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Vaccination against hepatitis B virus in Spain: a cost-effectiveness analysis

Roberto Garuz*[1], José Luis Torrea†, José María Arnal‡, Tarsicio Forcen§, Cristina Trinxet‖, Francisco Anton¶ and Fernando Antoñanzas[#]

A cost-effectiveness analysis was made to determine the effectiveness of the following strategies of mass immunization with the new recombinant vaccine against the hepatitis B virus in Spain: vaccination of adolescents, newborns, both populations, and vaccination plus passive immunization of newborns of HBsAg positive mothers. Decision trees supported on Markov models with Monte Carlo simulation have been used for the calculation of costs of the disease, and a mathematical model of differential equations was used for the simulation of the potential effectiveness of vaccination. The costs considered were those associated with the vaccination and travel of subjects, diagnosis, and treatment of the disease. The results are presented as additional cost or saving per case of infection prevented. In all assumptions, results showed that the most effective strategy for mass vaccination was the combination of vaccinating all adolescents together with active and passive immunization of children born to HBsAg positive mothers. © 1997 Elsevier Science Ltd.

Keywords: cost-effectiveness, vaccine, hepatitis B

Infection by hepatitis B virus (HBV) is a major public health concern in Spain. It is estimated that 60000 new infections occur every year, although only approximately 20% are symptomatic[1]. There is serological evidence of previous contact with the virus in at least 20% of the adult population. Moreover, about half a million people are chronic virus carriers, the prevalence being especially high in young adults[2,3]. The seroepidemiological surveys conducted in special collectives and in the general population indicate, in our environment, an epidemiological pattern of intermediate endemicity, similar to that of other Mediterranean countries[4].

Vaccination is the main method currently available to reduce the morbidity associated with HBV. In 1982 a vaccine derived from human plasma became available. Its manufacturing, however, limited the quantities available and conditioned its high price. These restrictions determined the vaccination strategies, due to its high cost-effectiveness, towards population groups with high risk practices[5].

*Primary Care Direction, Area 3, Zaragoza, Spain. †Department of Mathematics, Autonomous University, Madrid, Spain. ‡Actur Health Center, Zaragoza, Spain. §Tafalla Health Center, Navarra, Spain. ‖Catalonian Health Service, Barcelona, Spain. ¶Hospital San Millán-San Pedro, Logroño, Spain. [#]Department of Economics, University of La Rioja, Logroño and Soikos, Barcelona, Spain. [1]To whom correspondence should be addressed. C/Julio Garcia Condoy, 17. 4° B. 50015 Zaragoza, Spain.
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In the light of the experience acquired during those years, it has become apparent that this vaccination policy has not fulfilled initial expectations, with poor results due to the low level of compliance of vaccination programs in the higher risk groups, being in many cases immunization offered too late. On the other hand, it should not be forgotten that more than 30%[6] of infected people have no recognized risk practices.

In 1986 a new hepatitis B vaccine obtained by genetic engineering became available. Its efficacy (85–95%)[7–10] is identical to that of the existing vaccine, and its side-effects and adverse reactions are mild or benign in character[11,12]. The new recombinant vaccine is obtained from a yeast, in which a plasmid containing the gene responsible for HBsAg, the viral particle capable of inducing an immune response, is inserted. Thus, the original vaccine restraints have disappeared: the new vaccine can be obtained in unlimited amounts and its price is substantially lower. The recommended schedule for immunization comprises three vaccine doses, the last two separated by one and six months respectively from the first dose, a schedule which produces an adequate immune response in young and healthy subjects. This new setting has prompted the reappraisal of the policy to vaccinate only the groups at risk, after a screening for viral markers, as the sole advisable strategy. New strategies are designed which consider a universal immunization of the populations of adolescents and neonates having as end point the eradication of the disease[13]. The aim of this study is to contribute to the economic evaluations previously performed in our country on HBV vaccination[14–18]. This new analysis adds a non linear mathematical model,

supported by a system of differential equations, to simulate both the course of the disease in our community and the protective effects of universal vaccination.

