepatitis lose time from work with an average of 1 and 2 weeks, respectively (see Table 6).

Table 7 summarizes the direct and indirect costs of infection. As is shown in Table

Table 6. Indirect Costs, in Pesetas, of Hepatitis-B Infection

	First year	Subsequent	Total
Asymptomatic			
Resolution	0	0	0
Carrier	0	0	0
Persistent	0	7 × 4,500 = 31,500	392,553[a]
Active	0	14 × 4,500 = 63,000	785,106[a]
Mild symptoms			
Resolution	25 × 4,500 = 112,500	0	112,500
Carrier	25 × 4,500 = 112,500	0	112,500
Persistent	50 × 4,500 = 225,000	7 × 4,500 = 31,500	617,553
Active	50 × 4,500 = 225,000	14 × 4,500 = 63,000	1,010,106
Icteric/fulminant			
Resolution	100 × 4,500 = 450,000	0	450,000
Carrier	100 × 4,500 = 450,000	0	450,000
Persistent	150 × 4,500 = 675,000	7 × 4,500 = 31,500	1,067,553[a]
Chronic	150 × 4,500 = 675,000	14 × 4,500 = 63,000	1,460,106[a]
Fatal	0	0	0

[a] Calculated for 20 years discounted at 5%.

Table 7. Direct and Indirect Costs, in Pesetas, of Hepatitis-B Infection

	Nonvaccinated			Vaccinated
	High	Main	Low	Main
Direct costs	61,000	34,000	27,000	12,000
Indirect costs	207,000	153,000	138,000	65,000
Total	268,000	187,000	165,000	77,000

7, indirect costs far exceed direct costs. This is consistent with other studies from, for example, Spain and the United Kingdom. When we compare these studies with those in the United States, where direct and indirect costs are of the same magnitude, we must remember that the direct costs are much higher in the United States than in Spain and the United Kingdom.

EFFECTS ON QUALITY-ADJUSTED LIFE YEARS

Cost-benefit studies of vaccination programs have rightly been criticized for not including a measure of health benefit (46). One way to include such a measure is to estimate the effect of the vaccination program in terms of quality-adjusted life years (QALYs). One QALY is equal to one fully healthy year of life.

If we know the effect of a vaccination program on QALYs, we can use it in two ways. The first is as an effectiveness measure for calculations of costs per QALY. Such a measure can be used for comparison with other programs or risk groups. Second, we can assign a value to each QALY saved through the program. This makes it possible to add the health benefits to the direct and indirect costs.

Our calculations are done in four stages: (a) an estimate of the effect of infection on life expectancy; (b) an estimate of the effect of infection on quality of life; (c) an

