Is vaccination good value for money? A review of cost-utility analyses of vaccination strategies in eight european countries

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ABSTRACT

Objective: The objective of this study is to review published cost-utility analyses of vaccination strategies in eight European countries and to assess whether there are differences in cost-effectiveness terms among countries and vaccinations.
Methods: A systematic search of the literature was conducted using the National Health Service Economic Evaluation Database and the PubMed database. Cost-utility analyses of any type of vaccination that used quality-adjusted life years (QALYs) as measure of benefit and conducted in Belgium, France, Germany, Italy, Spain, Sweden, the Netherlands or the UK were included.
Results: A total of 94 studies were identified. As a result of our search methodology, the vast majority of studies were conducted in the Netherlands or UK (33 and 30 studies, respectively). The most frequent vaccination types were against Human Papillomavirus (HPV) with 23 studies, followed by vaccination against pneumococcal infections (19 studies). The analysed vaccinations were generally cost-effective but with high variability. Considering an incremental cost effectiveness ratio (ICER) of 40,000€/QALY, we noticed that the following vaccinations studies are below this threshold, i.e. all varicella and influenza (with one outlier) studies, 90% of the studies for HPV and 75% of the studies for pneumococcal vaccinations. Rotavirus vaccination was considered as not cost-effective, with only 30% of studies below the threshold of 40,000€/QALY. There was no clear trend for vaccinations being more cost-effective in some countries.
Conclusion: The published literature has shown that vaccination strategies are generally cost-effective in European countries. High heterogeneity in the results among studies and countries was found.

Key words: Vaccinations, Cost-utility, European Countries, Systematic Review

INTRODUCTION

Immunisation through vaccination is one preventive intervention with the potential to bring economic benefits in addition to health benefits of reduced mortality and morbidity. In 2012, a systematic review has shown that vaccines are cost-effective in low and middle-income countries [1]. Other studies have investigated the value for money of a single vaccination in developed countries [2, 3] or the cost-effectiveness of several vaccination strategies

in a single country [4]. However, there is no study to date that has considered the cost-effectiveness of all available vaccines in several European countries. Although it has been proved that vaccination is likely to be cost-effective in most countries, it is unclear if some vaccinations are more efficient than others or if there are some countries where the same vaccination policies are more cost-effective. For example, some vaccines might have benefits only over a relatively long time-horizon (e.g., Human Papillomavirus (HPV) vaccine for young girls), whereas others can provide immediate or short-term benefits (e.g. influenza or rotavirus vaccines). In addition, it is unclear whether this has consequences on the value for money of these strategies. There are also epidemiological and clinical practice differences among countries that could lead to a different impact of vaccination. This might be related also to different surveillance systems (also in developed countries) that can in some circumstances underestimate the real spread of the disease. Finally, some age-groups or some individuals at high risk for specific diseases could mostly benefit from vaccination and it is unclear whether it would be better to vaccinate only a specific group of individuals or provide universal vaccination. This might depend also on how much the disease is common in the population and on the impact of herd immunity effects. In this analysis, we attempt to answer these questions by reviewing the published cost-utility analyses of vaccination strategies in eight European countries and by assessing the possible trend for some vaccinations being more cost-effective options than others.

REVIEW

Methods

A search of the literature was conducted using two electronic databases: the National Health Service (NHS) Economic Evaluation Database (EED) and PubMed. The following inclusion criteria were applied:

1. Full economic evaluations of any type of vaccine and vaccination
2. Cost-utility analysis with quality-adjusted life years (QALYs) used as outcomes measure
3. Conducted in 8 European countries (Belgium, France, Germany, Italy, Spain, Sweden, the Netherlands, the UK)
4. Published in English language
5. Full published articles (no conference abstracts, posters, grey literature etc)

The choice of the eight mentioned European countries is based on a previous study conducted by Barbieri et al., that had shown that the majority of published economic evaluations on drugs in Europe was performed in those settings [5]. In addition, these eight European countries were those with the most references identified and we focused the analysis only on these.

The NHS EED was initially searched (June 12, 2013), as it includes only full economic evaluations, using the following search strategy: (VACCIN*) AND (QALY*) over a publication period from 1960 to present. Additional searches were performed using the keywords of each of the eight countries of interest (Belgium, France, Germany, Italy, Spain, Sweden, the Netherlands and the UK) plus SCOTLAND, ENGLAND and WALES.

Studies were analysed and compared in an attempt to explain the reasons behind the differences in the final incremental cost-effectiveness ratios (ICERs). We chose not to inflate study results to a single year not to use Purchasing Power Parities (PPPs) conversions since we aimed to assess whether a vaccine was cost-effective or not in each country at the time of each study and in each specific setting. The results of the searches are presented in the next paragraphs and in Figure 1.

