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Cost-Benefit Analysis of *Haemophilus influenzae* Type b Vaccination in Children in Spain

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Abstract

Objective: Invasive disease caused by *Haemophilus influenzae* type b (Hib), including meningitis, pneumonia, sepsis and epiglottitis, is associated with high mortality and serious neurological sequelae in children under 5 years of age. The availability of an efficacious vaccine suggests the need to perform an economic evaluation of its use. The objective of this study was to evaluate the costs and benefits of introducing a universal vaccination programme for children under 1 year of age in Spain.

Design & Setting: A cost-benefit analysis (CBA) was conducted over a 5-year period from the societal perspective in the Spanish healthcare setting. Both direct and indirect costs were included in the analysis [using 1996 Spanish pesetas (Pta); Pta126.5 = $US1 in April 1996].

Patients and participants: The target population used for cost and benefit estimation was the 384 883 Spaniards aged 1 year or less in the last Spanish Population and Housing Census of 1991.

Main outcome measures and results: The introduction of the universal Hib vaccination programme would imply vaccinating 346 395 children under 1 year of age, with a global expense of Pta2 444 855 910. For an average incidence of 15 cases of invasive disease per 100 000 children per year nationwide, the programme would prevent 219 cases of invasive disease and 8 deaths over a 5-year period, with a benefit of Pta2 182 868 907, a net benefit (i.e. benefit minus cost) of –Pta261 987 003, a benefit/cost ratio of 0.89 and a benefit per case prevented of –Pta1 196 288. Benefit/cost ratios above 1 would be obtained in the regions of highest incidence of invasive disease.

Conclusion: The decision to implement a universal vaccination programme should not be based only on economic factors, but our results suggest that the economic returns of the programme for children under 1 year of age in Spain would be at least of a similar magnitude as its expenses.

Haemophilus influenzae is a Gram negative bacteria that can be isolated in capsulated or uncapsulated forms. While uncapsulated strains usually cause nonsevere diseases, capsulated strains may cause invasive disease by haematogenous dissemination.[1] The most important clinical manifestation of invasive *H. influenzae* disease is purulent meningitis,[1] with a mortality of up to 5% even when appropriately treated,[2] and with neurological sequelae in 20 to 30% of the survivors.[3] Other less frequent clinical manifestations of invasive *H. influenzae* disease include arthritis, pneumonia, epiglottitis, cellulitis and sepsis. Most cases of invasive disease occur in children under 5 years of age[3] and are caused by *H. influenza* type b (Hib) capsulated strains in approximately 95% of the cases.[2]

In 1985, a vaccine against Hib constituted by polyribosylribitol phosphate became available, but its efficacy was limited and it did not induce immunity in children under 2 years of age.[4,5] Subsequently, more immunogenic vaccines were developed by conjugating polyribosylribitol phosphate with protein carriers. Conjugated vaccines showed a high efficacy, were well tolerated and had a good serological response even in breastfeeding infants.[6-9] Since 1994, 2 conjugated vaccines against Hib have been marketed in Spain, but they were indicated only in children between 2 months and 5 years of age who had asplenia, falciform anaemia, immunodeficiency or HIV infection.[10]

The segment of the population affected by Hib, the associated mortality, the important neurological sequelae, the appearance of Hib strains resistant to antimicrobials[11] and the availability of an efficacious vaccine, have led Spanish health authorities to consider a universal vaccination strategy against Hib in children.[12,13] This article reports on an economic evaluation of such a strategy.

Methods

A cost-benefit analysis (CBA) was performed to evaluate the introduction of a prevention programme by universal vaccination against Hib in children under 1 year of age in Spain. A sensitivity analysis was also performed to evaluate the robustness of the conclusions to changes in the assumptions used in the base case about the main determinants of the costs and benefits of preventing Hib invasive disease.