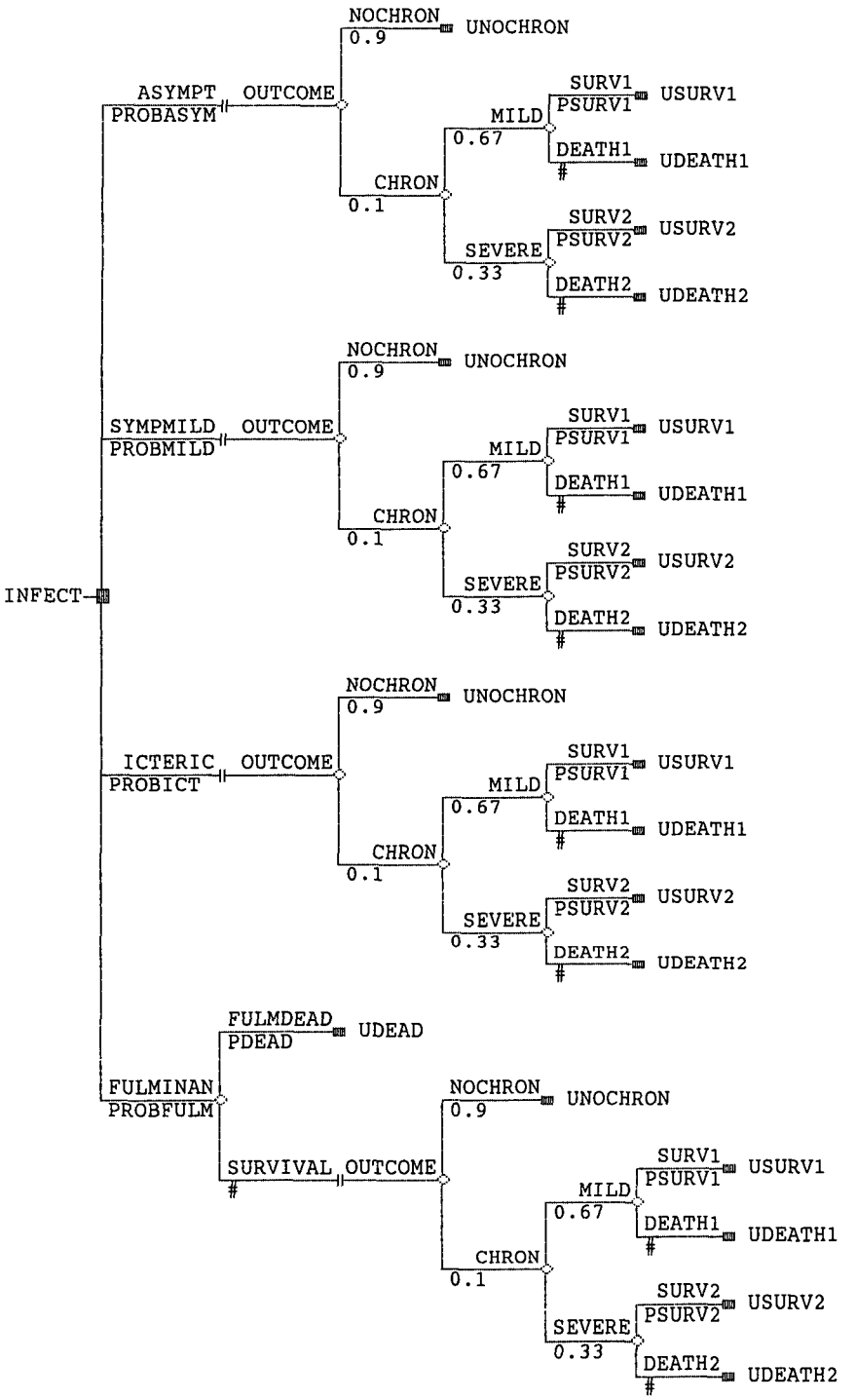

Figure 2. Model for calculating loss of life expectancy due to hepatitis-B infection.

Table 8. Sensitivity Analysis for Life Expectancy after Infection for Different Assumptions about Survival[a]

	High	Main	Low
PSURV1	0.90	0.80	0.70
PSURV2	0.60	0.50	0.40
USURV1	40	40	40
USURV2	40	40	40
UDEATH1	30	30	30
UDEATH2	20	20	20
Life expectancy	39.61	39.48	39.35
RISK U = 0	0.00140	0.00140	0.00140
RISK U = 20	0.01318	0.01648	0.01977
RISK U = 30	0.00669	0.01338	0.02007
RISK U = 40	0.97873	0.96874	0.95876

[a] See text for explanation of assumptions.

estimate of the loss in QALYs because of infection; and (d) an estimate of the costs of a QALY lost because of hepatitis-B infection.

The model used to estimate the number of years of life lost due to infection is shown in Figure 2. It is assumed that the average age when infected is 35 years for hospital personnel and that life expectancy is 40 more years. Life expectancy at 35 years of age is 39.5 years for men and 44.8 years for women in Spain.

We made the following assumptions:

- PSURV1 = 0.80 (the probability that a mild infection does not reduce life expectancy)
- PSURV2 = 0.50 (the probability that a severe infection does not reduce life expectancy)
- USURV1 = 40
- UDEATH1 = 30 (life expectancy reduced by 10 years)
- USURV2 = 40
- UDEATH2 = 20 (life expectancy reduced by 20 years)

With these assumptions, life expectancy after infection is 39.48 years. This means a reduction in length of life by only 1.25%. If we do a risk analysis using these assumptions, the number of deaths in a cohort of 100,000 infected will be: death from fulminant hepatitis, 140; death from cirrhosis or PHC, 2,986. This is of the same magnitude as has been estimated for the United States (2,500).