MATERIAL AND METHODS

The cost effectiveness analysis technique used compares several strategies of mass vaccination with the usual practice of vaccinating only risk groups, as reflected in the current epidemiological situation. Mass vaccination would be applied to three different populations in Spain: (1) adolescents 12–13 years old; (2) neonates during their first year of life; and (3) both populations simultaneously. In addition, a fourth alternative is analysed which combines the most effective of the above mentioned strategies, with a screening program for pregnant women followed by the active and passive immunization of neonates of HBV carrier mothers. The population cohorts used in the simulation correspond to the 1991 census of 13-year-old adolescents and neonates. The time horizons used in the follow-up of the costs of disease and in the benefits and effects derived from protection by universal vaccination were 10 years, 20 years and 30 years, respectively. Owing to uncertainty on the duration of immunity, the possibility of administering a 20 mg booster dose every 10 years after the first three doses has also been considered.

The vaccination and health care costs, both for chronic and acute infections, are valued in currency units (1993 $), as are the benefits derived from health care savings due to cases of infection prevented. The view point adopted for the costs and benefits assessment has been the societal, although an user view point has also been considered, taking into account the transportation costs for the target population. The final results reflect the additional cost or saving per prevented case of infection in the assessed alternative versus the current strategy. The effects (cases of infection prevented) are presented with and without a discount rate.

Alternatives, coverages and vaccination effectiveness

(1) Universal vaccination of adolescents 12–13 years of age (throughout almost all of Spain, a school health program is implemented which assigns to each school a health care team to administer several vaccines and to screen for certain disorders). During the academic year, three 20 mcg doses at 0, 1 and 6 months would be administered to adolescents.
(2) Universal vaccination for neonates during their first year of life, administering 10 mcg in hospital at birth, at 1 month and at 6 months, simultaneously with the administration of other scheduled vaccines.
(3) Combined vaccination of adolescents and infants, including both vaccination programs in the terms expressed for each single alternative separately.

A combination of the most effective of these programs with a screening of pregnant women for viral markers followed by passive and active immunization of neonates was also evaluated.

Since a previously published study quantified the prevalence threshold for the effectiveness ratio ((screening cost+vaccination cost in negative subjects)/(vaccination costs without screening)) at 23%[19], a figure very distant from that of the populations involved in the alternatives assessed, prevaccination anti-HBc screening was not considered.

The effectiveness assumed comes from several randomized clinical trials (90%)[7]. Losses to the second and third doses are assumed to be few because of the inherent traits of the alternatives evaluated in this analysis, for, in practice, the coverage adopted for the three doses given is guaranteed. In summary, a base line setting, using conservative assumptions, is presented where the immunogenicity conferred by the vaccine lasts for at least ten years and is prolonged for twenty or thirty years after administration of a booster dose every ten years; moreover, for these doses it is assumed that there is a non compliance of 20% on the starting coverages of 90% and 68% in infants and adolescents, respectively[20].

The cost of vaccination includes three vaccine doses, and one dose of HBIg in the case of infants born to HBsAg positive mothers, and the costs of personnel and materials needed to administer the gamma globulin or the vaccine. The transport cost for an escort in the case of neonates for the second and third doses, equivalent to 2 h of the minimal inter professional wage, is also included. (*Table 1*). The existence of the above mentioned school health program and the frequent contacts of nursing mothers with the public health system (covering nearly 98% of Spanish population) establishing in both cases health actions for children and adolescents independent of vaccination against HBV itself, enabled a shared valuation for the personnel, materials and transport costs. Costs arising from treatment of the possible adverse side-effects of

Table 1 Prevalence of hepatitis B markers in the Spanish population

	Age (years)	HBsAg (%)	Anti-HBsAg (%)	Anti-HBc (%)	Some marker (%)	n
Catalonia	6–11	0.2	1.5	–	–	538
	13–14	0.8	1.7	–	–	479
	15–24	1.2	9.3	–	–	86
	25–44	2.4	16.7	–	–	252
	45–64	1.9	19.9	–	–	211
	> 64	–	23.2	–	–	112
Madrid	22–35 months	0.5	–	3.9		281
	7–10	0.8	–	4.7		463
	20–39	2.9	–	22.4		519
	> 55	2.3	–	34.7		518

vaccination have not been considered due to the mild or benign nature of these reactions[21,22].