The target population used for cost and benefit estimation was the 384 883 Spaniards aged 1 year or less in the last Spanish Population and Housing Census of 1991.[14] Unitary costs used in the economic analysis are shown in table I. Direct and indirect costs were calculated using 1996 Spanish pesetas (Pta) [Pta126.5 = $US1 in April 1996].[15]

Cost and Benefit Estimation in the Base Case

Cost of the Universal Vaccination Strategy

Cost estimation was performed from the societal perspective. The establishment of a universal vaccination programme in Spain would share many infrastructure and organisational costs with the existing programme for diphtheria, tetanus and polio (DTP) immunisation. To estimate the direct costs of the Hib immunisation programme, we thus estimated the marginal cost of extending the DTP programme. It was also assumed that the extended programme would have the same coverage as the current DTP programme (about 90% of the target population nationwide).[19]

The following items were considered in estimat-

Table I. Unitary costs used in the economic analysis of *Haemophilus influenzae* type b vaccination programme in Spain

Item	Unit cost (Pta)	Study
Vaccine (1 dose)[a]	1434	manufacturer data
Nurse fee (1h)	1860	Guillén & Espín[16]
Visit to emergency unit	18 991	INSALUD[17]
Inpatient hospital stay (1 day)	37 982	INSALUD[17]
Intensive care unit stay (1 day)	113 946	INSALUD[17]
CT scan	28 758	INSALUD[17]
Outpatient consultation	9496	INSALUD[17]
Average earning of Spanish workers (1h)	1171	Instituto Nacional de Estadística[18]

a At 20% reduction of manufacturer's wholesale price.

CT = computerised tomography; INSALUD = Instituto Nacimal de Salud; Pta = Spanish pesetas (1996 values).

ing the cost of the vaccination programme: vaccine doses, vaccine warehousing and storage, nurse time used to administer the vaccine, training time for the nurses and adverse reactions produced by the vaccine (table II).

Information on the cost of the vaccine doses was provided by the manufacturer, Wyeth-Lederle, Madrid, Spain. We considered a 20% reduction of the manufacturer's wholesale price for a universal immunisation programme in the base case analysis. We also considered the recommended administration schedule of 3 initial doses, to be administered at 3, 5 and 7 months of age, with 1 additional recall dose between ages 15 and 18 months. We assumed that 10% of vaccine doses would deteriorate or would be lost during distribution.[16] The cost of storage and maintenance of the vaccines was estimated at 1% of the vaccine cost (at 20% reduction of the manufacturer's wholesale price), which includes vaccine losses during distribution. As for the cost of vaccine administration, it was considered that a nurse uses 5 minutes to administer each dose[16,20] and that a total of 15 000 nurses (half of those who work in primary healthcare in Spain)[21] should receive training about the vaccine (1 hour per nurse). To compute nurse costs, the number of nurse hours was multiplied by the average fee for a nurse in the Spanish National Health System.[16]

Adverse effects of the Hib vaccine are mainly mild and transitory, and most of them do not require medical attention. It was assumed that only 1 reaction per 60 000 administered doses would require medical attention.[22] The cost of adverse reactions requiring medical attention was estimated as the cost of 1 visit to an emergency service plus the cost of 2 days of hospitalisation,[22,23] based on the 1996 update of the Price Agreements for Health Services to External Providers of Spain's National Health Service.[17]

Cost Saving of Not Using the Current Strategy

The current strategy consists of vaccinating only children between 2 months and 5 years of age who have asplenia, falciform anaemia, inmunodeficiency or HIV infection, together with rifampin prophylaxis for contacts of meningitis cases. It was assumed that the frequency of children with risk factors for Hib infection was 3 per 1000, of whom up to 2 per 1000 would have HIV infection.[24] The costs of vaccinating these children would be the same as for those included in the universal vaccination programme except for the fact that no discounts are applied to vaccine doses in the current strategy. Due to the low number of contacts of children with Hib meningitis in this age group, the additional cost of prophylactic treatment with rifampin was negligible and it was not considered in the analysis.