A sensitivity analysis with higher and lower probabilities of survival is shown in Table 8. We also tried a quality adjustment of years of life lost, using the Rosser/Williams (25) method of quality adjustment. The quality adjustment is made in two steps. First, the patient's health status is classified in two dimensions, disability and distress. Then the different "cells" in the matrix are valued on a scale where healthy = 1.0 and dead = 0. For the full valuation matrix, see Kind et al. (25). It is extremely difficult to classify patients who have an HBV infection according to the Rosser/Williams scale. We make the following assumptions: (a) because the acute phase is short, we do not in-

Table 9. Utility Weights with Rating Scale (RS), Standard Gamble (SG), and Time Trade-Off (TT) for Mild and Severe Hepatitis[a]

	RS		SG		TT	
	Mild	Severe	Mild	Severe	Mild	Severe
United States	0.53 (0.2)	0.25 (0.2)	0.79 (0.3)	0.56 (0.4)	0.86 (0.2)	0.54 (0.3)
Sweden	0.66 (0.2)	0.34 (0.3)	0.91 (0.1)	0.60 (0.3)	0.83 (0.1)	0.58 (0.3)
Mean[b]	0.60	0.30	0.85	0.58	0.84	0.56

[a] Figures in parentheses are standard deviations.
[b] Used for calculations.

clude it in our quality adjustment; (b) patients with a mild chronic outcome are assumed to be in state IB, with no disability but mild distress (weight 0.995); and (c) patients with a severe chronic outcome are assumed to be in state IIB, with slight social disability and mild distress (weight 0.986).

The reduction in QALYs caused by infection will then be, for mild chronic outcome:

- USURV1 $0.995 \times 40 = 39.8$
- UDEATH1 $0.995 \times 30 = 29.8$

and for severe chronic outcome:

- USURV2 $0.986 \times 40 = 39.44$
- UDEATH2 $0.986 \times 20 = 19.72$

The expected number of QALYs is 39.45, compared with 39.48 when no quality adjustment is made. Thus, adjustment for quality of life does not significantly affect our result. One obvious reason for this outcome is that the valuation matrix we used shows rather small reductions in quality of life for those illness states that can be judged relevant after a hepatitis-B infection.

Because of this, we carried out an experimental sensitivity analysis on the quality adjustment. In Sweden and the United States, a small group of university students (11 Swedish students and 10 U.S. students) were asked to value mild and severe hepatitis. The methods used were rating scale, time trade-off, and standard gamble. The results are shown in Table 9.

The difference between these results and the results obtained with the Rosser/Williams matrix (25) is striking. It is also interesting to note that the utility weights implied by a rating scale are considerably lower than the weights implied by the standard gamble and time trade-off scaling methods. If we use the average utility weights from the different methods in Table 9 (0.76 for mild and 0.48 for severe), the expected number of QALYs in the model will be 38.35, varying still more from the 39.45 QALYs obtained earlier with the Rosser/Williams method.

RESULTS

Our empirical estimation is for health care personnel, the largest high-risk group for hepatitis B in Spain. We assume that vaccination is undertaken only in combination with a screening program. We further assume that 90% of those screened and found

to be negative will be vaccinated with one dose of vaccine. For the second dose and third dose, compliance is reduced 5% and 10%, respectively.

The attack rate is defined for the screened (and negative) population. When no screening is undertaken, the attack rate has to be adjusted for the proportion of the screened population that is marker positive.

Because vaccination will protect for more than 1 year, we have entered a duration factor D into the model. If we assume that protection lasts for 5 years, D will be given the value 5.0. Because it is appropriate to discount future benefits, the factor D will also be used to incorporate the discount rate in the sensitivity analysis. Costs are assigned to the terminal nodes; for example, a person not screened, not vaccinated, not exposed, and not infected will end up with zero cost. A person screened and vaccinated with three doses of vaccine will end up with costs of 1,250 plus 6,750 pesetas, a total of 8,000 pesetas if not infected.