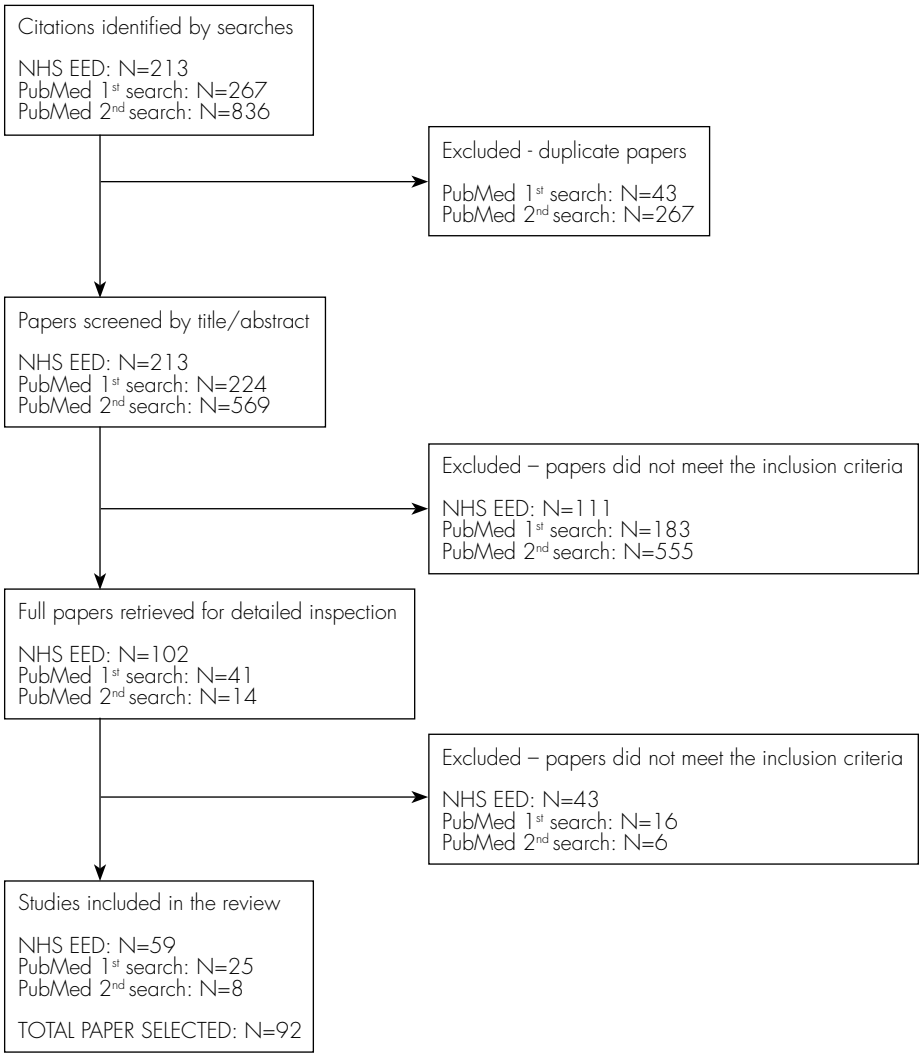
RESULTS

The results of the NHS EES search were as follows: 213 total references with no country restriction, which fell to a number of 128 references for the main eight countries. The search using the additional three keywords SCOTLAND, ENGLAND and WALES did not identify any further relevant study. After excluding duplicates and considering multicountry studies, a total of 102 studies were finally identified, 41 of which were excluded for the following reasons: 33 referred to other countries (19 were conducted in the USA), one was not published in English language, six did not focus clearly on vaccination strategies and one was not a full economic evaluation. Thus, 61 studies were finally included.

In PubMed, a first search was run on July 8, 2013 using the following search strategy: (vaccin*) AND (QALY*) without any country restrictions or time restriction. A total of 267 studies were identified. After excluding 43 references that had already been identified in the NHS EED database, 199 were excluded for the following reasons: 135 referred to other countries (61 were USA studies), 32 included no vaccination, 14 were in non-English language, 12 were reviews and 6 did not include cost per QALY or were not full economic evaluation. Overall, a total of 25 relevant studies were included in the spreadsheet (Figure 1).

On 21st of September 2013, a further search was carried out in the PubMed database to identify potential missed references using alternative search strategies, supplemented by a manual search of references lists of selected articles found in the first round of the search. The additional search used the following strategy: (vaccin*) AND (qualit*) AND (cost*) without any country restrictions over a publication period from 2000 to present. A total of 836 studies were identified and after excluding non-relevant studies and references that had already been

FIGURE 1. Flow diagram of literature search findings.



identified, six additional studies were included, leading to a total of 92 relevant references. Only two studies were published in the 1990s, 53 studies between 2000 and 2010, and 39 between 2011 and 2013. Figure 1 summarises the findings of the review.

In general, the majority of studies focused on the value for money of HPV vaccination and pneumococcal vaccination, with respectively 23 and 19 studies (Table 1). The other infectious diseases were represented by a sufficient number of studies, as rotavirus with 13 studies, influenza with 12 and varicella/herpes with a total of 11 combining the two infections. For the remaining vaccinations, the number of studies were comprised between one and five. The vast majority of studies were conducted in the Netherlands (33) and UK (30), while we reviewed 11 studies in Belgium and between five and ten in each of the lasting countries (Table 2). Only few studies reported not cost-effective results, and in many cases, the incremental cost-effectiveness ratios (ICERs) were below the threshold of 40,000€/QALY, or even dominant, particularly when the societal perspective was used. When considering the variability of results, the highest homogeneity was found in the HPV studies and the lowest in rotavirus vaccination.

HPV vaccination

The summary measures of the analysis are presented in Table 3. Methodology, study population and results are particularly homogeneous among all studies. HPV vaccines were cost-effective given standard thresholds: the ICERs ranged from 5,525 to 32,665€/QALY from the payer perspective. Only four studies, in the Netherlands, evaluated the vaccines also from the society perspective with a range of 18,472 to 53,500€/QALY for the ICER. Publications are the most recent of the entire sample of the reviewed studies (2008-2013), given the new technology. All studies had a lifetime horizon and used a decision-analytic model, either transmission dynamic model or

TABLE 1. Number of studies by type of vaccination.

TYPE OF VACCINATION	NUMBER OF STUDIES
Human Papillomavirus	23
Pneumococcal	19
Rotavirus	13
Influenza	12
Varicella/Herpes zoster	11 (6 varicella+ 5 Herpes zoster)
Meningococcal (B, C)	5
Pertussis	5
Hepatitis (A, B)	3
S. pneumoniae (SP) or Neisseria meningitidis (NM)	1
Total	**92**

TABLE 2. Number of studies by country.

COUNTRY	NUMBER OF STUDIES
The Netherlands	28 (+5) = 33
UK	25 (+5) = 30
Belgium	8 (+3) = 11
Italy	6 (+2) = 8
France	6 (+4) = 10
Germany	5 (+4) = 9
Spain	4 (+2) = 6
Sweden	3 (+2) = 5
Multicountry (Ned 5, Ger 4, UK 5, Fra 4, Swe 2, Bel 3, Ita 2, Spa 2)	7
Total	**92**

The numbers under brackets represent the multicountry studies.

Markov model. Assumptions about the age of starting vaccination affect the cost-effectiveness of HPV vaccination with a more efficient ICER by starting at early age (12 years). Also the discount rate and the price of vaccine impacted the ICER, particularly in the models published in the Netherlands.

