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Review

Systematic review of economic evaluation analyses of available vaccines in Spain from 1990 to 2012

Isabel Cortés[a], Santiago Pérez-Camarero[a], Juan del Llano[b], Luz María Peña[c], Álvaro Hidalgo-Vega[c,*]

[a] Instituto Max Weber, Majadahonda, Madrid, Spain
[b] Gaspar Casal Foundation, Madrid, Spain
[c] University of Castilla-La Mancha, Toledo, Spain

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ABSTRACT

Objective: The objective of this survey was to describe the evolution of economic evaluation studies on vaccines available in Spain.
Methods: We conducted a systematic review of the economic evaluations published by Spanish researchers in major bibliographic databases available online from 1990 to 2012. For all references identified, we limited them to full economic evaluation carried out in Spanish vaccine programs. The following variables were analyzed: type of study, year of publication, vaccine evaluated, the herd immunity and the main methodological aspects proposed by international guidelines. The type of vaccines studied were Hepatitis A and B, Rotavirus, Influenza, Varicella, Tetanus, Measles, Human papillomavirus, *Streptococcus pneumoniae* infection and *Neisseria meningitides* serogroup C infection.
Results: A total of 34 references was included in the study. The number of economic evaluations has been increasing over the years by 86%. For many of the vaccines there were no economic evaluations, while others such as the vaccine against *S. pneumoniae* infection took up most of the studies. The non-vaccinated comparison was the most used strategy. The cost-effectiveness model was selected in 60% of cases. The most common health outcome was "cost per case prevented" and in 82% of the studies did not consider herd immunity. The results showed a cost-effectiveness ratio which was below breakeven.
Conclusions: It is clear that the existence of a huge gap in this kind of work compared to other countries. Although the quality of the work discussed here was significant, we found many areas which could be improved. The reviewed literature exposed the great benefit of vaccination for society by analysing the health outcomes achieved for decades since its implementation. However, the evidence on the efficiency and effectiveness vaccination is not very high, and there are few studies about economic evaluation.
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* Corresponding author. Tel.: +34 91 6362342; fax: +34 91 6346643.
E-mail addresses: alvaro.hidalgo@uclm.es, alvaro.hidalgo@imw.es (Á. Hidalgo-Vega).

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1. Introduction

Vaccination is probably the most significant public health outcome since its development by Edward Jenner and Louis Pasteur. It has substantially improved survival and quality of life in millions of people around the globe, contributing to better development and welfare of nations [1–3]. Thanks to vaccination, eradication of smallpox was achieved, and now we are able to reduce the incidence of diseases with a greater associated burden, helping to reduce the morbidity and mortality from diseases such as tuberculosis, polio, diphtheria, yellow fever, and tetanus, among others [4].

Most vaccine development took place in the 20th century, starting from the most basic techniques, until reaching much more advanced and innovative procedures based on genetic engineering and [4,5]. Nowadays, there are multiple vaccine research platforms, aimed at making vaccines safer and more effective, through a simple, single delivery system capable of conferring immunity over a long time [6].

These efforts are aimed at achieving better public health tools for reducing child deaths and at extending the benefits of childhood immunization to the rest of the life cycle, helping to establish herd immunity. The decrease in the burden of preventable disease is another effort that mainly influences the direct and indirect costs caused by these infections, and globally it provides great benefits for social systems [7–10].

In Spain the first vaccines introduced were smallpox, tuberculosis, and diphtheria vaccines. Subsequently, these poliomyelitis, tetanus, pertussis, measles, rubella and influenza vaccines were introduced [11]. The following vaccines were against *Haemophilus influenzae* type b infection, *Neisseria meningitidis* serogroup C infection, *Steptococcus pneumoniae* infection, rotavirus and human papillomavirus infection. In addition, other vaccines that are recommended when traveling to risk areas outside Spain, such as the yellow fever vaccine [1,12–14]. In Spain, the implementation of vaccines has always followed World Health Organization guidelines [15]. The development of science in recent years has meant that the development of new vaccine is an enormous challenge for decision-making institutions, due to the cost of production processes as well as to the costs of their implementation by the Spanish National Health System (SNHS). The budget restriction currently affecting the SNHS and the high costs of new vaccines is giving rise to some concern about the efficiency of vaccines among decision makers.

This study tries to provide a comparative analysis of the economic evaluation literature available in Spain about vaccines, in order to determine their impact on the health of the population and on the overall efficiency of the SNHS.

The aim of this study was to conduct a systematic review to obtain full economic evaluations on vaccines carried out in Spain between 1990 and 2012, showing the result of each study in detail and providing a global vision of vaccines. A recently article [52] has been published in which a systematic review of economic evaluation studies on vaccines in Spain is carried out, providing the methodological characteristics of each study. This paper is a complementary study in which not only the metrological features of the studies are provided, but also the economic evaluations resulting from each individual study, thus providing a detailed view of the results obtained in the published studies.

2. Methods

We conducted a literature search in different databases: PubMed, Medline (National Library of Medicine), EMBASE Drugs and Pharmacology (Elsevier), Spanish Medical Index (SMI; CSIC) and other CSIC electronic resources. The search strategy varied slightly depending on the database used.

In the PubMed database different search strategies were employed. In addition, we also included the term for each immunopreventable infection in the search. In Medline, EMBASE Drugs & Pharmacology and SMI/CSIC, we selected the "title" field to search "vaccines" o the name of each infection for which a vaccine is available. In all cases, the search was restricted to publications that included "Spain" or "España" or any of the Spanish regions/cities. These strategies can be found in Annex 2, Supplementary Table 1.

For the inclusion criteria, we followed the quality indications as recommended in the literature [16,17]. However, the references were limited to full economic evaluation, those that evaluated vaccination programs in Spain and those that were published in any scientific journal between 1990 and 2012. Exclusion criteria were studies that did not address vaccination programs in Spain, those that did not constitute a full economic evaluation, those that were not published in English or Spanish, those that were not published between 1990 and 2012, and those that were accepted for publication but have not yet been published.

We conducted a review of the literature from 1990 to 2012. We did not take into account any informal or inaccessible literature, or oral communications nor conference papers, so gray literature was not included. Studies whose results were expressed in the *peseta* currency were changed to euros, according to the irrevocable conversion rate between *peseta* and euro (Ptas.116.386/€).