Table 10 summarizes the expected medical costs per patient with and without vaccination. The cost per patient increases with the attack rate for both vaccinated and unvaccinated persons. However, costs increase faster for those who are not vaccinated, and at an attack rate of 4.9%, both alternatives cost the same. At this threshold value, the cost of the vaccination program is just offset by savings in medical expenditures from fewer cases being infected. The threshold value is 2.7% for the high cost of the infection alternative and 6.3% for the low cost.

If one assumes that the rate of attack averages 1.0% for health care personnel, the expected costs per person for screening and vaccination are 6,000 pesetas compared with 1,600 pesetas if no vaccination is undertaken. This means that the net cost for a vaccination program for all hospital personnel, 340,000 persons, is $340{,}000 \times (6{,}000 - 1{,}600) = 1{,}500$ million pesetas. We will now see how sensitive our result is to changes in some of the basic assumptions. This sensitivity analysis is summarized in Table 11.

Discounting does not significantly change the result. However, extending the benefits to 10 years at a 5% discount rate reduces the threshold for the attack rate from 5.7% to 3.2%. The probability of accidental exposure does not affect the result of the analysis, and neither does the assumption about the share of the screened population that is found to be marker positive. If the probability of markers is less than 0.19, it is less expensive to vaccinate without prior screening.

The result is very sensitive to the cost of the vaccine. A reduction in the price of one dose from 1,800 to 1,500 pesetas reduces the threshold for the attack rate from 4.9% to 4.4%. Improving compliance and the efficacy of the vaccine reduces the threshold, but the sensitivity is not very high.

Table 12 shows the expected cost per patient when indirect costs are included. The expected costs per person are 7,700 pesetas for no screening/no vaccination and 7,200 pesetas for screening/vaccination for hospital personnel at an attack rate of 1.0% and a marker-positive rate of 20%.

These results mean that for 340,000 hospital employees, the screening/vaccination program will save $340{,}000 \times (7{,}700 - 7{,}200) = 170$ million pesetas. If the high alternative of costs of infection is used, the threshold for the attack rate is reduced to 0.6%. As shown in Table 11, the result is not very sensitive to the high or low estimate of indirect costs. However, including indirect costs reduces the threshold for the attack rate from 5% to 1%.

Table 13 presents the cost-effectiveness ratio measured as cost per QALY. The cost-effectiveness ratio is calculated both excluding and including indirect costs. It is also shown for 0% and 5% discount rates. The cost per QALY increases when the risk

Table 10. Expected Direct Medical Costs, in Pesetas, per Patient with and without Vaccination at Different Rates of Attack

	High		Main		Low	
Attack rate (%)	Vaccinated	Nonvaccinated	Vaccinated	Nonvaccinated	Vaccinated	Nonvaccinated
1	6,200	2,700	6,000	1,600	6,000	1,400
2	6,600	5,100	6,300	3,000	6,200	2,400
3	7,000	7,600	6,500	4,400	6,400	3,500
4	7,400	10,000	6,700	5,700	6,600	4,600
5	7,800	12,400	7,000	7,100	6,800	5,700
Threshold	2.7%		4.9%		6.3%	

Table 11. Sensitivity Analysis for the Attack Rate: Main Alternative for Cost of Infection

Variable	Threshold for attack rate (%)
Period of protection (yr)	
5	5.7
10	3.2
Discounting rate (%)	
0	4.9
5	5.7
Probability of accidental exposure (%)	
0	5.2
1	5.0
2	4.9
3	4.8
4	4.7
Probability of positive marker (%)	
10	4.8
20	4.9
30	5.0
40	5.2
Compliance (%)	
100	4.87
80	4.93
50	5.05
Vaccine efficacy (%)	
90	4.93
98	4.74
Price for one dose of vaccine (pesetas)	
2,100	5.5
1,800	4.9
1,500	4.4
1,200	3.8
900	3.3
600	2.8
300	2.2

of infection is reduced. The gross domestic product (GDP) per capita in Spain is about 750,000 pesetas. If one assumes that the decision maker values an extra QALY at 750,000 pesetas, risk groups with an attack rate of 0.35% or higher should be vaccinated, if we include both direct and indirect costs and discount at 5%. If only direct costs are counted, the threshold is about 0.5%. We also performed a sensitivity analysis on cost per QALY using the utility weights implied by the experiment illustrated in Table 9.