The costs of health care needed in the cases of acute and chronic HBV infections have been supported by two decision trees, using Markov models with Monte Carlo simulations[23]; these decision trees represent the course of disease in a cohort of 10000 affected individuals (*Figure 1* and *Figure 2*). The different branches in each tree incorporate the probabilities of clinical disease categories, assessed from bibliographic review and expert opinion. Likewise, they incorporate the costs of the corresponding health-care actions (*Table 2*). These costs have been obtained from several sources belonging to the public health network. This model allows us to calculate the mean cost expected for both chronic and acute HBV infections in children and adults[16] (*Table 3*). The first costs have been used up to 10 years of age and the second from 10 years onwards. The mean cost of an acute infection is weighted by the existence of a significant number of asymptomatic infections that generate no costs. The follow-up period considered for chronic infections was 20 years. It has been estimated that a third of HBV DNA negative patients corresponding to asymptomatic carriers are not clinically detected and generate no costs. As the mathematical model provides prevalent cases of chronic infection, it was necessary to calculate a yearly cost for these cases, the result of dividing the mean cost by an annuity factor[30]. For the cases of chronic infection, the costs associated with interferon therapy and liver transplantations were taken into account. Vaccinees who are not protected by vaccination were assumed to be as likely to suffer HBV infection and its sequelae as non vaccinated subjects.

Potential effectiveness: epidemiological assumptions used in the model

The interaction between the infecting microorganism and its human host varies widely among different individuals and no linear function can describe it in a population as a whole. Therefore, it is difficult both to address in an intuitive manner and to predict the impact of mass vaccination programs. The mathematical descriptions of the typical course of an individual infection, and the details of person to person transmission have started to provide a scientific rationale to help to predict the results of the different vaccination programs and to highlight those that may appear in the future[31].

Our mathematical model comprises a system of ordinary first order non linear differential equations