Focusing at country level, the three studies conducted in Belgium showed ICERs of 10,546, 32,665 and 9,171€/QALY, respectively [6-8]. These studies used the same comparisons in the same population (in the base case at least), but the study by Thiry et al. assumed the use of a booster dose of HPV vaccine at age 22 [7], and this might explain the higher ICER compared to the other two studies (the addition of a booster represented the most influential input also in the paper by Annemans and colleagues [6]). In a scenario without the booster dose at age 22, the ICER for vaccination was reduced to €14,382. The two French studies showed very similar ICERs (9,706 and 13,809€/QALY) [9, 10], as the two German studies (5,525 and 10,530€/QALY) [11, 12]. In Italy, the study by Mennini and colleagues reported an ICER of 9,569€/QALY [13], while La Torre et al. reported an ICER of 22,055€/QALY [14]. One of the reasons for this difference might be the use of the same discount rate for costs and benefits in the La Torre paper (3%), while Mennini et al. applied a higher discount rate for costs (3%) than benefits (1.5%). In the third Italian study by Favato and colleagues, the ICER for vaccination compared to screening alone ranged between 12,013 and 15,890€/QALY [15]. Discount rate was a very important parameter in most of HPV cost-effectiveness analyses (given the potential large delay of benefits for girls that receive the vaccination at 12 years). This was shown in the Dutch paper by O'Mahony et al. where the ICER for HPV vaccination compared with screening alone ranged from 22,100 to 29,900€/QALY when a 4% discount rate was applied to costs and 1.5% to benefits, but this rose to 101,700€/QALY applying a 4% discount rate to both costs and benefits [16]. In the other eight studies conducted in the Netherlands (one multicountry that included also the UK), the ICER was below the

TABLE 3. Overview of published Human Papillomavirus (HPV) vaccination cost-utility models.

Country	No. of studies	Patient population	Intervention (I) Comparator (C)	Perspective	Range ICER €/QALY (or £/QALY for UK)
Belgium	3	12-year-old girls (also from 12- to 40-year-old with increments of 2 years in 1 study)	I: Bivalent (1 study), Quadrivalent (2) C: Conventional screening	Third party payer (TPP)	9,171-32,665 (12 years)
France	2	12- or 14-year-old girls	I: Bivalent (1), Quadrivalent (1) C: Conventional screening	TPP	9,706-13,809
Germany	2	12-year-old girls or 12- to 17-year-old girls	I: Quadrivalent (2) C: Conventional screening	TPP	5,525-10,530
Italy	3	12-year-old girls (also 15, 18, 25 in 1 study)	I: Bivalent (1), Quadrivalent (2) C: Conventional screening	TPP	9,569-22,055
The Netherlands	9	12-year-old girls (6 studies) range 12-50 years in other studies	I: Bivalent (8), Quadrivalent (1) C: Conventional screening/no vaccination	TPP (4) Society (4) Not reported (2)	5,815-19,429 18,472-53,500 19,900-29,900
UK	5	12-year-old girls (also possible catch-up at different ages in 2 studies)	I: Bivalent (3), Quadrivalent (3) Conventional screening/no vaccination	TPP	5,917-22,474

The numbers between brackets represent the number of studies concerned.
Note: 1) No studies on HPV vaccination were found in Spain and Sweden; 2) 1 multicountry study (UK and Netherlands); 3) The ranges of ICERs reported represent minimum and maximum values found in the base case of the various studies found for each country.

threshold of 50,000€/QALY in the seven analyses that used a 4% discount rate for costs and 1.5% for benefits [17-23] and slightly over this threshold (53,500€/QALY) in the only study that applied the same discount rate for costs and benefits (3%) [24]. It should be noticed that the Netherlands was the only country where the perspective of the society was adopted in the majority of the analyses (as recommended in the Dutch guidelines). Finally, relatively similar findings were found in the UK (one multicountry analysis that included also the Netherlands) [23, 25-28] and the ICER ranged from 5,882 to 22,474£/QALY with most studies showing ICERs close to the threshold of 20,000£/QALY. UK analyses appear very similar in terms of intervention compared, population considered, methods adopted and data sources.

Pneumococcal vaccination

The findings of the pneumococcal vaccination studies showed ICERs value generally below the thresholds (Table 4). Only in four studies (three in the Netherlands, one in the UK), the vaccination resulted not cost-effective, and the study population consisted of infants in all cases. On the opposite, the vaccination was always cost-effective in the elderly. Herd immunity assumption might change the results from not cost-effective to cost-effective. Vaccines including a higher number of serotypes were generally more cost-effective or dominant with respect to vaccines with less serotypes (e.g., PCV10 over PCV7 or PCV13 over PCV10).

Pneumococcal vaccination in Belgium was investigated in two studies, both multicountry, that showed that PCV-14 or PCV-23 are likely to be cost-effective in an elderly population (22,847 and 25,907€/QALY in the two analyses) [29, 30]. In one of these two multicountry studies, France was included and showed a similar ICER (19,182€/QALY) [29]. A total of four studies were conducted in Germany (two multicountry) [30-33]. Two analyses showed the dominance of PCV-10 over PCV-7 and PCV-13 over PCV-10 in infants and young children [31, 32]. Very similar results were found in the other two studies that showed, respectively, the cost-effectiveness of PCV-23 vaccination in adults at high-risk and elderly (17,065€/QALY) and of PCV-14 or PCV-23 in the elderly (17,093€/QALY) [30, 33]. The same conclusions were obtained in two Italian studies that also showed, in the elderly population, the cost-effectiveness of PCV-13 (16,987€/QALY) and of PCV-14 or PCV-23 (16,544€/QALY) [30, 34]. Less homogenous results were obtained

TABLE 4. Overview of published pneumococcal vaccination cost-utility models.