In order to minimize the risk of bias in each study included in the review scope, a quality assessment of the studies' methodology was carried out on all studies, applying the predefined inclusion and exclusion criteria.

Table 1
A variable description of studies analyzed.

Variable	Description
Journal	National or international journal
Date of publication	Economic evaluations made in Spain from 1990 to 2012
Target population	Studies conducted nationally or by province or region
Disease/infection to prevent	Systematic or not systematic vaccination
Economic analysis used	We consider: Cost–benefit analysis (CBA) if the effect result is expressed in monetary units Cost-effectiveness analysis (CEA) if the effect result is expressed in clinical units Cost–utility analysis (CUA) if the effect result is expressed in utility units incorporating the concept of quality of life Cost-minimizing analysis (CMA) if the effect of the different strategies is equivalent and the effect result is expressed in monetary units
Model used	Markov model, decision tree, others
Perspective analysis	User perspective, family perspective, societal perspective and provider perspective
Alternative analysis	Vaccination strategy comparison: not to vaccinate, by age group or risk population vaccination, vaccinate by previous screening, immunizing with different vaccine formulation, or combination of several of the alternatives proposed
Cost analysis	Direct (medical or nonmedical) cost and indirect costs
Herd immunity	We take into account whether or not to include the effect of herd immunity
Healthcare effects analysis	Results expressed as the measure of monetary units, effectiveness units or quality of life units
Information source	We verify the costs and results information source: primary source (randomized clinical trials, epidemiological studies, review of medical histories, public institutions, expert consultation), secondary (systematic reviews, meta-analysis), or both
Results analysis	We consider if results are expressed in terms of ratios (CE, CU and CB) or also in terms of incremental ratios
Time horizon and discount rate	Time horizon: less than one year, $\geq$ than one year and life expectancy. We also include discount rate and if this is applied only in costs or costs and results
Sensitivity analysis	We check the presence of sensitivity analysis, and if it was deterministic or probabilistic analysis
Decision making	We contemplate the possibility of medical/policy decision making based on the results of each study analyzed
Funding source	Public, private or both financial support

Regarding the data extraction method, an extraction sheet was specifically designed for this study in which the main features of the studies were collected: journal, date of publication, target population, infection, type of vaccine, economic analysis used, model used, perspective analysis, cost analysis, herd immunity, healthcare effects analysis, information source, results, currency, year, sensibility analysis, time horizon, discount rate, country, decision making and financial support (Table 1). Although the quality of the work cannot be directly inferred from the presence of these elements, their lack makes their validity questionable. Moreover, the researchers were contacted in order to obtain and confirm missing s (it was necessary to contact two different researchers on two occasions in order to obtain the data required).

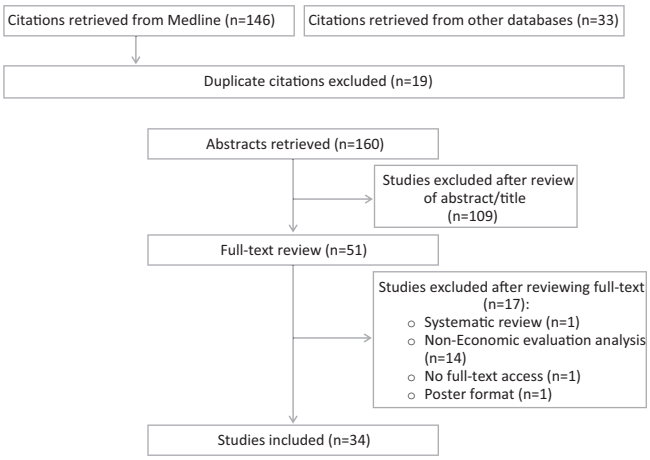


Fig. 1. Flowchart of the performed systematic review.

3. Results

The search strategy identified 179 original studies. A check for duplicates was then conducted. 19 studies were excluded on the basis of their appearance in two or more databases. After that, the titles and abstracts of 160 references were reviewed. Following this initial examination, 109 papers were excluded on the basis of their not meeting the inclusion criteria. The complete text of 51 references was reviewed and finally 34 studies were finally included in the systematic review (Fig. 1).

The most frequent cause of exclusion was that the studies did not have a full economic evaluation (14 studies). Another exclusion criteria were: being a systematic review (1 study), the unavailability of the full text (1 study), and being an informal format (such as poster format or conferences papers).

Of the 34 studies reviewed, 42% were published in Spanish journals and 57% in international journals. 45% of the studies were conducted state wide and the other 54% was held in a Spanish city or region. Among all the currently vaccines available in Spain, we found literature on the following preventable diseases: (a) systematic: seasonal Influenza, varicella, tetanus, measles, hepatitis B virus, *N. meningitidis* serogroup C (meningococcal C) infection, *S. pneumoniae* (pneumococcus) infections, *H. influenzae* type b (Hib) and HPV infection; (b) not systematic: hepatitis A virus and rotavirus infections. Table 2 shows the features of the studies reviewed.

3.1. Number and type of analysis evaluated

The cost-effectiveness analysis (CEA) was used more frequently during the study period, (60% of the 33 articles), followed by cost–benefit analysis (CBA; 39%), cost–utility (CUA, 24%) and finally, the cost–minimization analysis (CMA, 6%). Study evolution over time is shown in Figs. 2 and 3. Fig. 2 shows the study type for each vaccine-preventable disease.

3.2. Perspective analysis and model type

In 28 studies the perspective analysis was mentioned, and the user's perspective and user's family perspective were used in 1 case. In 15 cases the study assumed societal perspective, while the payer perspective (Spanish National Healthcare System) was assumed 18 times. Among the different models applied, decision trees were used by 39%, 21% were Markov models, 21% were other models and in 18%, they were not explicit.