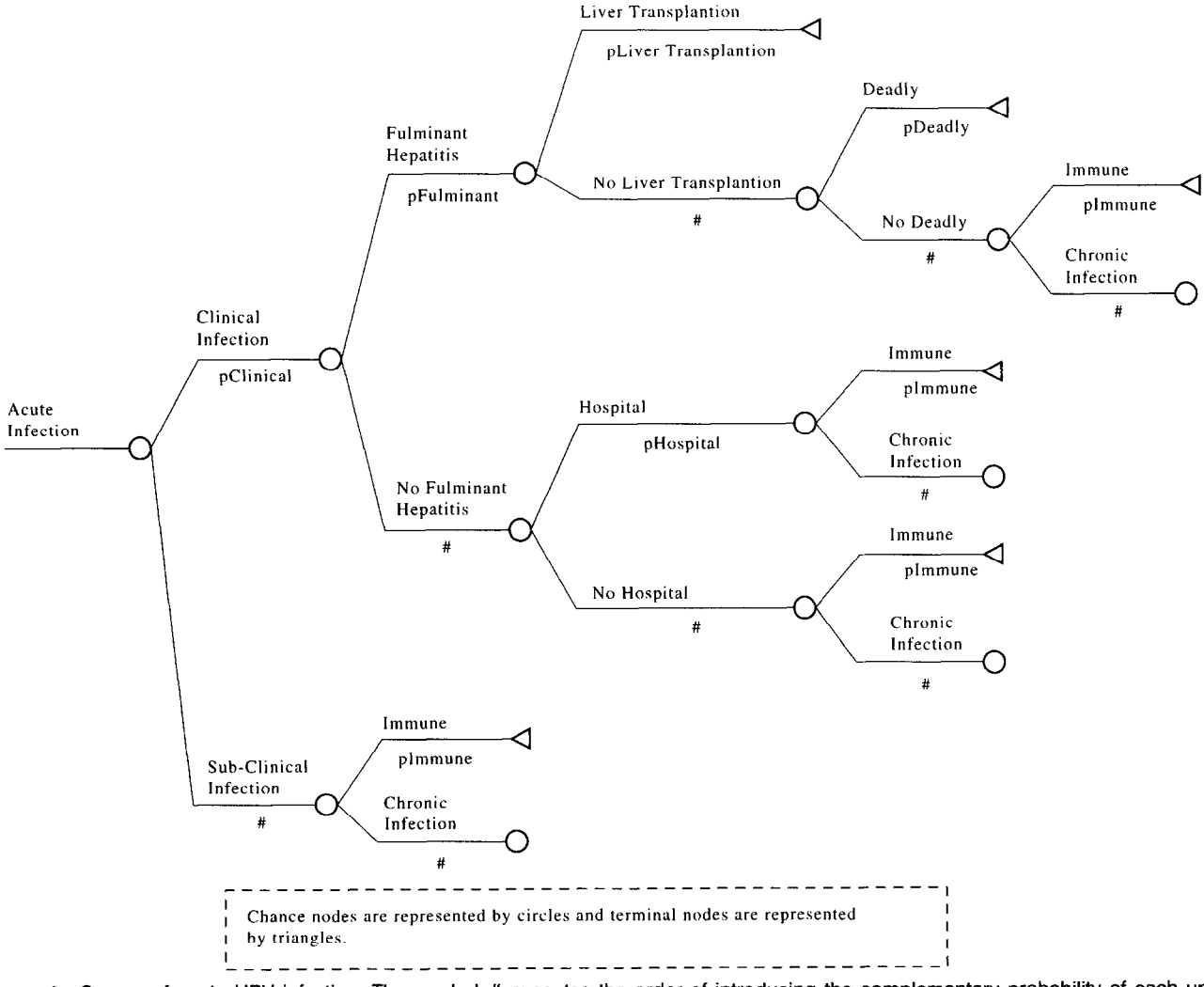

Figure 1 Course of acute HBV infection. The symbol # executes the order of introducing the complementary probability of each upper branch into the lower branch of each one of the tree's nodes. It simplifies the task of tree building, so that the sum of probabilities of both branches is equal to 1

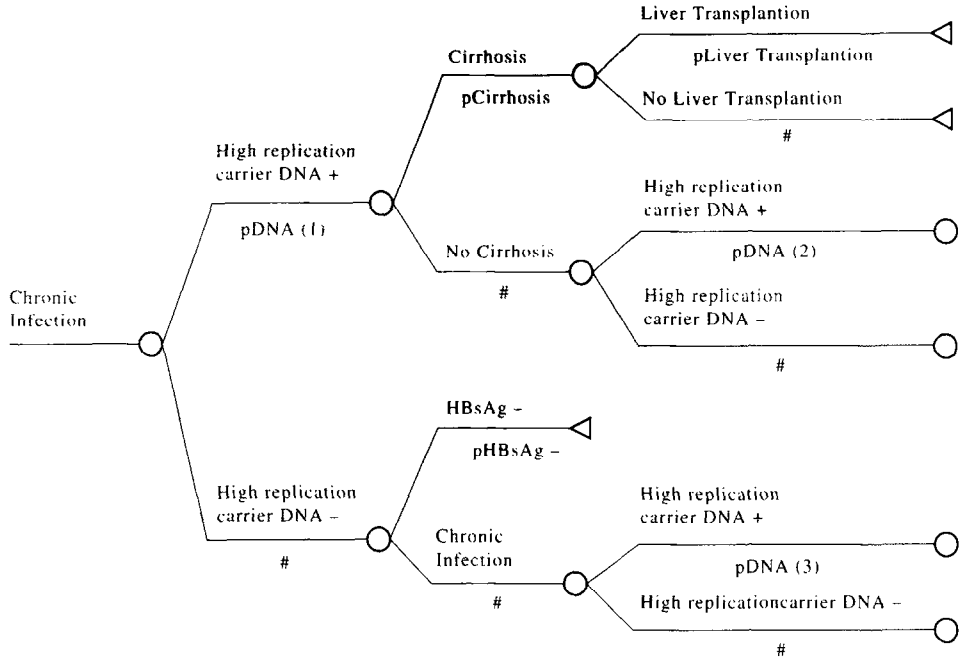

Figure 2 Course of chronic HBV infection

with non constant coefficients represented by the epidemiological outcome of HBV infection in our community, with and without universal vaccination programs[32]. Each equation corresponds to the derivative of five classes or categories into which the population has been classified: susceptible, infected (clinical and subclinical), chronic carriers (of high and low viral replication), immune, and deceased due to acute and chronic HBV infection. These deaths are due to chronic infection complications and have been estimated at around 3–5% annually from 30 years of age in the high replication carriers. Other possible causes of mortality have not been taken into account, since both age groups affected have low mortality rates and the possible overestimation, affecting both costs and effects, is likely to be negligible. Immunity has been considered to persist lifelong.