Country	No. of studies	Patient population	Intervention (I) Comparator (C)	Perspective	Range ICER €/QALY (or £/QALY for UK)
Belgium	2	>65 years	I: PCV-7 (1); PCV-14, PCV-23 (1) C: No vaccination	TPP (1) Society (1)	22,847-25,907
France	2	>65 years	I: PCV-7 (1); PCV-14, PCV-23 (1) C: No vaccination	TPP (1) Society (1)	17,444-19,182
Germany	4	Infants and young children (2) >65 years (1) Adults and elderly (1)	PCV-10 vs PCV-7 PCV-13 vs PHiD-CV, PCV-7 PCV-23 vs no vaccination PCV-23 or PCV-14 vs no vaccination	TPP (3) Society and payer (1)	PCV-10 dominated PCV-7; PVC-13 dominated PHiD-CV 17,065-25,687 (PCV-23 and PCV-14 over no vaccination)
Italy	2	>65 years	I: PCV-13 (1); PCV-14, PCV-23 (1) C: No vaccination	TPP (2)	16,544-21,493
The Netherlands	7	>65 years (2) Infants (5)	I: PCV-7 (3), PCV-13 (2), PCV-7, PHiD-CV and PCV-13 (1), PCV-14 and 23 (1) C: No vaccination (6), PCV-7 and PHiD-CV (1)	TPP (2) Society (5)	PCV13 dominated PCV10 and 38 over PCV7; PCV-7 over no vaccination 14,000-113,891 PCV-14 and 23 over no vaccination 13,740 PCV-10 or PCV-13 over no vaccination 14,416-approx. 50,000
Spain	3	>65 years (2) Infants (1)	I: PCV-7 (1), PCV-13 (1), PCV-14 and PCV-23 (1) C: No vaccination	TPP (2) Society (1)	10,407-12,027
Sweden	5	>65 years (2) Infants (3)	I: PCV-7 (2), PHiD-CV(2), PCV-14 and 23 (1), PCV-13 (1) C: no vaccination (4), PCV-13 (1)	TPP (2) Society (3)	PCV-13 dominated PHiD-CV PHiD-CV dominated PCV-13 23,657-32,675
UK	6	>65 years (2) Infants (4)	I: PCV-7 (2), PCV-13 (2), PHiD-CV (1); PCV-14 and 23 (1), PCV-13 and 23 (1) C: No vaccination (5), PCV-7 (1)	TPP (5) Society (1)	PHiD-CV dominated PCV-13 PCV-13 cost-effective over PCV-7 in 100% simulations PCV-13 plus 23 in high-risk children not cost-effective 13,920-14,892 (Scotland) 17,228-59,945 (Eng/Wal)

The numbers between brackets represent the number of studies concerned.
Note: 1) Three multicountry studies; 2) The ranges of ICERs reported represent minimum and maximum values found in the base case of the various studies found for each country.
PCV: Pneumococcal conjugate vaccine; PHiD-CV: Pneumococcal non typeable Haemophilus influenzae protein D conjugate vaccine.

in the Netherlands [30, 32, 35-39]. Five of the seven Dutch studies on pneumococcal vaccination focused on the population of infants and young children. Among these, two studies, that assessed the cost-effectiveness of universal PCV-7 vaccination in infants, ended up with very different ICERs (71,250 and 14,000€/QALY, respectively) [35, 36]. The reason for this difference appears to be the inclusion or exclusion of herd immunity, which is considered in the Hubben study but not in the Bos analysis [35, 36]. This point is explicitly reflected in a study by Rozenbaum et al. that found an ICER of 72,360€/QALY for PCV-7 in infants when herd effects were not considered but a much lower ratio (16,750€/QALY) when these indirect effects were included [38].

Similarly, another study by Rozenbaum et al. showed that the cost-effectiveness of PCV vaccines (PCV-7, PCV-10 or PCV-13) is strongly influenced by vaccine price and doses and by herd immunity assumptions [37]. The other Dutch studies conducted on the elderly population showed cost-effective results (13,740 and 14,416€/QALY) [30, 39]. As regards Spanish studies (three studies, two multicountry), similar findings were obtained for pneumococcal vaccination both in the elderly and in infants (compared to no vaccination) with ICERs ranging from 10,407 to 12,027€/QALY [29, 30, 40]. Also in Sweden (five studies), PCV vaccination always resulted cost-effective, regardless of the population studied (elderly or infants) and number of serotypes included in the vaccine [29, 30, 41-43]. However, also in Sweden, two elements previously emphasised were confirmed: a) vaccination with more serotypes are cost-effective or dominant compared with those with less serotypes; b) the inclusion of herd immunity has a very strong effect on ICERs. Finally, in the UK, key results of the six studies selected can be synthesised as follows: pneumococcal vaccination appears not cost-effective in infants (59,945£/QALY) unless herd immunity is included; vaccination instead could be cost-effective only in certain groups of high-risk adults (those with chronic liver disease) and in the elderly [29, 30, 44-47].

Rotavirus vaccination

In all studies, the societal perspective was analysed and in some cases, the payer perspective as well (Table 5). These assumptions strongly influenced the results, which were generally cost-effective from the societal perspective (ICERs often lower than 50,000€/QALY and in some cases dominant), but not cost-effective from the payer perspective. Regarding the two available vaccines, Rotarix™ and Rotateq, the former was always more cost-effective, probably due to the lowest number of doses (two vs. three). Assumptions about herd immunity, hospitalisation risk, work lost by caregivers and incidence of the infections explained most the variability of the results.

Italy was the country with the best results in terms of value for money for rotavirus vaccine, probably due to the higher probability of hospitalisation following a diarrhoea episode compared to the other European settings. In the study by Panatto et al., the ICER of vaccination with Rotarix™ compared to no vaccination in new-borns was 9,186€/QALY using the third-party payer perspective, while it was dominant from the societal viewpoint [48]. Higher ICERs were found in the other countries. In Belgium, in the two studies identified (one multicountry), both vaccines were cost-effective from the societal perspective (7,572 and 30,227€/QALY), but not from the third-party payer perspective (using a threshold of 50,000€/QALY) [49, 50]. The same conclusions were obtained in the only Spanish study identified, with both vaccines cost-effective at a threshold of 50,000€/QALY using the societal perspective but not from the third-party payer perspective [51]. The 3 French studies (one multicountry) showed contradictory results, as in one study, the ICER was above 130,000€/QALY, in another study over 60,000€/QALY (from the healthcare provider perspective) and in a third one lower than 50,000€/QALY [50, 52, 53]. The reasons for these differences are unclear, although it should be noticed that the study with the lowest cost-effectiveness ratio was the only one that used a lower discount rate for benefits (1.5%) than for costs (3%). However, since benefits for rotavirus vaccination generally occur in the first years of life, it is unclear if this could be a key element to explain the different findings. Assumptions on disease incidence, hospitalisation and indirect protection might be other influential parameters. The majority of the studies on rotavirus were conducted in the Netherlands (six) [50, 54-58]. In three studies that adopted both the payer and the societal perspective, the ICERs resulted higher than 50,000€/QALY from the third-party payer viewpoint and lower than this threshold from the societal viewpoint [50, 54, 55]. In the other three studies that used only a societal perspective, ICERs were quite different, ranging from a minimum of 15,600 to a maximum of 46,717€/QALY [56-58]. One of the Dutch studies showed that vaccination in high-risk infants was much more cost-effective than universal vaccination [55]. Vaccine prices appear to be an important parameter that could have determined differences among Dutch studies. Finally, two out of three UK studies showed not cost-effective findings for both vaccines (ICERs much higher than 20-30,000£/QALY) [50, 59], while the study by Martin et al. showed an ICER of 23,298£/QALY from the NHS perspective and 11,459£/QALY from the societal perspective [60]. Reasons for these differences appear to be assumptions on QALYs lost by caregivers per diarrhoea episode, risk and costs of hospitalisations, vaccine prices and inclusion of indirect protection. However, it is not possible to quantify the impact of each of these factors on cost-effectiveness results.