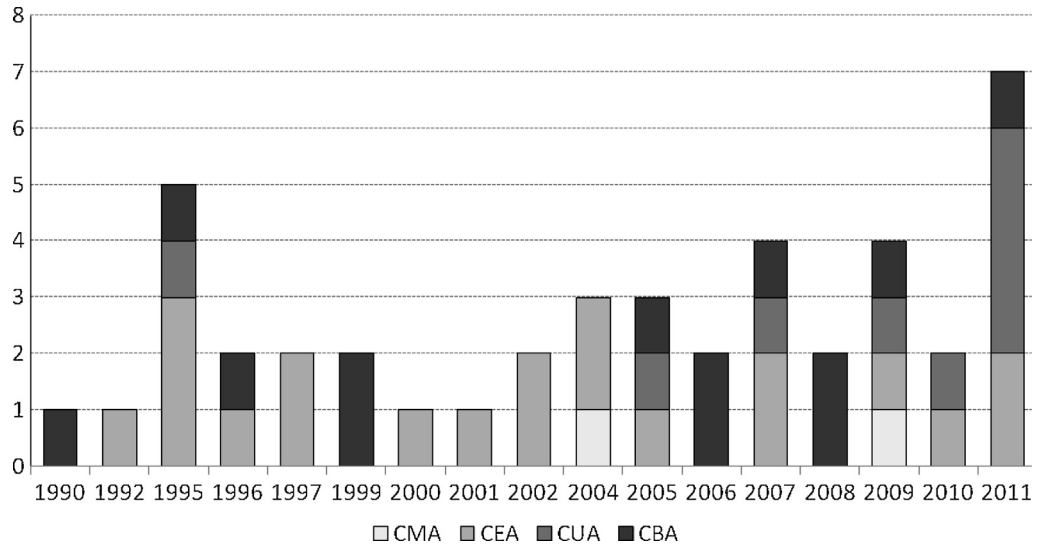


Fig. 2. Evolution of economic evaluations of vaccines from 1990 to 2012.
The total amount does not have to rise to 33, which is the total number of publications reviewed, as is often found in the same article several types of economic analysis. CMA, cost-minimizing analysis; CEA, cost-effectiveness analysis; CUA, cost–utility analysis, CBA, cost–benefit analysis.

3.3. Strategy analysis

Comparison to the non-vaccination alternative (do nothing) was chosen most frequently (57% of the studies). Comparison between vaccination by age groups or risk population and between various alternatives (described in Table 1) was used in 15 and 12%, respectively. 9% of articles used new formulation vaccine as a term of comparison. Finally, the least common strategy was to perform a serological test prior to vaccination on a target population.

3.4. Cost analysis

All studies quantified direct healthcare costs, and 36% of them also took non-health direct costs into account. Indirect costs were mentioned in 15 papers, and were quantified in 14 of them. Intangible costs were not mentioned or quantified in any of the studies.

3.5. Health effects and herd immunity analysis

Clinical effectiveness results were taken into account in 66% of studies and quality of life quantification was only used in 24% of them. Herd immunity, which refers to the protection of the unvaccinated population that is achieved through high vaccination coverage, should also be taken into account. This immunity breaks the transmission chain and gets better results than the sum of individual immunities [18]. This immunity type modifies results from the point of view of efficiency, effectiveness and quality of life. Only 18% of the studies analyzed included herd immunity.

3.6. Information source and funding source

The main source of information was mixed (90%) in items related to the resource used, costs and health outcomes. Only in one case the information had primary origin, and in two publications it was only secondary information. 57% of the studies reviewed did not specify the source of funding. For studies that explicitly include the funding source, it was private in 21% of cases, public in 9% of cases and mixed in 12%.

3.7. Results analysis

The cost-effectiveness ratio was performed in 15 studies reviewed, only 6 of which showed an incremental CE ratio. The cost–utility ratio was used in 6 studies, and only 4 of them described the incremental ratio.

3.8. Time horizon and discount rate

The time horizon was less than one year (six months) in two papers. In most of the studies (81%) the time horizon was equal to or longer than one year (from 1 to 9 years: 16 studies, between 10 and 50 years: 15 studies, above 50 years: 1 study). Only 2 studies applied a life expectancy horizon. Of all the studies where the time horizon was less than a year, the discount rate was applied only to costs in 6, whereas it was applied to both costs and results in 15. Studies with life expectancy used the discount rate for both costs and outcomes. In three articles neither time horizon nor discount rate were explicitly described.

3.9. Sensitivity analysis

This analysis was performed in 88% of the publications. A deterministic analysis was used in all cases, and a probabilistic analysis in 18%.

3.10. Guidance for decision making

The majority of the studies reviewed (85%) were explicitly positioned to advise the competent institutions in decision-making on vaccine or specific strategy implementation.

3.11. Effectiveness, utility and benefit results of the studies analyzed

The articles included in this study have been classified in Table 3 by different aspects such as vaccination strategy, measure healthcare result, model proposed and the most relevant results obtained in each study. As in many other articles and reviews in health economics, we applied the threshold accepted by the scientific community of £30,000 or €30,000–50,000 per QALY/LYG [19].

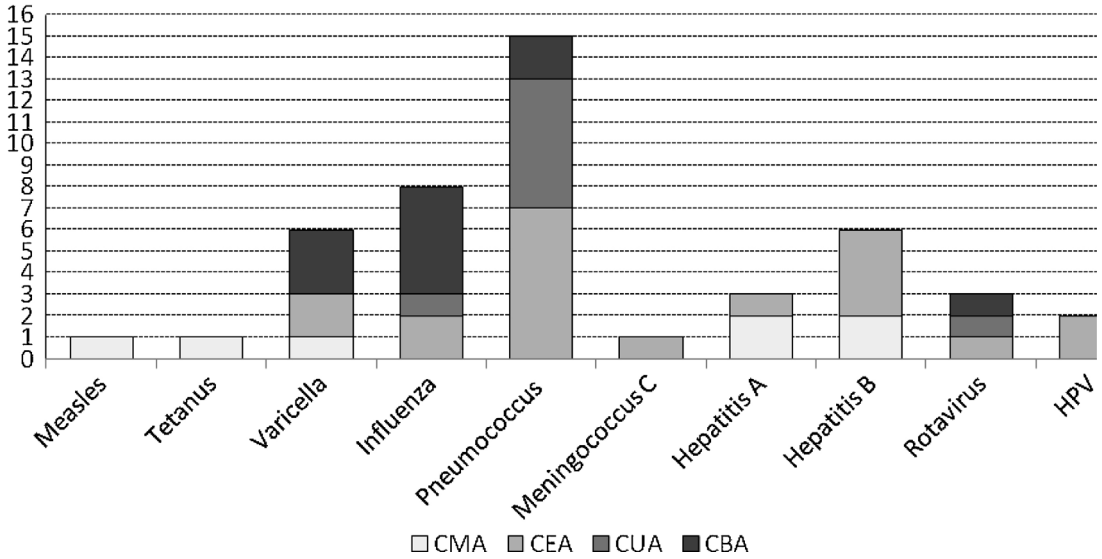


Fig. 3. Evolution of economic evaluations based on vaccine-preventable disease during the study period. The total amount does not have to rise to 33, which is the total number of publications reviewed, as is often found in the same article several types of economic analysis. CMA, cost-minimizing analysis; CEA, cost-effectiveness analysis; CUA, cost–utility analysis, CBA, cost–benefit analysis.