Table II. Cost estimates per vaccinated child (base case)

Item	Unit cost (Pta)
Vaccine (4 doses)[a]	
Vaccine losses during distribution (10% of vaccine cost)[a]	
Cold storage and warehousing	63
Nurse time for vaccine administration	620
Share of nurse time for training	81
Adverse reaction	6
Cost saving due to not using alternative programme	−22
Total	**7058**

a At 20% reduction of manufacturer's wholesale price.
Pta = Spanish pesetas (1996 values).

Benefit of the Universal Vaccination Strategy

To estimate benefits, we calculated the cost of the cases of disease prevented by the vaccination programme. The average yearly incidence of Hib invasive disease in Spain has been estimated between 10 and 15 cases per 100 000 children under 5 years of age,[25] although there are wide geographical variations within the country (the Basque Country, for instance, has an estimated incidence of 26.3 cases per 100 000 children under 5 years of age).[26] These annual rates resulted in a cumulative 5-year incidence of about 50 to 75 cases for a cohort of 100 000 children. Following the available information on the age-distribution of invasive Hib disease in Spain, it was assumed that 17% of cases would occur during the first 6 months of age, 27% during the second half of the first year, 39% during the second year and 17% between the

second and fifth years of age.[27] It was also assumed that 67% of cases of invasive disease would correspond to meningitis, 11% to pneumonia, 7% to epiglottitis, 5% to cellulitis, 3% to arthritis and 7% to sepsis and other manifestations.[28]

The number of cases of invasive disease and associated deaths prevented by the vaccine was calculated using the estimated incidence of invasive disease, an estimated mortality rate of 3.5%,[29] a coverage of the vaccine programme of 90%, and assuming that the effectiveness of the vaccine is 26% after the first dose and 99% after the second dose.[6-9]

To estimate the cost of treating invasive disease, we assumed that all patients were hospitalised. In Spain, the reported mean hospital stay for children under 5 years of age with Hib invasive disease was 17 days for meningitis, 20 for pneumonia, 7 for epiglottitis, 11 for cellulitis and 15 for arthritis.[30] Due to the lack of information on mean stay for sepsis, we assumed that it was the same as for general invasive disease (14.5 days).[30] Given the severity of the processes, it was assumed that all cases of invasive Hib disease attended a hospital emergency department and had an average stay of 5 days in intensive care (except for arthritis), and that 30% of the children with meningitis had a computerised tomography (CT) scan during hospitalisation.[29,31] It was also assumed that all cases were followed-up after discharge, with 4 outpatient consultations for meningitis and 2 for other clinical manifestations.[32] The direct costs of inpatient hospital stays, inpatient CT scans and outpatient consultations were obtained from the 1996 update of the Price Agreements for Health Services to External Providers of Spain's National Health Service.[17] The cost of 1 day in the intensive care unit was estimated to be equal to the cost of 3 days of hospitalisation.[27]

For estimating the cost of Hib invasive disease sequelae, it was considered that 10% of meningitis cases were associated with serious sequelae (blindness, severe neurological damage) and an additional 11% with moderate sequelae (hearing loss, mild neurological damage).[32] It was also assumed that 11% of the children with Hib arthritis had moderate sequelae (joint dysfunction)[33] and that other manifestations of Hib invasive disease resolved without sequelae. To assign costs to the sequelae, we followed the approach of Clements et al.,[34] who assigned to severe sequelae a cost between 30 (low limit) and 90 times (high limit) the cost of hospitalisation, and to moderate sequelae a cost between 10 and 30 times the cost of hospitalisation. In the base case analysis, the high limits were used.

As indirect costs of Hib invasive disease, we considered the loss of income due to lost work days of 1 of the parents. Thus, we assumed that for each case of invasive disease, a number of work days equal to the mean hospital stay for the corresponding process plus an additional week was lost. The price of 1 hour of work lost was the average hourly earning in Spain as of the fourth quarter of 1994.[18] This value was multiplied by 1.5 to include other indirect costs (transport, domestic help, etc).