Influenza vaccination

Results suggest that influenza vaccination has been studied in a very heterogeneous population, from six-month-old children to over 65-year-olds (Table 6). Also the time-horizon ranged from one year to lifetime. In spite of these differences in the two crucial assumptions, the vaccination showed to be cost-effective in all cases (the only exception is a UK study with an ICER of 304,000£/QALY by Allsup et al., in 2004 [61]). We found, like in other vaccinations, better results from the societal perspective, where in some cases the vaccination was dominant. In terms of study countries, UK published six studies out of the total of ten (the total number is 12 including two multinational studies).

One multicountry study considered the cost-effectiveness of extending influenza vaccination to the healthy population

TABLE 5. Overview of published rotavirus vaccination cost-utility models.

Country	No. of studies	Patient population	Intervention (I) Comparator (C)	Perspective	Range ICER €/QALY (or £/QALY for UK)
Belgium	2	Infants	I: Rotarix (2), RotaTeq (2) C: No vaccination	TPP and society	Rotarix 51,030, RotaTeq 65,767 (payer); Rotarix 7,572, RotaTeq 30,227 (society) Not cost-effective (>50,000 per QALY) from payer perspective in both studies
France	3	Infants	I: Rotarix (3), RotaTeq (2) C: No vaccination	TPP (1) Society (2)	Rotarix 44,583-98,000 RotaTeq 151,000
Italy	1	New-borns	I: Rotarix C: No vaccination	TPP and Society	Dominant (society), 9,186 (payer)
The Netherlands	6	Infants	I: Rotarix (5), RotaTeq (5), Targeted Rotarix (1) C: No vaccination (5), Universal vaccination (1)	TPP and society (3) Society (3)	Targeted (high risk) more cost-effective than universal; 3,800 - >50,000 (depending on price, study, herd immunity) Rotarix more cost-effective than RotaTeq
Spain	1	Infants	I: Rotarix, RotaTeq C: No vaccination	TPP and society	Rotarix 52,603 (payer), 23,435 (society); RotaTeq 74,958 (payer), 45,624 (society)
UK	3	Infants	I: Rotarix (3), RotaTeq (2) C: No vaccination	TPP (1) Payer and society (2)	Rotarix 11,459 (society); 23,298-60,928 (payer); RotaTeq 79,905 (payer)

The numbers between brackets represent the number of studies concerned.
Note: 1) No studies found for Germany and Sweden; 2) One multicountry study (Belgium, France, UK and the Netherlands); 3) The ranges of ICERs reported represent minimum and maximum values found in the base case of the various studies found for each country.

aged 50 to 64 years (in addition to those at-risk at that age) in Germany, Italy and France [62]. In all countries, this strategy resulted cost-effective both from the third-party payer and the societal perspective: the ICER from the perspective of third-party payer was 13,156€/QALY in France, 31,387€/QALY in Germany and 15,652€/QALY in Italy; from the societal perspective, universal vaccination was dominant in Germany and Italy, while the ICER was 7,989€/QALY in France. The same analysis was conducted in Spain on the same patient population, with similar findings; the ICER of vaccination was 14,919€/QALY from the perspective of the third-party payer and 4,149€/QALY from a societal perspective [63]. In the other French study identified, influenza vaccination in children aged less than five years resulted in a cost-effective option (about 5,000 to 10,000€/QALY, converting French francs to Euros) [64]. Similar results were found in an Italian study that investigated influenza vaccine in the same population (13,333€/QALY) [65]. In another Spanish study, Navas and colleagues found even better results in vaccinating children between three and 14 years (18€/QALY from third-party payer perspective and dominant from societal perspective) [66]. In a more recent study by Lugnér et al. conducted in Germany, the Netherlands and the UK, three strategies for vaccination against influenza in a pandemic framework were considered: vaccination for the whole population, vaccination of people 65 years old or older and vaccination of people with a high transmission rate (those aged five to 19 years) [67]. Vaccination was cost-effective for all scenarios: in particular, the ICER for vaccinating high transmitters was 7,325€/QALY in Germany, 10,216€/QALY in the Netherlands and 7,280€/QALY in the UK. All the remaining economic evaluations were performed in the UK [61, 68-72]. These studies focused on different populations: children, pregnant women, adults, those aged over 65 years and those aged between 65 and 74. In all cases but one, influenza vaccination resulted cost-effective assuming a threshold of 20,000 to 30,000£/QALY or dominant. The only exception, as previously mentioned, was a study by Allsup et al. (2004) that showed that vaccinating community-dwelling people between the ages of 65 and 74 years, without any of the chronic illnesses for

TABLE 6. Overview of published influenza vaccination cost-utility models.

Country	No. of studies	Patient population	Intervention (I) Comparator (C)	Perspective	Range ICER €/QALY (or £/QALY for UK)
France	2	50-64 years <5 years	I: Universal vaccination C: Vaccination only at high risk 50-64 years (1) No vaccination (1)	TPP and society (1), TPP and co-payments (1)	7,989 (society)-13,156 (payer) (universal vs high-risk) 34,050FF/QALY (payer), 64,688FF/QALY (payer and co-payments)
Germany	2	50-64 years Whole population, elderly, 5-19 years	I: Universal vaccination C: Vaccination only at high risk 50-64 years (1) No vaccination (1)	TPP (2) Society (1)	Dominant (society), 31,387 (payer) (universal vs high-risk) 7,325 (no vaccination)
Italy	2	50-64 years 6-60 or 6-24 months	I: Universal vaccination C: Vaccination only at high risk 50-64 years (1) Vaccination children at high risk (1)	TPP and society (2)	Dominant (society), 15,652 (payer) (universal vs high-risk) Dominant (society) in children 10,000 (children 6-60 months) 13,333 (children 6-24 months)
The Netherlands	1	Whole population, elderly, 5-19 years	I: Universal vaccination C: No vaccination	Payer	10,216
Spain	2	50-64 years 3-14 years	I: Universal vaccination C: Vaccination only at high risk 50-64 years (1) No vaccination (1)	TPP and society (2)	4,149 (payer)-14,919 (society) (universal vs high-risk) Dominant-18,26 in children
UK	7	65 to 74 years > 65 years Pregnant women Whole population, elderly, 5-19 years Elderly 2-18 years Adults	I: Universal vaccination C: No vaccination/ only high risk	TPP (7) Society (1)	304,000 20,000-30,000 <20,000 in most cases 15,000-23,000 7,280 Dominant in most cases 6,174 (payer)-10,766 (society)