3.12. Hepatitis B virus vaccination

Studies about the effectiveness of different vaccination strategies against hepatitis B virus agreed that the most cost-effective (cost per case prevented) occurred in adolescent vaccination. The cost-effective serological screening in pregnancy and immunization of newborns when positive mother's serology is one of the most cost-effectiveness as well. Regarding CMA, which takes into account different alternatives with the same effectiveness, the least expensive strategy targeted adolescents and adults vaccination without serologic screening. The exception were patients with a hepatitis C viral infection when the incidence of the disease was over 32%, in which screening was the most beneficial option.

3.13. Interpandemic influenza vaccination

The main interest of these papers was the benefit obtained by vaccination among the working population, and the inclusion of certain sensitive groups, such as adults aged 50–65, and children aged 3–14. In the active population, it has been clearly demonstrated that vaccination provides a great benefit, especially when indirect costs of infection are included. Vaccination in people who are 65 years old or older is highly efficient, and could be extended to 50 years old, according to the results of cost per LYG and QALY. Children vaccination was not cost-effective but may be beneficial from a societal perspective. Pradas-Velasco et al. assesses the importance of including herd immunity in the model as it provides additional benefits.

3.14. Streptococcus pneumoniae vaccination

As regards *S. pneumoniae* infection, there were different types of vaccines, with different designs and target populations. The 23-valent polysaccharide vaccine was advised for adults only, and therefore, the objective was to evaluate the age range at which the vaccine was cost-effective, useful and beneficial. All studies showed that adults 65 years old or older were the best target group. The studies also discussed the possibility of vaccination of 45 year olds according to data for cost per LYG and QALY. Suitable formulation for the pediatric population (children aged 0–5 years), are conjugated vaccines that include 7, 10 or 13 serotypes. The 7-valent vaccine was represented by two studies. One of them concluded that the intervention was not efficient. 10 and 13-valent formulations were evaluated in 4 studies, 2 of which found that 10-valent prevails over 13-valent, and the others found the opposite. The reason was that each study took different aspects into account in the model (serotype efficiency, effectiveness in prevent invasive infection, 10-valent protection against non-typificable *H. influenzae*, herd immunity, dose administration, indirect costs).

3.15. Measles, mumps and rubella vaccination

The studies evaluated mainly focused on the population target: infants under 15 months and children aged 2–13. In all evaluations, except for Forcén et al. which concluded that there was no net societal benefit, the intervention was considered cost-effective and cost-beneficial from the NHS and societal point of view. Only one work considered herd immunity. The cost-minimizing article which included varicella vaccination concluded that vaccination with previous serologic screening in adolescents and adults was the least expensive strategy. The same study also evaluated the vaccine against tetanus and measles in adolescents and adults. In this scenario, the most favorable strategy from the monetary point of view was universal vaccination without previous screening.

3.16. Hepatitis A virus vaccination

There was one study about the cost-effectiveness of this vaccine based on the age group, risk population and selective mass immunization. The study concluded that the most cost-effective (cost per case prevented) method was to vaccinate adolescents and adults selectively. In the case of cost-minimizing papers, one of them recommended universal vaccination without prior serologic screening for individuals aged 15–24. For population older than 24,the least expensive strategy was screening before vaccination. On the other hand, for hepatitis C patients universal vaccination was the best option in the case of patients under 30, and after that age selective vaccination was less expensive, with a €10,000 savings in direct costs.

Table 2
Features of the studies examined.

Variables		N
Economic analysis		
CMA		2
CEA		21
CUA		8
CBA		13
Immunopreventable infections		
Not systematic	Hepatitis A virus	3
	Rotavirus	1
	Hepatitis B virus	6
	Influenza	6
	Varicella	6
	Tetanus	1
Systematic	Measles	1
	Human papillomavirus	3
	Streptococcus pneumoniae infection	9
	Haemophilus influenzae type b infection	2
	Neisseria meningitidis serogroup C infection	1
Model perspective		
Society		15
Provider		18
Familiar		1
User		1
Other		5
Herd immunity		
It has been allowed		6
Strategy employed		
Not vaccinate "do nothing"		19
By age group vaccination		5
By previous screening vaccination		2
Different vaccine formulation		3
Different strategies at the same time		4
Results		
CE, CB, CU ratio		31
Incremental CE, CU ratio		10
Others		4
Time horizon		
Less than one year		1
≥ One year		27
Life expectancy		2
Not specified		3
Discount rate		
Applied to costs		6
Applied to costs and results		17
Not applied		3
Sensitivity analysis		
Is conducted		27
In not conducted		4

The total amount need not rise to 33, which is the total number of publications reviewed, as several types of economic analysis, ratios, etc. are often found in the same article.

3.17. Haemophilus influenzae type b vaccination

The two published studies agreed with the great vaccination benefit against this pathogen and its clinical symptoms in children under 1, with a net benefit of €2,2 billion in five years.

3.18. Human papillomavirus vaccination

Although the vaccine against this disease was recently introduced in Spain, there are two economic evaluation works in which the target population were 11-year-old girls. The paper, published in 2007, indicated a cost-effectiveness ratio of almost €6,000 per LYG. The other one, published in 2010, took into account not only the vaccination, but also cytological monitoring (frequency and age). In this study, the most cost-effective strategy was adolescence vaccination with subsequent prophylactic screening every 5 years from age 30 to 65 (€24,350 per year of life saved).

3.19. Rotavirus vaccination

There are two vaccines that help in the prevention of this infection, although it is currently is not provided due to security problems. Pérez-Rubio et al. evaluated the two available vaccines from different points of view (effectiveness, utility and benefit) and the results indicated that, given the current vaccine price, implementation is not recommended.