The passage from the susceptible class to the infected class is determined by the transmission coefficient (β) which represents the number of infecting collisions between the infecting and susceptible population at each time (t); this coefficient depends on age (in adolescence, the number of infecting collisions increases due to the starting of sexual relations and parenteral drug abuse), and is the only non constant coefficient in the equations. The value of β is adjusted by a function that minimizes the difference between the cases expected according to the mathematical model and the cases observed for each age, extrapolated from seroepidemiological studies carried out on representative samples of the population[1,2,23]; all this was performed from the first to the last year of simulation. Thus, different settings are offered under the current conditions of HBV infections in our

Table 2 Vaccination costs

Strategy	Coverage (%)	Variable	Unit costs ($)	Total costs ($)
Adolescents	68	Vaccine dose (20 mcg)[a]	8.8	28.4
		Personnel and disposable material[b]	0.7	
	48	Booster dose at 10 years (20 mcg)[c]		12.4
	48	Booster dose at 20 years (20 mcg)[c]		8
Infants	90	Vaccine dose (10 mcg)[a]	5.6	21.2
		Personnel, disposable material and travel time[b]	1.4	
	70	Booster dose at 10 years (20 mcg)[d]		5.8
	48	Booster dose at 20 years (20 mcg)[d]		8
Screening program for pregnant women	70	HBsAg determination[e]	6.7	42.2
	90	Vaccine dose (10 mcg)	5.6	
		Personnel, disposable material and travel time[b]	1.4	
		Specific gamma globulin (HBIG)	21.3	

[a]Prices are those offered for collective vaccination by one of the two laboratories selling the vaccine in Spain; [b]the costs of personnel, disposable materials and displacements are shared with other health activities common in neonates and school children (the travel costs are assessed in two ways: equivalent to 2 h of minimal interprofessional wages when the subject or accompanying person is displaced, as for with infants, or included in the personnel costs when health personnel are displaced, such as for adolescents); [c]the booster dose for infants and adolescents is discounted by a 5% rate at 10 years and 20 years, respectively, and includes costs equivalent to 2 h of minimal interprofessional wages as an assessment of travel time; [d]the booster dose for infants is discounted by a 5% rate at 10 years and 20 years, respectively, and includes costs equivalent to 2 h of minimal interprofessional wages as an assessment of travel time in the second booster dose; [e]includes costs of laboratory personnel, sample drawing, machine amortization, reagents, etc.

Table 3 Summary of data used in the decision trees for the calculation of costs of therapy against HBV

Type of infection	Clinical category	Procedures	Branch in tree	Value of probability in adults[a]	Value of probability in children[a]	References	Costs in adults ($)	Costs in children ($)
Acute						1, 15, 38, 39	123	120
	Subclinical infection	–		0.8	0.975		–	–
	Clinical infection	Physician visit, diagnostic tests	pClinical	0.2	0.025		368	389
	Liver transplantation	Liver transplantation	pLiver transplantation	0.001	0.001		97520	97520
	Fulminant hepatitis		pFulminant	0.01	0.00001		–	–
	Deadly	4-day hospitalization ICU	pDeadly	0.7	0.7		1846	1195
	No deadly	7-day hospitalization ICU, 12-day hospitalization, 3 follow-up visits		0.3	0.3		5767	7433
	Clinical requiring hospitalization	12-day hospitalization, 3 follow-up visits	pHospital	0.1	0.95		2536	6237
	Immune	–	pImmune	0.9	0.1		–	–
Chronic		Physician visit, laboratory tests, ultrasonogram, household contacts screening and vaccination if indicated[b]				1, 18–21, 24–29	3662 294[c]	4047 325[c]
	High replication carrier (DNA+)	Liver biopsy, interferon treatment, 8-day hospitalization and 6 follow-up visits	pDNA+ (1)	0.25	0.25		5032	4645
	High replication carrier with active liver disease or cirrhosis	2-yearly follow-up visits, yearly ultrasonogram, yearly measure of serum alphafetoprotein and 17-day yearly hospitalization for 50% patients	pCirrhosis	0.05	0.05		32636	31425
	Liver transplantation	Liver transplantation	pLiver transplantation	0.25	0.25		97520	97520
	High replication carriers that remain as DNA+	2-yearly follow-up visits, yearly ultrasonogram and yearly measure of serum alphafetoprotein	pDNA+ (2)	0.9	0.9		9268	9755
	Low replication carriers (DNA−)	1-yearly follow-up visits, yearly ultrasonogram, yearly measure of serum alphafetoprotein and testing for HBV markers		0.75	0.5		1125	1280
	HBsAg−	–	pHBsAg−	0.05	0.05		–	–
	Transform into high replication	Liver biopsy, interferon treatment, 8-day hospitalization and 6 follow-up visits	pDNA+ (3)	0.01	0.01		–	–