For the base case, we did not assign any economic value to life. Finally, a 5% discount rate[35] was used to update the economic benefit of preventing future invasive disease cases until the cohort of children who were vaccinated reached 5 years of age. This update was done taking into account that 34% of prevented cases would correspond to the first year, 46% to the second year and 20% to the third to fifth years.

Sensitivity Analysis

Table III shows the values of epidemiological and economic parameters used to define the base case and sensitivity analysis. Given the limited information on Hib invasive disease incidence in Spain and its geographical variation, alternative yearly incidence rates of 10, 15, 20, 25 and 30 cases per 100 000 children under 5 years of age were evaluated. Other variables considered in the sensitivity analysis were the cost of the vaccine (a high limit with the manufacturer's wholesale price without discount, and a low limit with a discount of 35%), the vaccine efficacy (a high limit which assumed the eradication of the disease due to herd immunity after universal vaccination), the cost of the sequelae

Table III. Parameter values for the base case and limits used in the sensitivity analysis of a *Haemophilus inluenzae* type b vaccination programme in Spain

Variable	Base case	Sensitivity analysis	
		low limit	high limit
Incidence rate of invasive disease (cases per 100 000 children[a] per year)			
Cost of vaccine dose (Pta)	1434	1165	1792
Vaccine efficacy (%)	99		100
Cost of sequelae (number of times multiplied by the cost of hospitalisation)			
moderate	30	10	
serious	90	30	
Cost of life (Pta)	0		200 000 000

a Incidence rate for children under 5 years of age.

Pta = Spanish pesetas (1996 values).

(only the low limits were considered) and the assignment of an economic value to lost lives (Pta200 000 000 per life, approximately $US1 500 000).[36]

The results of the economic analyses are presented as net value (benefit minus cost), as a ratio (benefit/cost) and as net value per case prevented.

Results

The universal vaccination programme would imply vaccinating 346 395 children under 1 year of age, with an individual cost per vaccinated child of Pta7058 and a global expense of Pta2 444 855 910. The estimated costs for the different forms of Hib invasive disease were Pta1 091 116 for meningitis, Pta968 542 for sepsis, Pta683 677 for epiglottitis, Pta1 177 443 for pneumonia, Pta607 713 for arthritis and Pta455 785 for cellulitis.

Table IV presents the number of cases and deaths prevented over 5 years for a cohort of children under the universal vaccination programme. For the base case rate (15 cases of invasive disease per 100 000 children per year), the universal vaccination programme would prevent 219 cases of invasive disease and 8 deaths.

For the base case, the vaccination programme would result in a benefit of Pta2 182 868 907 over a 5-year period (Pta2 114 765 191 from direct costs and Pta68 103 716 from indirect costs), for a net benefit (benefit minus cost) of –Pta261 987 003, a benefit/cost ratio of 0.89 and a benefit per case prevented of –Pta1 196 288.

Sensitivity Analysis

Table V presents the results of the sensitivity analysis. The cost of the sequelae, the incidence rate of the disease, the assignment of an economic value to life and the cost of the vaccine were important determinants of the economic results. Figure 1 presents the estimated benefit/cost ratio as a function of the incidence rate and the vaccine cost. Benefit/cost ratios above 1 were obtained for incidence rates between 15 and 20 cases per 100 000 children when other parameters of the base case were held constant, as well as for incidence rates below 15 cases per 100 000 with a 35% discount in the vaccine price. For incidence rates above 20 cases per 100 000, benefit/cost ratios above 1 were obtained for all evaluated vaccine prices.