4. Discussion

In recent years there has been an increase in the number of economic evaluations about vaccines in Spain published by Spanish authors. This study reports the growing interest in this topic as a result of the rapid development of new vaccines or formulations and modes of administration [6]; but in any case, without reaching the existing international publication rate [20–23]. Moreover, we have added to the original publications and also we have begun to introduce systematic reviews to cover different studies (international and Spanish articles) in order to provide a more comprehensive view of the subject [24–26].

Most of the studies reviewed correspond to newly introduced vaccines in Spain, with the exception of the cost-minimizing analysis where Rubió Plans includes the tetanus vaccine (introduced in Spain in 1965) and the measles vaccine (introduced in Spain in 1978) [27]. Vaccine against hepatitis A and hepatitis B virus, varicella, Hib, meningococcal C were introduced during the 90s decade [1,14,28,29]. Vaccine against pneumococcus, HPV and rotavirus are the most recent, introduced in the first decade of the 21st century [30,31]. The rotavirus vaccine is currently being reviewed due to potential side effects, so the Spanish Agency for Drugs and Health Products recommended temporary suspension of its use, pending in any new statement by the Committee for Pharmaceutical Products in Human Use [1].

Vaccines whose introduction took place between the first half of the 20th century and the 80s have no national economic evaluation representations. This is understandable because most vaccines have demonstrated that their benefits were a successful tool regarding both population morbidity and mortality [32–34]. This would have been economically efficient if we had carried out economic evaluation studies in the past. These vaccines became a great tool designed to solve important public health problems such as tuberculosis, poliomyelitis, diphtheria, tetanus, rubella, measles, mumps, influenza, etc. The problem is that as the vaccines were achieving their goal, the population focused on safety and proportionally adverse reactions became more visible. Vaccines are therefore the victims of their own success, and they are currently the subject of a debate on risk-benefit profiles [1].

CEA studies clearly dominate the economic evaluation analysis, followed by studies about CBA and CUA. The high cost-effectiveness evaluations observed may show that this is the type of analysis that best reflects the direct effects of vaccination (case prevented or LYG). The vaccination itself is a healthcare technology that is certainly complicated as there are so many factors and sources of uncertainty to take into account, such as, the efficiency/effectiveness of the vaccine, vaccine coverage, vaccine adherence, number of doses, vaccine serotypes, ability to generate immunity, immunological protection duration, herd immunity, infection epidemiology, among others. Generally, there are many aspects which depend exclusively on distinct biology issues, and therefore are out of control. For these reasons, the inclusion of quality of life is especially complicated, and only 24% of the studies include some measure of utility. It is clearly the low number of CUA in relation to other countries such as Canada [35].

Table 3
Summary of the main characteristics of the articles included.

Infection	Vaccine	Reference	Currency year	Vaccination strategy	Cost focus	Measure healthcare result	Model	Result	Time horizon	Discount rate	Region or country	Financial support
Hepatitis B virus	HBV	Antoñanzas et al.	Ptas.1990	Post-screening risk group, pubescent youth or newborns without screening (screening program in pregnant women and newborn immunization) and accidental exposure	D	Case prevented	CEA	Cost per case prevented: risk population = 998–2663€; pubescent youth = 258–781€; newborns = 2404€; accidental exposure = 3005€	20 years	Costs and effects: 4%–7%	Guadalajara	
	HBV	Guillén Grima y Espín Rios	Ptas.1993	Newborns, children 11 years old or both populations	D	Case prevented	CEA	Cost per case prevented: newborn = 715€; 11 years old = 387€; both populations = 498€	20 years	Costs and effects: 2%–3%–5%–7%–10%	Murcia	
	HBV recombinant vaccine	Antoñanzas et al.	Ptas.1992	Infant, adolescent or both populations plus pregnant screening women with newborn passive immunization	D	Case prevented	CEA	10 years CE ratio: infants = 1526/1100€; adolescents = 493–367€; both populations = 775–1100€	10 and 20 years	Costs and effects: 5%	Cataluña	
	HBV recombinant vaccine	Garuz et al.	US$1993	Neonates ≤1 year old, adolescents 12–13 years old and both populations. Most effective of the above plus pregnant screening women with newborn passive and active immunization	D	Case prevented	CEA	10–20–30 years CE ratio in US$: neonates = 2564/960/409; adolescents = 850/177/29 (pregnant screening = 820); both = 1,170/311/128	10, 20 and 30 years	Costs and effects: 5%	Spain	Public
	HBV	Plans Rubió	€2001	Adults and adolescents with or without prevaccination screening	D		CMA	Vaccination without screening is the least costly immunization strategy			Cataluña	
	HBV	Díez Redondo et al.	€2003/2004	Universal or selective vaccination in patients with chronic hepatitis C	D		CMA	Universal vaccination is the least costly immunization strategy when the prevalence of seropositive result is lower than 32%, when is higher the selective strategy will be the best option			Spain	
Influenza	Routine influenza vaccine	Gavira y Lardinois	Ptas.1986	Vaccination by age groups (>3 years old, 3–14 years old, 15–24 years old, 25–44 years old, 45–64 years old, ≥65 years old)	D + I		CBA	Improved profitability in age group ≥65 years old in 2 of the 4 years of study. CB ratio = 0.009€	4 years		Córdoba	
	Routine influenza vaccine	de Juanes et al.	€2003	Working population 16–65 years old	D + I		CBA	In a cohort of 1000 workers vaccination result in net savings of 35.000€/year (20€/worker)	1 year		Spain	Private
	Routine influenza vaccine	Aballéa et al.	€2004	Individual vaccination 50–64 years old	D + I	LYG, QALY	CEA, CUA	NHS ICER = 9731€/LYG; societal ICER = 2706€/QALY. NHS incremental CU ratio = 14,919€/QALY; societal incremental CU ratio = 4149€/QALY	5 years	Costs and effects: 3%	Spain	
	Routine influenza vaccine	Navas et al.	€2006	Children 3–14 years old	D + I		CBA	Vaccination net benefit = 7,587.03€. CB ratio = 1.80€	6 months	5% for prevented death	Cataluña	
	Routine influenza vaccine	Pradas-Velasco et al.	€2004/2005	Working population	D		CBA	CB ratio static model = 0.28€; CB ratio dynamic model = 1.22€. Cost saving per PCCA static model = 61,278€ and dynamic model = 263.563€	1 year		Spain	Public and private
	Routine influenza vaccine	Salleras et al.	€	Children 3–14 years old	D + I		CBA	CB ratio = 2.15€. Vaccination net savings = 21,551.62€	6 months		Cataluña	
Pneumococcal pneumonia	23-Valent pneumococcal polysaccharide vaccine PSV23	Plans Rubió et al.	Ptas. 1983 updated to 1992	Vaccination by age groups (5–24 years old, 25–44 years old, 45–64 years old, ≥65 years old)	D	LYG and QALY	CEA and CUA	By age groups: 5–24 years old = 60.702€/LYG; 25–44 years old = 25.242€/LYG; 45–64 years old = 6.010€/LYG; ≥65 years old <0 €/LYG; 5–24 years old = 25,843€/QALY; 25–44 years old = 11,419€/QALY; 45–64 years old = 2.404€/QALY; ≥65 years old <0 €/QALY	8 years	Costs and effects: 5%	Cataluña	
	23-Valent pneumococcal polysaccharide vaccine PSV23	Jiménez et al.	Ptas. 1991 in US$ with exchange of 1996	Adults ≥65 years old	D + I	Case prevented	CEA and CBA	Cost per case prevented = 2.656$. CB ratio = 2.0$; net benefit = 127,142,481$	5 years	Costs and effects: 5%	Spain	