The numbers between brackets represent the number of studies concerned.
Note: 1) No studies found for Belgium and Sweden; 2) Two multicountry studies; 3) The ranges of ICERs reported represent minimum and maximum values found in the base case of the various studies found for each country.
FF: French franc.

which influenza vaccine was recommended would lead to an ICER of 304,000£/QALY [61].

Varicella/herpes zoster vaccination

As described in Table 7, this vaccination is generally cost-effective and often close to threshold levels (ICERs in some case dominant and from 1,251 to 42,004€/QALY). Vaccination for varicella obtained better results in children than herpes zoster in the elderly and the results are similar among countries. Whereas in the other vaccination, we found also the comparison between different vaccines, in varicella/herpes zoster studies the comparison was always with no vaccination.

Three studies were conducted in Belgium: Bilcke et al. in a recent analysis focused on a varicella vaccination programme for children and infants, finding that this costs less than 35,000€/QALY gained for any time horizon [73]; both Annemans et al. (2010) and Bilcke et al. (2012) instead investigated on the cost-effectiveness of herpes-zoster vaccination in individuals aged >60 years and found cost-effectiveness ratios ranging from 1,251 to 303,705€/QALY depending on starting age and favourable or unfavourable assumptions about vaccine efficacy and vaccine price [74, 75]. Similarly, one study conducted in France and two Dutch studies showed that vaccinating the elderly for herpes-zoster represents a cost-effective strategy, with ICERs ranging from 9,513 to 18,385€/QALY in France and from 21,716 to 42,004€/QALY in the Netherlands, depending on the age at vaccination and the perspective [76-78]. Vaccine

TABLE 7. Overview of published varicella/herpes zoster (HZ) vaccination cost-utility models.

Country	No. of studies	Patient population	Intervention (I) Comparator (C)	Perspective	Range ICER €/QALY (or £/QALY for UK)
Belgium	3	>60 years (2) Children (varicella) and adults (HZ) (1)	I: Varicella (1), HZ (3) C: No vaccination	TPP (2) TPP and society (1)	1,251-303,705 (HZ, depending on age and best-worst scenarios) <35,000 in children plus booster
France	1	>65 years	I: HZ vaccination C. No vaccination	TPP	9,513-18,385
The Netherlands	2	Elderly	I: HZ vaccination C: No vaccination	TPP (1) Society (2)	21,716-42,004
UK	5	Chidren (1) Adults (45, ≥50 years) (2) Elderly (1) Children and elderly (1)	I: Varicella (2), HZ (4) C: No vaccination	TPP (5) Society (2)	Children: dominant (society)-18,000 (payer) Adults and elderly: 11,109-20,412 Key findings: Generally cost-effective, often close to threshold levels Possibly better varicella in children than HZ in the elderly Relatively similar results among countries Always lifetime horizon and always compared to no vaccination Children-elderly: high probability of being cost-effective

The numbers between brackets represent the number of studies concerned.
Note: 1) No studies found for Italy, Germany, Spain and Sweden; 2) No multicountry studies; 3) The ranges of ICERs reported represent minimum and maximum values found in the base case of the various studies found for each country.
HZ: Herpes zoster.

price and duration of protection were generally the most influential inputs. The remaining studies (five) were conducted in the UK [79-83]. Three studies evaluated the cost-effectiveness of herpes-zoster vaccination in the adults aged 45-50 years or in the elderly [79, 81, 82], one study focused on varicella vaccine in infants or children [80] and another one considered both varicella vaccine in children and herpes-zoster vaccination in the elderly [83]. In general, varicella vaccination was very cost-effective ranging from dominant (from the societal perspective) to an ICER of 18,000£/QALY from the payer perspective. Also herpes-zoster vaccination is likely to provide good value for money in the UK with ICERs ranging between 11,109 and 20,412£/QALY.

Other vaccinations

Due to relative low number of studies, it is difficult to investigate the characteristics and also to make any comparison for the remaining type of vaccinations. Details on each study identified are given in the online appendix.

In general, the key findings are the following:

- Meningococcal (Men) B vaccination was cost-effective in two Dutch studies by Bos and colleagues conducted in 2001 and 2006 (combined with pneumococcal vaccination in the 2006 study) with ICERs of 15,721 and 17,700€/QALY, respectively [84, 85], but not cost-effective in a more recent analysis also conducted in the Netherlands by Pouwels et al. [86] who referred to a value of 243,000€/QALY).
- Quadrivalent meningococcal vaccination was not cost-effective with ICERs higher than 600,000€/QALY compared to MenC vaccination in the Netherlands when started at age 12 years, but it was dominant if started at 14 months [87].
- MenC vaccination was a cost-effective option in the UK compared to no vaccination (2,760£/QALY in the best scenario) [88]
- Compared to no vaccination, adolescent pertussis vaccination was cost-effective in two Dutch studies (with ICERs ranging from 4,200 to 6,371€/QALY) [89, 90], but infant vaccination did not

provide good value for money [91]. Pre-school pertussis vaccination might be cost-effective in the UK (14,500 to 35,000£/QALY depending on vaccine efficacy assumptions) [92] while adult vaccination was a cost-effective option in Germany [93] (5,800 to 7,200€/QALY)

- Contrasting results were found for hepatitis B vaccination for infants or adolescents in the UK, with an old study showing cost-effective results with ICERs ranging from 2,515 to 8,388£/QALY [94] and a more recent analysis showing very high ICERs from 90,000£/QALY for selective infant vaccination to almost 500,000£/QALY for adolescent immunisation [95]. Hepatitis A vaccination in adults was not a cost-effective option in Belgium (around 200,000€/QALY) [96].