The cost per QALY is extremely sensitive to the method chosen for quality adjustment. Our experimental data on quality adjustment implies a cost per QALY at only about a third of that obtained with the Rosser/Williams method (25). If one assumes again that the decision maker values an extra QALY at 750,000 pesetas, risk groups with an attack rate of approximately 0.15% or higher should be vaccinated.

Table 12. Expected Direct plus Indirect Costs, in Pesetas, per Patient with and without Vaccination at Different Rates of Attack

	High		Main		Low	
Attack rate (%)	Vaccinated	Nonvaccinated	Vaccinated	Nonvaccinated	Vaccinated	Nonvaccinated
0.5	6,700	5,600	6,500	4,000	6,400	3,600
1.0	7,600	11,000	7,200	7,700	7,100	6,900
1.5	8,500	16,300	7,900	11,500	7,700	10,000
2.0	9,500	21,600	8,600	15,200	8,300	13,400
2.5	10,400	27,000	9,300	18,900	9,000	16,700
Threshold	0.6%		0.9%		1.0%	

Table 13. Cost, in Pesetas at 5% Discount Rate, per QALY at Different Attack Rates

	Cost per QALY			
	Direct cost only		Direct plus indirect costs	
Attack rate (%)	Rosser/ Williams (25)	Jönsson et al.	Rosser/ Williams (25)	Jönsson et al.
0.1	3,500,000	1,200,000	3,200,000	1,100,000
0.2	1,800,000	600,000	1,500,000	500,000
0.3	1,200,000	400,000	900,000	200,000
0.4	900,000	300,000	590,000	200,000
0.5	700,000	230,000	400,000	130,000
0.6	570,000	190,000	270,000	91,000
0.7	480,000	160,000	180,000	63,000
0.8	410,000	140,000	110,000	38,000
0.9	360,000	120,000	60,000	20,000
1.0	320,000	110,000	18,000	6,000

DISCUSSION

Cost-benefit and cost-effectiveness studies of vaccination against hepatitis-B have generally included only medical costs (20;31). This restriction can be defended if the decision maker's main interest is to know how the program affects the health budget. However, most countries do not have a single health budget; vaccination programs are usually funded separately from medical services. The decision maker in charge of vaccinations cannot benefit from calculated savings in health care costs that are due to fewer infections. This fact means that the usual approach to cost-benefit analysis is consistent neither with incentives for cost minimization nor with the relevant concept of social cost. Only in situations where savings in health care costs can be assumed to correspond to a minimum value of health improvement that exceeds the cost of prevention can a study be used for conclusions about the net social value of the program. Ideally, such a study should also take into account the savings in other preventive expenditures due to the protection given by the vaccination. However, since preventive measures against hepatitis-B infection are the same as those against HIV, this has no practical significance in this case. For a more detailed discussion about the relation between cost saving and social benefit, see Berger et al. (5).

The cost-saving approach to prevention has a legitimate place in economic evaluation when the decision maker is looking for different alternatives for containing health care expenditures. Ideally, such an approach should also take into account effects on health care expenditures from changes in probabilities of other diseases. However, such financial studies are not a substitute for social cost-benefit studies.

Studies of the economic costs of hepatitis B have revealed that indirect costs due to loss of production are a significant part of the direct costs of hepatitis B. It seems natural to include these costs in a more comprehensive measure of the social cost of hepatitis-B infections and the benefits of vaccination.

This study shows that inclusion of indirect costs reduces the threshold for vaccination from a 5% to 1% risk of infection for the largest risk group, hospital personnel. Because the expected attack rate in this high-risk group is estimated to be 1.5%, the inclusion of indirect costs has a significant effect on the outcome of the study.