Table 3 (*Continued*)

Infection	Vaccine	Reference	Currency year	Vaccination strategy	Cost focus	Measure healthcare result	Model	Result	Time horizon	Discount rate	Region or country	Financial support
	23-Valent pneumococcal polysaccharide vaccine PSV23	Plans	€1996	Vaccination by age groups (5–4 years old, 25–44 years old, 45–64 years old, ≥65 years old)	D	LYG	CEA	By age groups; 5–24 years old = 113,177.12€/LYG; de 25–44 years old = 19,482.51€/LYG; de 45–64 years old = 7122.8€/LYG; ≥65 years old <0 €/LYG. Cost-savings ratio = 1.58€	4 years	Costs and effects: 5%	Cataluña	
	7-Valent pneumococcal conjugate vaccine PCV7 Prevenar	Asensi et al.	€1998/1999	Children less than 5 years old	D + I	Case prevented and LYG	CEA	Cost per case prevented = 202€, cost per LYG = 22,500€. Total savings = 81 million €	10 years	Costs and effects: 3%	Spain	Private
	7-Valent pneumococcal conjugate vaccine PCV7 Prevenar	Navas et al.	€2000	Children less than 2 years old	D + I	Case prevented, death prevented, LYG and QALY	CEA, CUA and CBA	Cost per case prevented (NHS) = 958€; cost per case prevented (society) = 529€. NHS = 80,291€/QALY gained; society = 44,307€/QALY gained. CB ratio = 0.59€	2, 3.5, 10 years	Costs and effects: 5%	Cataluña	Public and private
	10-Valent pneumococcal conjugate vaccine (Synflorix) or 13-valent pneumococcal conjugate vaccine (Prevenar 13)	Picazo et al.	€2010	Vaccination with 10v or 13v by age groups (0–2 years old, 2–4 years old, 5–14 years old, 15–34 years old, 35–49 years old, 50–64 years old, ≥65 years old)	D	QALY	ACU	Incremental CU ratio = 16,908.27€/QALY gained with 13v versus 10v	1 year	Costs and effects: 3%	Comunidad de Madrid	Public and private
	13-Valent pneumococcal conjugate vaccine Prevenar 13	Díez-Domingo et al.	€2009	Vaccination with 13v or 7v to children less than 1 years old	D	LYG and QALY	CEA and CUA	ICER = 12,794€/LYG. Incremental CU ratio = 10,407€/QALY	Life expectancy	Costs and effects: 3%	Comunidad Valenciana	Private
	10-Valent pneumococcal conjugate vaccine (Synflorix) or 13-valent pneumococcal conjugate vaccine (Prevenar 13)	Morano et al.	€2010	Vaccination with 10v or 13v to children less than 2 years old	D	QALY	CUA	10v vaccine result in a benefit of 143 QALYs.10v vaccine result in a benefit of 22 million €	1 year		Spain	Private
	23-Valent pneumococcal polysaccharide vaccine PSV23	Ament et al.	ECU 1995	Adults ≥65 years old	D	QALY	CUA	Spain: 10.511 ecu/QALY; Belgium: 25.907 ecu/QALY; France; 19.182 ecu/QALY; Scotland; 14.892 ecu/QALY; Sweden; 32.675 ecu/QALY	1 year	Cost and effects: 3%	Spain, France, Scotland, Belgium, Sweden	
	23-Valent pneumococcal polysaccharide vaccine PSV23	Evers et al.	€ 1999	Adults ≥65 years old	D	QALY	CUA	Spain: 12,720 ecu/QALY; Belgium: 22,847 ecu/QALY; France; 17,444 ecu/QALY; Scotland; 13,920 ecu/QALY; Sweden; 23,657 ecu/QALY; Denmark: 9239 €/QALY; UK; 17,228 €/QALY; Germany; 17,093 €/QALY; Italy; 16,544€/QALY; Netherlands; 13,740 €/QALY	7 years	Cost and effects: 3%	Spain, France, Scotland, Belgium, Sweden Denmark, UK, Germany, Italy, Netherlands	
Varicella	OKA/Merck vaccine	Díez Domingo et al.	Ptas. 1994	Infants 15 months of age vaccination	D + I		CBA	Saving costs by vaccination = 6,7 millions €	20 years	Costs: 5%	Comunidad Valenciana	Public
	OKA/Merck vaccine	Forcén et al.	Ptas. 1995	Infants 15 months of age universal vaccination	D + I	Case prevented	CEA	CE ratio (10 and 20 years) = 21–24€ per case prevented. Reimbursement of 0.002€ per each Ptas. inverted	10 and 20 years	Costs and effects: 6%	Navarra	
	OKA/Merck vaccine	Plans Rubió	€2001	Adolescents and adults vaccination with or without previous screening	D		CMA	Vaccination with previous screening is the least costly immunization strategy			Cataluña	
	OKA/Merck vaccine	Peña-Rey et al.	1999 adapted to €2002	Children 13 years old vaccination	D	Case prevented	CEA	ICER = 131€	30 years	Costs and effects: 3%	Spain	
	OKA/Merck vaccine	Lenne et al.	€2004	No vaccination or mass vaccination for children 1-2 years old or above plus a catch up program during the first year of vaccine marketing for children aged 2–11 years	D + I	LYG	CEA and CBA	Cost per LYG = 3982€. CB ratio (NHS) = 0.91€, ratio CB (society) = 3,7€. Vaccination net savings = 11.6–47 million € (NHS and societal perspective respectively)	50 years	Costs: 3%	Spain	Private