DISCUSSION

Most of the studies were conducted in the Netherlands (33) and UK (30) and only two studies were published before year 2000. In general, the majority of studies focused on the value for money of HPV vaccination and pneumococcal vaccination, with respectively 23 and 19 studies (Table 1), probably because these vaccines have been quite recently introduced in many countries compared to the other vaccines.

The analysed vaccinations were generally cost-effective and often close to threshold levels in almost every study. However, even in the most homogenous vaccination group, i.e. the HPV, the variability in ICER values is quite high ranging from 5,525 to 101,700€/QALY. The rotavirus case is even more relevant with ICERs ranging from dominant to 98,000€/QALY.

The reason for this variability, which is normally not observed in the economic evaluations of drugs, might be due to the following two features. On the one hand, a vaccination programme is quite complex to simulate since it requires many data and hypotheses, many epidemiological uncertainties, a wide number of influencing variables such as vaccine coverage, herd immunity, cross protection, age of vaccination, high risk versus low risk patients, etc. Also the discount rate applied can have an effect, especially for those diseases that can occur over a long-term after vaccination (e.g. HPV vaccination). On the other hand, the architecture of models might be very different among studies, with different unit costs and organisational settings. The use of an inflation rate or/and PPPs might have led to the contradictory result that a vaccine cost-effective, for example, in the year 2002 for the country analyses, would not be cost-effective in 2014 only because of an increase in the ICER, which might not instead have occurred in the reality. Another possible explanation for the high variability within and among countries is that the QALY gain for some vaccines is very marginal or small per individual. As the ICER is a ratio, if the denominator is small, if the health benefit is marginal (like often in the particular case of vaccines), a small change in the denominator inflates exponentially this ratio.

According to our results, it appears difficult to assess whether there is a trend for some vaccinations being more cost-effective options than others. When considering the variability of results, the highest homogeneity was found in the HPV studies and the lowest in rotavirus vaccination.

However, based on the cluster shown in the Figures 2-6, a tentative ranking to classify different vaccination strategies on the basis of their ICERs is the following:

1. Influenza and varicella have ICERs all below 40,000€/QALY (apart from one outlier study in the influenza);
2. HPV has the majority of ICERs below 40,000€/QALY (13% of the studies have a greater ICER)
3. Pneumococcal has also the majority of ICERs below 40,000€/QALY, but 26% above this value
4. Rotavirus has only 30% of the studies with the ICER below 40,000€/QALY.

The economic evaluation of drugs is largely applied by comparing one drug with one or more other drugs (comparators). On the opposite, vaccination strategies are mainly compared to "no vaccination" strategy rather than to other vaccines. There are two reasons for this choice. First, the efficacy of different products for the same vaccination is often assumed as almost equivalent. Second, prices of different branded vaccines for the same disease are frequently similar. Actually, since for the public health decision maker the final choice is between introducing a new vaccination campaign or leaving an existing screening or doing nothing (no prevention activity for that specific disease), the decision is often an on-off decision: in case of alternative branded vaccines, the public authority would buy the vaccine trough tender, and in most cases, the price would be similar. Moreover, in most of the European countries, tender is the normal practice to buy the vaccines, which sometimes implies a dramatic reduction of the acquisition cost of vaccines for the public providers compared to the official price, which has been used in the economic evaluation. This means that in most of the cost-effectiveness studies we reviewed in this article, the final ICERs could be even lower according to the real price. Normally, the pricing and reimbursement process is strongly influenced by national or local authorities who are responsible for prevention rather than by physicians or healthcare providers. Then, the ICER of a vaccine compared to another vaccine for the same disease is normally very low or dominant (as we have found for pneumococcal vaccinations). With our "league table", it is not possible (or at least in this paper) to take into account the quality of the studies, the different mechanics of the models, the differences due

FIGURE 2. ICERs of HPV vaccination by countries.

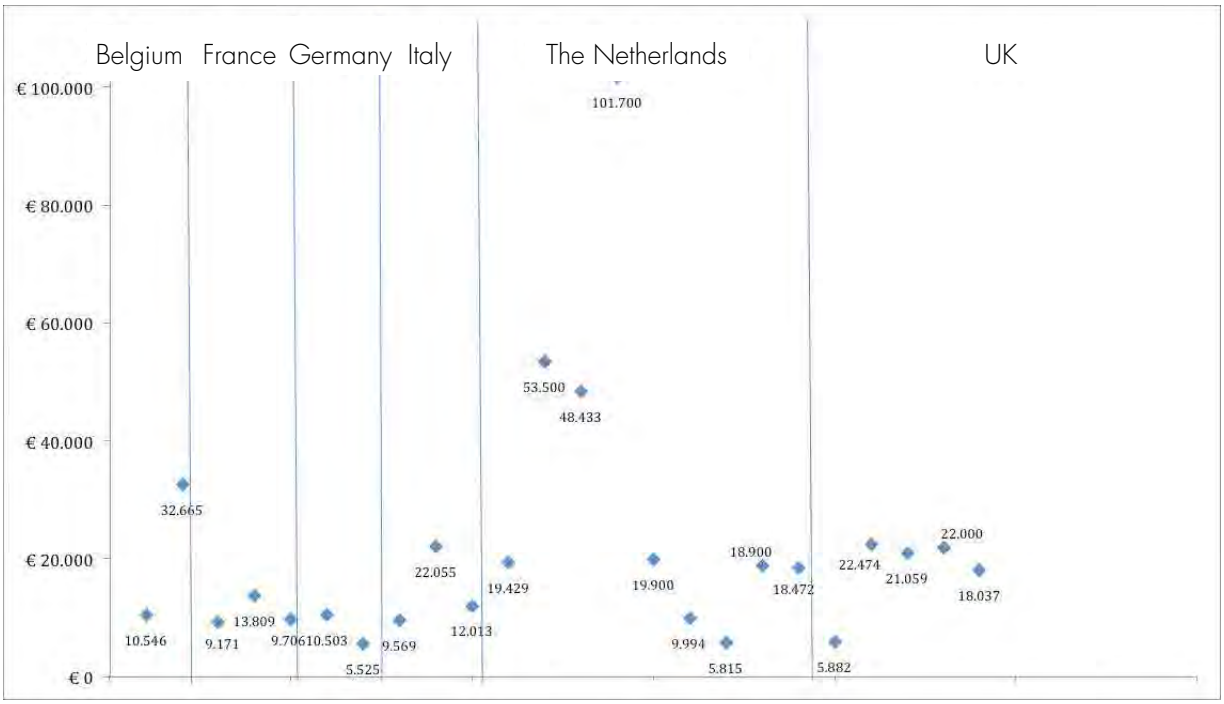


FIGURE 3. ICERs of pneumococcal vaccination by countries.