Direct and indirect costs underestimate the true social costs of hepatitis-B infec-

tion. A measure of health benefit should be included in the estimation. We estimated the increase in QALYs from the vaccination program. This makes it possible to calculate net cost per QALY at different risks of infection. Vaccination programs against hepatitis B can then be compared with other interventions that improve the health of the population (44;47).

Ideally, estimates of improvement in quantity and quality of life should be based on data from controlled trials for different risk groups. Lack of such data makes it necessary to make approximations. However, we think it is better to include the best available estimates than to disregard health benefits. There is a need for more careful studies of the quality of life of patients suffering from chronic sequelae of hepatitis-B infections.

Russell (36) has pointed out that including both the value of improved health and increased earnings results in counting some health effects twice. While this is a valid point, it has to be qualified. First, the major health benefit from the vaccination program is an increase in life expectancy. Because we have not counted any indirect costs due to reduced mortality, this measure counts nothing twice. Second, the degree of double counting depends on how quality of life has been adjusted. We cannot rule out the possibility that the weights in the Rosser/Williams matrix (25) are influenced by opportunities to earn income. However, the existence of health insurance and cash benefits in case of sickness or disability makes it reasonable to assume that respondents take only limited account of the effect of their health status on their income when asked to state their preferences for different health states. When performing the valuation experiment, the students were instructed to value "pure" health effects and not include the value of extra earnings. Therefore, we argue that taking indirect costs into account in this study does not imply any double counting.

CONCLUSIONS

Cost and benefits from vaccination against hepatitis B depend on epidemiological, clinical, and economic factors that show significant variation between risk groups and over time. Therefore, a generally applicable computer model was developed as a tool for decision making. The model allows easy changes in basic assumptions as well as opportunities for sensitivity analysis for uncertain variables.

Estimates were undertaken for health care personnel, the major risk group for hepatitis B in Spain. The benefits from vaccination included reductions in direct and indirect costs from fewer infections as well as improvements in length and quality of life.

The result shows the importance of including not only savings in medical expenditures but also reductions in indirect costs in the estimate of benefit. A vaccination program will reduce the total health care expenditures for hepatitis B only if the attack rate is higher than 4.9%. However, if reductions in indirect costs are included, the threshold for the attack rate is reduced to 0.9%, which is below the estimated average risk of infection of 1.0%.

Calculating the gross and net cost per QALY makes it possible to compare vaccination against hepatitis B with other preventive and curative health investments. If one assumes that the decision maker is prepared to use resources for prevention if the cost of producing 1 QALY is less than the average GDP, all hospital personnel with a higher risk than 0.35% should be vaccinated.

NOTE

[1] Chronic virus carrier = person who remains actively infected with HBV for more than 6 months.