[a]Values of probability in each case refer to the preceding category in the tree; [b]initial procedures for chronic infection; [c]the annual cost for chronic infection is obtained by dividing the mean cost by an annuity factor of 12.462 (which corresponds to a discount rate of 5% over 20 years)

community. The model provides the cases of acute and chronic infection, the first in terms of incidence (new cases per year, *Figure 3*) the second, in terms of prevalence (cases existing per year, *Figure 4*). The scenarios simulating the potential efficacy of universal vaccination were obtained by merely transferring the proportion of vaccinees from the susceptible to the immune class (taking into account the assumed efficacy for vaccination) and resolving once again the equation system with the new initial conditions. The cases prevented in each alternative were obtained by differences between each scenario (no vaccination – vaccination of neonates, no vaccination – vaccination of adolescents, and no vaccination – vaccination of adolescents and neonates). Coverages were taken from forecasts of regions with implemented HBV vaccination programs and from experience with other childhood vaccines. The model is non linear and provides an estimate of the indirect effect of universal vaccination which is added, as a benefit, to each alternative assessed.

Cost-effectiveness

Cost effectiveness was obtained by dividing the net cost by the number of cases avoided by vaccination in each alternative[34] (*Table 4*). The net cost is equal to the difference ($C1-C2$), where $C1$ represents the costs of immunization and $C2$ the benefits arising from the savings in health care that would correspond to cases of acute infection avoided. The health care costs are obtained from the sum of the existing cases of chronic infection multiplied by the mean cost of a case, plus the sum of the existing cases of chronic infection multiplied by the yearly cost. The discount rate to update future costs and benefits was 5%.

Sensitivity analysis

A sensitivity analysis was conducted to address the uncertainty of variables such as disease costs, vaccine costs, discount rate and seroepidemiological data. Disease cost and vaccine costs and discount rate were increased or decreased by 25%, and seroepidemiological data from the Autonomous Community of Madrid were used instead of those of the original model from Catalonia.

RESULTS

The alternative of mass adolescent vaccination was the most effective. The net cost per avoided case becomes