	Varivax vaccine	Pérez-Rubio et al.	€2002	Universal infants 15 months old vaccination	D + I		CBA	CB ratio = 1.23€. Vaccination net savings = 808,493.36€	13 years and 7 months	Costs and effects: 3%	Castilla y León	
Tetanus	DTPa vaccine	Plans Rubió	€2001	Adolescents and adults vaccination with or without previous screening	D		CMA	Vaccination without screening is the least costly immunization strategy			Cataluña	
Measles	MMR vaccine	Plans Rubió	€2001	Adolescents and adults vaccination with or without previous screening	D		CMA	Vaccination without screening is the least costly immunization strategy			Cataluña	
Meningitis	Meningitec vaccine (conjugated C polysaccaride with diphtheria toxin)	Barricarte et al.	Ptas.1996	Vaccination by age groups (newborns, infants 1-5 years old, children 6-15 years old, adolescents16-19 years old)	D	Case and death prevented	CEA	Cost per case prevented: newborns = 47,772€; infants 1–5 years old = 19,208€; children 6–15 years old = 43,320€; adolescents 16–19 years old = 495,688€			Navarra	
Hepatitis A virus	HAV	Arnal et al.	Ptas. 1994 like ECU[a]	Universal vaccination infants of 15 months of age, adolescents universal vaccination, selective vaccination in risk population by age groups, selective passive immunization in risk population by age groups	D	Case prevented	CEA	Cost per case prevented: infants of 15 months = 6394–3498ECU; adolescents (universal, selective, selective passive) = 18,863–<0 ECU; young adults (selective, selective passive) = 9169–<0 ECU; adults (selective, selective passive) = 3696–<0 ECU	10 years	Costs and effects: 6%	Spain	Public
	HAV	Plans Rubió	€2001	Adolescents and adults vaccination with or without previous screening	D		CMA	In the population 15–24 years old universal vaccination is the least costly immunization strategy without previous screening. In the population >24 years old the least costly immunization strategy is with previous screening			Cataluña	
	HAV	Díez-Redondo et al.	€2003/2004	Universal or selective vaccination in patients with chronic hepatitis C	D		CMA	Universal vaccination is the least costly immunization strategy in population < 30 years old, and from that age the selective vaccination is the least costly immunization strategy with costs savings of 9907.02€.			Spain	
Hib	*Haemophilus influenzae* type b vaccine (Act-Hib and Hib-Titer)	Asensi et al.	Ptas.1993	Children less than 1 year old	D		CBA	Vaccination net benefit in Ptas. versus suffer the invasive infection	9 years		Valencia	
	Haemophilus influenzae type b conjugate vaccine	Jiménez et al.	Ptas.1996	Children less than 1 year old	D + I		CBA	Benefit per case prevented = 7189€; CB ratio = 0.006€; net benefit = 1,574,574€	5 years	Benefits: 5%	Spain	Private
VPH	Gardasil	López Alemany et al.	€2007	Girls 11 years old vaccination	D	Case prevented and LYG	CEA	Costs per LYG = 5688.39€	89 years	Costs in strategy of not vaccine: 5%	Spain	
	Gardasil-Cervarix	Díaz et al.	€2005	Girls 11 years old vaccination with or without later screening to check HPV (differents ages and frequencies)	D	Year of live saved	CEA	ICER = 24,350€/LYS (the most cost-effective strategy)	Life expectancy	Costs and effects: 3%	Spain	Public and private

Table 3 (*Continued*)

Infection	Vaccine	Reference	Currency year	Vaccination strategy	Cost focus	Measure healthcare result	Model	Result	Time horizon	Discount rate	Region or country	Financial support
Rotavirus	Rota Teq and Rotarix	Pérez-Rubio et al.	€2011	Vaccination of from birth to 5 years old	D + I	Case prevented, hospitalization prevented and QALY gained	CEA, CUA and CBA	Rota Teq cost per case prevented: (NHS) = 389,84€, (society) = 237.28€. Rotarix cost per case prevented: (NHS) = 273.57€; (society) = 121.88€. Rota Teq cost per QALY gained: (NHS) = 74,958.99€; (society) = 45,624.83€. Rotarix cost per QALY gained: (NHS) = 52,603.33€; (society) = 23,435.93€. Rota Teq CB ratio: (NHS) = 1.18€; (society) = 0.50€. Rotarix CB ratio: (NHS) = 0.19€; (society) = 0.69€	5 years	Costs and effects: 5%	Castilla y León	

D, direct costs; CMA, cost-minimizing analysis; CEA, cost-effectiveness analysis; CE, cost-effectiveness; Ptas., pesetas; €, euros. Results shown in pesetas were converted euros by the irrevocable conversion rate between peseta and euro (Ptas.116,386/€).
I, indirect costs; CUA, cost–utility analysis; CBA, cost–benefit analysis; ICER, incremental cost-effectiveness ratio; CU, cost–utility; CB, cost–benefit; LYG, live years gained; QALY, quality-adjusted life year; NHS, National Health System; Ptas., pesetas; €, euros. Results shown in pesetas were converted euros by the irrevocable conversion rate between peseta and euro (Ptas.116,386/€).
DTPa, acelular diphtheria-tetanus-pertussis vaccine; MMR, measles–mumps–rubella vaccine. Results shown in pesetas were converted euros by the irrevocable conversion rate between peseta and euro (Ptas.116,386/€).
VHC, Hepatitis C Virus; MCA, cost-minimizing analysis; $US, US dollar.
[a] ECU, European Currency Units (1 ECU = 1.3 $US).