Discussion

A programme of universal vaccination against Hib in Spain would be cost saving for annual incidence rates above 20 cases of invasive disease per 100 000 children under 5 years of age, while for lower rates, a net economic benefit would depend on the price of the vaccine dose. Apart from

Table IV. Health benefits over 5 years of a universal vaccination programme against *Haemophilus* influenzae type b in children under 1 year of age in Spain

Prevented cases	Incidence rate of invasive disease (cases per 100 000 children[a] per year)				
	10	15[b]	20	25	30
Invasive disease	146	219	292	365	438
meningitis	98	147	196	246	295
sepsis	10	15	20	25	30
epiglottitis	10	15	20	25	30
pneumonia	16	24	32	40	48
arthritis	5	7	9	11	13
cellulitis	7	11	15	18	22
Death	5	8	10	13	15

a Incidence rate for children under 5 years of age.

b Base case.

Table V. Results (base case and sensitivity analysis) of an economic analysis of a universal vaccination programme against *Haemophilus influenzae* type b in children under 1 year of age in Spain

	Hypothesis	Net benefit (Pta)	Benefit/cost	Net benefit per prevented case (Pta)
Base case				−1 196 288
Sensitivity analysis[a]				
Incidence	10[b]	−988 087 282	0.60	−6 767 721
	30[b]	1 922 404 594	1.79	4 389 051
Efficacy	100%	438 789 392	1.18	1 520 079
Cost of the vaccine	Pta1792	−806 105 245	0.73	−3 680 845
	Pta1165	149 528 454	1.07	682 778
Cost of sequelae	Low	−1 527 984 147	0.37	−6 977 096
Cost of life	Pta200 000 000	1 205 458 336	1.49	5 504 376

a See text (Methods section) for details.

b Cases of invasive disease per 1000 children under 5 years of age per year.

Pta = Spanish pesetas (1996 values).

economic considerations, however, the implementation of the vaccination programme would prevent an important number of cases of serious disease, deaths and long term sequelae.

Some aspects must be considered in the interpretation of these results. First, data on the incidence of Hib invasive disease in Spain were available only for limited geographical regions.[25] The annual rate used in the base case analysis (15 cases per 100 000 children under 5 years), obtained after a review of available studies of Hib incidence in Spain,[25] is likely to underestimate the real incidence of the disease due to incomplete reporting of cases and lack of information on the causal agent for a high proportion of meningitis cases. The review also showed important geographical differences in incidence, with communities such as the Basque Country with rates above 25 cases per 100 000.[26]

Second, the economic evaluation of the vaccination programme required certain assumptions. With regards to the cost of the vaccination programme, the value of 10% of lost vaccine doses and the marginal costs assumed to extend the DTP vaccination programme probably represent a worst case scenario (in fact, some authors consider only the cost of the vaccine doses).[31,32] Furthermore, with the advent of vaccine cocktails, the marginal costs of the vaccination programme will be 0.[13] Our estimates of the cost of the programme are, thus, conservative, and probably higher than the cost of an actual programme. When estimating the prospective benefits of the vaccination programme, an important difficulty was the estimation of the cost of the sequelae. This cost was assigned in a theoretical way by multiplying the cost of the hospitalisation by a factor that varied as a function of the severity of the sequelae, with a wide difference between the high and the low limits assumed. In Spain, it seems reasonable to use the high limit of cost of sequelae since the almost universal coverage of the National Health System guarantees the access of affected patients to future healthcare and the use of available resources. Furthermore, even the high limit of the cost of the sequelae used in this study is lower than the value assigned to a life, while, from a societal perspective, it is more expensive to survive with a neurological deficit than to die.[20,35]

With respect to the cost of treating Hib invasive disease, we considered the direct costs due to hospitalisation, CT scans and follow-up visits, based on the figures available from published Spanish data series.[29,30,32] Although costs were based on the prices charged by the National Health Service to external providers,[17] they were similar to those derived by analytical accounting from a sample of Spanish hospitals,[27] and to the estimates of other authors based on a single hospital.[32] The estimates of hospitalisation costs were thus rather robust, although the total cost of treating Hib invasive dis-

ease was probably underestimated since outpatient costs prior to hospitalisation were not included. The assignment of an economic value to life is controversial. In our base case, we did not assign any economic value to life, but its consideration would result in a favourable cost-benefit ratio for the implementation of the vaccination programme for most combinations of the economic parameters analysed.