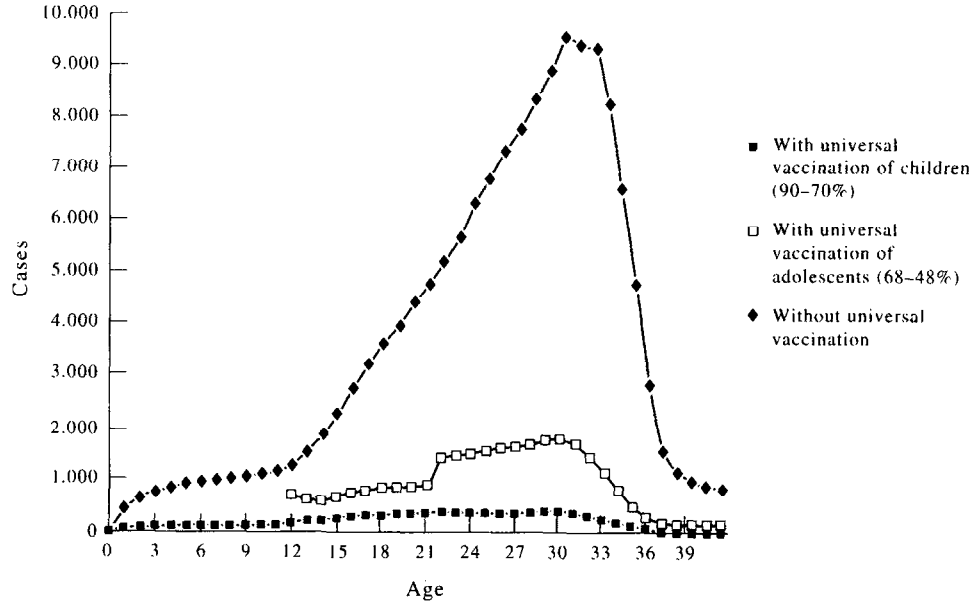

Figure 3 Cases of acute HBV infection in Spain

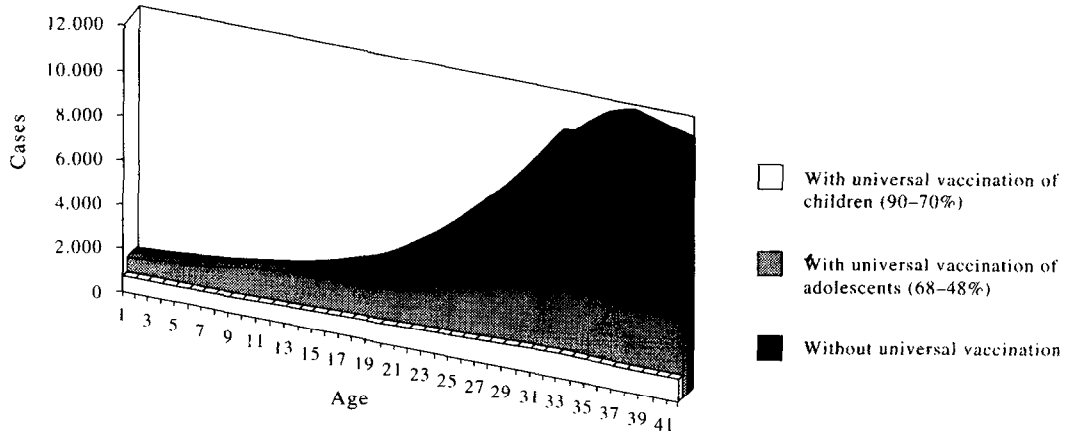

Figure 4 Cases of chronic HBV infection in Spain

Table 4 Results of cost-effectiveness analysis

Alternative	10 years follow-up		20 years follow-up		30 years follow-up	
	C/E[a]($)	Avoided cases[b]	C/E[a]($)	Avoided cases[b]	C/E[a]($)	Avoided cases[b]
Children	1875	3569	500	13648	146	43733
Adolescents	603	16055	92	66024	13	99308
Combined	834	19622	162	79672	53	143041
Adolescents plus screening program for pregnant women	590	16665				
Results with discounted effects						
Children	2564		960		409	
Adolescents	850		177		29	
Combined	1170		311		128	
Adolescents plus screening program for pregnant women	820					

[a]Results of cost-effectiveness analysis from the societal point of view (cost per case of infection prevented); [b]prevented cases are estimated by the mathematical model based on neonates and adolescents in the Spanish population corresponding to the 1991 census

almost negligible—only USD 13 in the long run. According to our results, the mixed strategy in which pregnant women are screened for HBsAg and newborns are actively and passively immunized is even more efficient, with a marginal cost of USD 240 per avoided case, thus becoming the most cost-effective. Combined newborns and adolescents strategies were less cost-effective.

In the sensitivity analysis, vaccine price was the most sensitive variable: a reduction of 25% resulted in the same reduction of net cost per effect in the short term, and was even larger in the long term (Table 5). Threshold analysis set the price that generates net savings (short term follow-up and not taking into account costs of vaccine administration and travelling expenses) at USD 0.6 for the 10 mg dose and USD 1.9 for the 20 mg dose.

Seroepidemiological parameters were less sensitive than vaccine price. Changing disease costs modified the final results only slightly in the long run. Discount rate showed little sensitivity.