Although we have not performed a rigorous evaluation of their quality, the inclusion or exclusion of certain elements may be indicative of the overall quality of the Spanish studies carried out on vaccines. As a positive aspect, in a large number of studies the alternatives proposed were commonly used in usual practice. The use of a time horizon longer than one year is also positive, although a long-term study is required to confirm that immunity can be conferred by a specific vaccine, reaching in some cases life expectancy. Additionally, the discount rate applied in the base case and in sensitivity analyses or the use of a mixed information source enriches the study. A proposal for methodological standardization was recently was published in the SNHS, which could help to improve the quality of future work [17].

Sensitivity analysis is highly represented (88%), which is a positive factor, but it depends on the type of work evaluated, and the presence of a probabilistic analysis becomes much more necessary. In this issue, we are quite far from the optimal situation, since all international guidelines indicate that this type of analysis is a marker of correct economic evaluation [36,37]. Globally, the most trending and sensitive variables are: the vaccine cost, immunity duration, vaccine efficacy, vaccine coverage and the disease side effects when the population is not immunized. Similarly, any studies should indicate their source of funding in order to avoid unnecessary conflicts of interest [38,39]. This information was only given in slightly over half of the reviewed works.

Less than half of the studies evaluated indirect monetary costs, and none evaluated intangible costs. In others countries, indirect costs are usually taken into account, as authors are aware of its importance and recommend incorporating these costs in economic evaluation studies [40]. The results of economic evaluation studies should not be reduced to expressions of difference between cost-effectiveness and cost-utility ratios (present in over 70% of the studies reviewed). These ratios may be useless in the decision-making process if they are not complemented by the corresponding incremental ratios. The decision-makers' interest should not be only the cost of a particular health outcome, but also the additional cost per each additional unit of effectiveness or utility that would be obtained by applying a specific vaccine strategy.

A model is used to perform the economic evaluation in 81% of the studies. The option most frequently used was decision trees. In 21% of the cases a Markov model was used. This is a good marker of quality, all the more so in topics that required a more dynamic view, such as vaccination. This aspect is particularly important in the herd immunity study [41]. This immunity will help to break chain transmission and obtain better results than through the sum of individual immunities [18]. Taking herd inmmunity into account modifies the results modify positively both from the efficiency, effectiveness and utility point of view.

We have analyzed economic evaluations for eleven immunopreventable diseases in the Spanish context. Depending on the type of vaccine, the vaccination strategy has been different but has always complied with WHO recommendations. In all papers except two, the author recommends following one of the proposed baseline immunization strategies. Hepatitis B virus vaccination is recommended primarily for adolescents, as indicated in Salleras and Domínguez, as only universal vaccination of children and especially young adolescents can lead to the control of this disease in Spain [42]. Selecting vaccination is the most beneficial strategy only when serology is above 32%. For the hepatitis A virus, vaccination is usually selective, due to its pathogenesis. This is reflected in the papers reviewed. Universal vaccination is envisaged (in terms of benefits) for adolescents and young adults only [43]. Seasonal Influenza is characterized for being highly contagious among the working population, causing work absenteeism and most of the analyzed studies focus on this population. Some papers also set a different age target population (elderly or children), and in this

case vaccination is recommended for its benefits, either due to its effectiveness or to improvement in quality of life.

The available pneumococcal vaccines employ different formulations according to the target population. The 23-valent polysaccharide vaccine is not useful in children as it is not able to sufficiently stimulate the immune system to create a long lasting immunity [44]. By contrast, 7/10/13-valent conjugate vaccines are indicated in children. The analysis of the studies on the 23-valent vaccine concluded that it provides cost-effectiveness, cost–benefit and cost–utility not only for people over 65 years old, but also for people who are 45 years old. According to the results, formulated vaccines for the infants are almost always recommended, although the different versions (7/10/13-valent) are not clear about what the best strategy and/or vaccine of choice would be.

The varicella vaccine seems to be justified in children 15–24 months when we take into consideration the indirect costs associated with having the infection. The recommendation for adolescents and adults, according to published reports, is a selective vaccination strategy. This strategy is currently being implemented in Spain. The literature recommends adolescent vaccinations in schools and adult vaccinations in primary healthcare centers and in the workplace, in order to achieve high vaccination coverage [45]. Vaccination against measles and tetanus has been performed universally in the Spanish population for decades and the study reviewed concluded that the least expensive strategy remains universal vaccination with no pre-screening [34,46].

Vaccination against meningococcal C infection is considered more cost-effective from to the ages of 1–5 according to Barricarte et al., although, according to the Spanish schedule published by the Ministry of Health, Social Policy and Equality, primary vaccination occurs at 2 months and the last booster dose at 18 months [47]. Vaccination for prevention of *H. influenzae* type b is justified by the net benefit observed in the results published in the two articles analyzed and despite recent administration. The same result was obtained for the HPV vaccine. Data shows its effectiveness through the cost per year of life gained and saved. Finally, vaccines for the prevention of rotavirus intestinal infections are neither cost-effective nor cost-beneficial due to their high purchase price. The strategy that could be effective is Rotarix vaccination in children up to 5 years old at a cost of €23,435 per QALY. At the moment, the implementation of vaccines has not been scheduled and the results of clinical trials recommend caution and safety [1].

One limitation of this study is the potential existence of publication venues. For many vaccines, no articles assess their impact from any point of view. For others, the number of publications number is so low that there is not enough material for comparison in order to provide comprehensive and precise information on the subject. The literature is limited and this makes this report somewhat poor by comparison to other Spanish healthcare technologies. The information available internationally is more extensive, not only in developed countries but also in developing countries where these diseases are a currently real public healthcare problem for both endemic and tourist populations [48–50]. Another limitation that should be taken into account is the fact that the publications would tend to publish studies with favorable results and, as a result, selection bias has become an important issue in this study. So there is a risk related to the capacity to identify studies, but we have tried to minimize it using predefined inclusion and exclusion criteria.

The limited economic evaluation articles related to vaccines in Spain has not prevented the authors in a clear advisory position from making decisions about the effectiveness–utility–benefit of including a vaccine or not, or even from modifying vaccination strategies to obtain the best results. So it would be necessary to conduct further studies where results were final and transparent, completing the information gap for many of the vaccines available in Spain (both systematic and non-systematic). Finally, the great goal of this kind of evaluation in the future will be healthcare decision-making [51].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.05.097.

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