The efficacy of the conjugated vaccine against Hib is very high (about 99%), and it has also been shown that widespread vaccination reduces oropharyngeal carriage of Hib,[37] resulting in protection even of children who are not vaccinated and thus, contributing to the virtual eradication of Hib invasive disease.[38] The implementation of a universal vaccination programme in Spain would probably result in the eradication of the disease, increasing the benefits of the programme.

Previous economic analyses of Hib vaccination carried out in different populations have consistently shown that the vaccination programme would result in a net benefit,[20,22,34,39-43] while in our study, the benefit and the cost tend to be more balanced. The main reason for this difference is that the reported incidences of Hib invasive disease in Spain are lower than those in other countries analysed, even for the highest limit considered in our study.

Conclusion

The economic analysis of a universal Hib vaccination programme in children in Spain shows that such a programme would result in a net benefit when the annual incidence of invasive disease was between 15 and 20 cases per 100 000 children under 5 years of age or greater. Additionally, an important number of cases of disease, deaths and sequelae would be prevented with few significant adverse effects. The final decision on the implementation of such a universal vaccination programme should not be based only on economic factors. However,

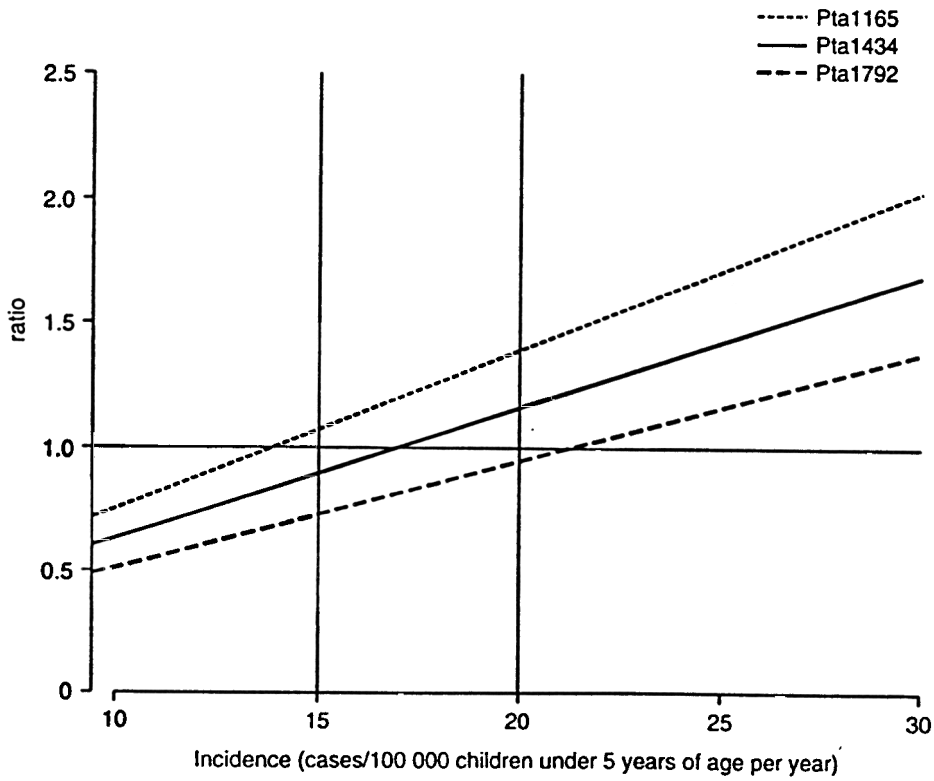

Fig. 1. Benefit/cost ratio of a universal vaccination programme against *Haemophilus influenzae* type b in children under 1 year of age in Spain as a function of the incidence of invasive disease and of the cost of the vaccine. Pta = Spanish peseta (1996 values).

our results suggest that from an economic standpoint, the returns of the programme would be at least of a similar magnitude as its expenses.

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