REFERENCES

1. ACIP. Recommendations for protection against viral hepatitis. *Morbidity and Mortality Weekly Report*, 1985, 34, 313-35.
2. Adler, M. W., et al. Should homosexuals be vaccinated against hepatitis-B virus? Cost and benefit assessment. *British Medical Journal*, 1983, 80, 139-48.
3. Aparicio, J. A., Dean, C. A., Tellez, A. R., et al. Aspectos de la transmisión intrafamiliar del virus de la hepatitis B en una familia de raza gitana. *Medicina Clínica (Barcelona)*, 1987, 88, 828.
4. Bengoechea, M. G., Cortes, A., Francisco, C., et al. Infección por el virus de la hepatitis B en los odentólogos de Guipuzcoa. *Medicina Clínica (Barcelona)*, 1987, 88, 179-81.
5. Berger, M. C., Blomquist, G. C., Kenkel, D., & Tolley, G. S. Valuing changes in health risks: A comparison of alternative measures. *Southern Economic Journal*, 1987, 53, 967-84.
6. Bortollotti, A., et al. Chronic evolution of acute hepatitis type B: Prevalence and predicative markers. *Infection*, 1986, 14, 64-67.
7. Bove, J. R. Transfusion-associated hepatitis and AIDS: What is the risk? *New England Journal of Medicine*, 1987, 317, 242-45.
8. Bruguera, M. La hepatitis B en el personal sanitario. *Medicina Clínica (Barcelona)*, 1986, 86, 676-80.
9. Bruguera, M., Ardiaca, C., Semente, M., et al. Epidemiologia de la hepatitis B en personal hospitalario. *Revista de Medicina Clínica*, 1980, 74, 1-4.
10. Bruguera, M., Caballeria, J., Acero, D., et al. Transmisión intrafamiliar del virus de la hepatitis B. *Gastroenerologia y Hepatologia*, 1980, 3, 13-18.
11. Bruguera, M., Tapias, J. M. S., Latorre, X., et al. Marcadores serológicos de la hepatitis A y B en los homosexuales masculinos. *Medicina Clínica (Barcelona)*, 1987, 88, 869.
12. Buti, M., Esteban, R., Sanjose, R., et al. Prevalencia de marcadores de infección de los virus de la hepatitis B: Delta y HLTV-III en deficientes mentales. *Revista Clínica Española*, 1986, 179, 175-77.
13. Caballero, L. R., Lopez, F. V., Manuel, C. A., et al. Prevalencia de los marcadores séricos del virus B de la hepatitis en varones heterosexuales con enfermedas de transmisión sexual. *Medicina Clínica (Barcelona)*, 1986, 87, 309-12.
14. CDC. Recommendations for prevention of HIV transmission in health-care settings. *Morbidity and Mortality Weekly Report*, 1987, 36, 2S.
15. Coursaget, P., Yvonnet, B., Chotard, J., et al. Age- and sex-related study of hepatitis B virus chronic carrier state in infants from an endemic area (Senegal). *Journal of Medical Virology*, 1987, 22, 1-5.
16. Economic aspects of communicable diseases. *European Reports and Studies*, No. 68. Copenhagen: WHO Regional Office for Europe, 1982.
17. Fos, E., Dieguez, A., Hierro, F. R., et al. Infección por el virus de la hepatitis B en la población de raza gitana. *Medicina Clínica (Barcelona)*, 1986, 86, 304.
18. Genesca, J., Esteban, J. I., Esteban, R., et al. Difusión intrafamiliar del virus de la hepatitis B. Estudio de contactos familiares de portadores crónicos. *Medicina Clínica (Barcelona)*, 1986, 87, 271-74.
19. Hadler, S. C., Francis, D. P., Maynard, J. E., et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. *New England Journal of Medicine*, 1986, 315, 209-14.
20. Hatziandreu, E. I., et al. A cost-effectiveness analysis of vaccination against hepatitis-B infection (paper presented at the Third Annual ISTAHC Meeting).
21. Horisberger, B., & Jönsson, B. Economic burden of hepatitis-B in Spain (mimeo).
22. Instituto Nacional de Sanidad, Centro Nacional de Microbiologia, Virologia e Inmunologia Sanitarias, Majadahonda, Madrid, May 27, 1986.
23. Jauregui, S. J. M., Garay, S. C. F., Odriozola, M. P., et al. Prevalencia de infección por virus de la hepatitis (VHB) en drogadictos asintomáticos. *Medicina Clínica (Barcelona)*, 1984, 82, 13-15.