DISCUSSION

Mass adolescent vaccination is, under every assumption, the strategy that shows the best cost-effectiveness. This ratio can be further improved when this strategy is combined with a pregnant women screening program for HBsAg, as suggested by some authors[35]. Moreover, HBsAg prevalence in this population varies widely among different Spanish regions. It is a crucial variable to establish the efficiency of a systematic screening program, and maybe the figures considered in this study and coming from studies conducted in Catalonia are too high for the whole population of Spain. In places with lower prevalence women[36] could be selected for detection of viral markers according to the existence of risk factors, thus avoiding mass screening costs.

The most effective strategy is the combination of mass children and adolescent vaccination. It has the advantage of making adolescent vaccination unnecessary after 12 years of program implementation, when the first cohort of vaccinated children reached that age, with only booster doses necessary thereafter. In the long run, the net differential cost between adolescents and combined strategies is only USD 40. Some studies suggest that mass newborn vaccination confers protection against vertical transmission[37], a benefit that if confirmed, should be added to the strategies including it.

The scope from several time horizons provide useful information about the short and long term effects of different strategies. The benefits derived from mass vaccination increases with time, even if booster doses are to be administered.

Table 5 Results of the sensitivity analysis (in 1993 USD per avoided case of HBV infection)

	Reference case	Reduction of vaccine price (25%)	Increase of indirect costs (25%)	Other epidemiological assumptions	Discount rate		
					3.75%	6.25%	10%
Vaccination of children							
10 years	1875	1467	1831	1621	1860	1888	1921
20 years	500	366	462	404	488	509	525
30 years	146	79	103	94	108	148	171
Vaccination of adolescents							
10 years	603	428	565	467	589	615	646
20 years	92	35	55	37	72	108	139
30 years	13	<0	<0	<0	<0	37	79
Combined vaccination							
10 years	834	617	795	666	820	847	878
20 years	162	92	124	95	143	176	205
30 years	53	3	11	7	20	71	108

The mathematical model gives a measure of the indirect effects of mass vaccination, and adds them as a benefit to all strategies analysed. However, this must be balanced by the fact that this model is supported by a principle of homogeneous mixing which assumes that for high vaccination coverage, those people with future risk practices for HBV infection are vaccinated in the same proportion as those without those practices. With low coverages this would no longer be acceptable.

Mass adolescent vaccination would generate an effect of scale economics with possible reduction in vaccine price, the most sensitive variable for cost-effectiveness ratio. The current therapeutic practices include a growing number of patients treated with α-interferon, other antivirals, and hemopoietic growth factors, as well as liver transplant. This could be reflected by an increase in disease cost in the near future, but sensitivity analysis showed this variable to be not very sensitive.

The validation of the data generated by the mathematical model, in terms of cases of HBV infection as well as benefits stemming from mass vaccination is supported on seroepidemiological data from Catalonia and Madrid. Those regions include near a 30% of the Spanish population. If new information would show very different prevalence rates this analysis would need a revision.

It is likely that other diseases, namely HIV infection, could have an impact on sexual behaviour and on parenteral drug abuse (the main ways for transmission of HBV in our environment), affecting preventive measures other than vaccination. This could not be accounted for in these studies, yet it may affect the cost-effectiveness analysis, causing an overestimation of mass vaccination benefits. For instance, a 30% decrease in the transmission coefficient (β) could be derived from preventive measures such as using condoms for sexual intercourse and stopping needle sharing, raising cost-effectiveness for mass adolescent vaccination to USD 774 per avoided case, at 10 years in the base scenario. Some costs and benefits have not been considered in the analysis we have performed, for example the costs of vaccines that are currently administered to populations at risk that would no longer be necessary.

Indirect benefits, in particular working hours gained as a consequence of vaccination, have been estimated for our environment as threefold or fourfold the amount of the direct benefits[15,20]. The adoption of this point of view would imply net savings under every considered assumption. However, since it is questionable (for equity reasons) to penalize with low or absent productivity some populations at risk, we did not include this kind of indirect benefits in any of the strategies assessed.

Other benefits, such as avoided cases of delta hepatitis, and death and suffering associated with HBV infection, have also not been considered because of the selected endpoint 'avoided cases'.

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