24. Jönsson, B. Cost–benefit analysis of hepatitis-B vaccination. *Postgraduate Medical Journal*, 1987, 63(suppl. 2), 27–32.
25. Kind, P., Rosser, R., & Williams, A. Valuation of quality of life: Some psychometric evidence. In M. W. Jones-Lee (ed.), *The value of life and safety.* Amsterdam: Elsevier/North Holland, 1982.
26. Kumar, M. L., Dawson, N. V., McCullough, A. J., et al. Should all pregnant women be screened for hepatitis B? *Annals of Internal Medicine*, 1987, 107, 273–77.
27. Leal, M., & Lissen, E. Infección por el virus de la hepatitis B en prostitutas: Un problema de la salud pública. *Medicina Clínica (Barcelona)*, 1986, 87, 326–27.
28. Leal, M., Ollero, M., Garcia de Pesquera, F., et al. Prevalencia de marcadores séricos de los virus de la hepatitis A y B en varones homosexuales andaluces. *Medicina Clínica (Barcelona)*, 1985, 84, 757–58.
29. Miranda, M. L., Lissen, E., Vinuesa, M., et al. Hepatitis vírica en pacientes hemofílicos tratados con concentrados comerciales de factor VIII y IX. *Medicina Clínica (Barcelona)*, 1985, 84, 516–19.
30. Moestrup, T., et al. Clinical aspects of Delta infection. *British Medical Journal*, 1983, 286, 87–89.
31. Mulley, A. G., Silverstein, M. D., & Dienstag, J. L. Indications for use of hepatitis-B vaccine, based on cost-effectiveness analysis. *New England Journal of Medicine*, 1982, 307, 644–52.
32. Okada, K., Kamiyama, I., Inomata, M., et al. E antigen and anti-e in the serum of asymptomatic carrier mothers as indicators of positive and negative transmission of hepatitis B virus to their infants. *New England Journal of Medicine*, 1976, 294, 746–49.
33. Remis, R. S., Rossignol, M. A., & Cane, M. A. Hepatitis B infection in a day school for mentally retarded students: Transmission from students to staff. *American Journal of Public Health*, 1987, 77, 1183–86.
34. Rivera, F., et al. Análisis costo-beneficia de un programa de vacunatión contra la hepatitis-B en personal sanitario hospitalario. *Medicina Clínica (Barcelona)*, 1984, 83, 611–14.
35. Roumeliotou-Karayannis, A., et al. How often does chronic liver disease follow acute hepatitis-B in adults? *Infection*, 1985, 13, 174–76.
36. Russell, L. *Is prevention better than cure?* Washington, DC: The Brookings Institution, 1986.
37. Saenz Gonzalez, M. C., et al. (Groupo Español de Estudio de la Hepatitis B). Hepatitis-B en personal hospitalario: Morbilidad, exposición accidental, vacunación, y análisis de costes. *Medicina Clínica (Barcelona)*, 1987, 88, 232–36.
38. Sanchez-Quijano, A., Rivera, F., Lissen, E., et al. Prevalencia de los marcadores séricos del virus B hepatitis en el personal sanitario y no sanitario de un hospital general. *Medicina Clínica (Barcelona)*, 1984, 83, 1–3.
39. Schatz, B. L., Kane, M. A., & Francis, D. P. The economic effects of hepatitis-B in the United States (mimeo). Phoenix, AZ: Centers for Disease Control.
40. Seeff, L. B., Beebe, G. W., Hoofnagle, J. H., et al. A serologic follow-up of the 1942 epidemic of postvaccination hepatitis in the United States Army. *New England Journal of Medicine*, 1987, 316, 965–70.
41. Stevens, C. E., Alter, H. J., Taylor, P. E., et al. Hepatitis B vaccine in patients receiving hemodialysis—Immunogenicity and efficacy. *New England Journal of Medicine*, 1984, 311, 496–501.
42. Subero, R. C., Fernandez, F. C., Castiel, J. F., et al. Estudio de las enfermedades profesionales diagnosticadas en un período de cuatro años al personal del hospital clínico de San Carlos de Madrid. *N Arch Fac Med*, 1984, 42, 153–59.
43. Szmuness, W., Stevens, C. E., Harley, E. J., et al. Hepaptitis B vaccine in medical staff of hemodialysis units—Efficacy and subtype cross-protection. *New England Journal of Medicine*, 1982, 307, 1481–86.
44. Torrance, G. W. Measurement of health state utilities for economic appraisal. *Journal of Health Economics*, 1986, 5, 1–30.

45. *Viral vaccines and antiviral drugs.* WHO Technical Report Series, No. 693. Geneva: WHO, 1983.
46. Weisbrod, B. A., & Huston, J. H. Benefits and costs of human vaccines in developed countries: An evaluative survey. PMA Cost-Effectiveness of Pharmaceuticals, Report 2, 1983.
47. Williams, A. Economics of coronary artery bypass grafting. *British Medical Journal*, 1985, 291, 326–29.
48. Hollinger, F. B. Hepatitis B virus. In B. N. Fields, D. M. Knipe et al. (eds.), *Virology.* New York: Raven Press, 1990, 2171–236.