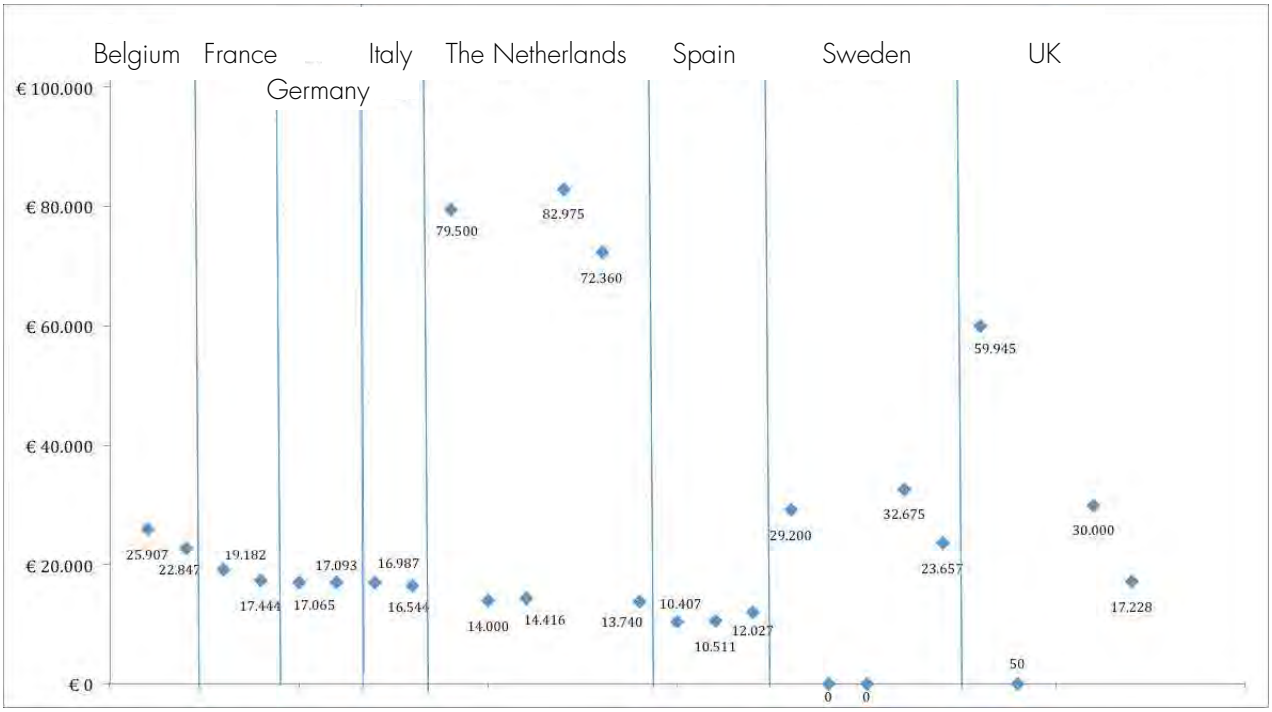


FIGURE 4. ICERs of rotavirus vaccination by countries.

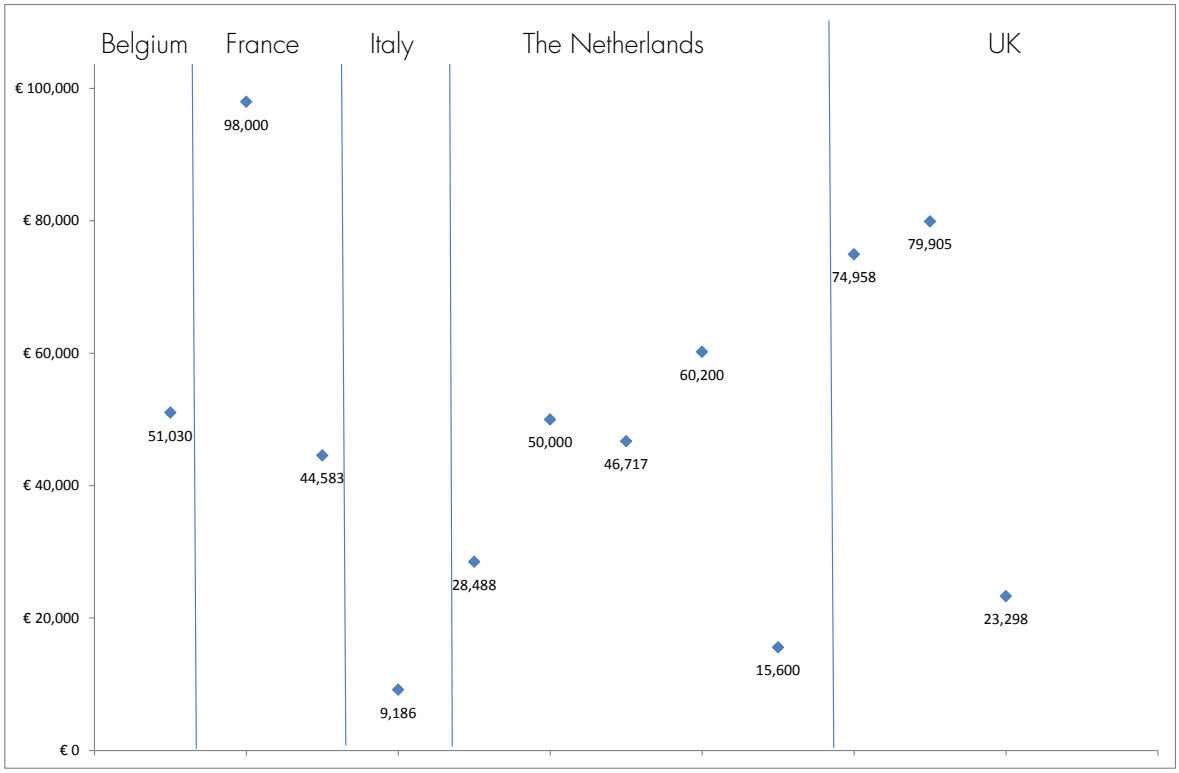


FIGURE 5. ICERs of influenza vaccination by countries.

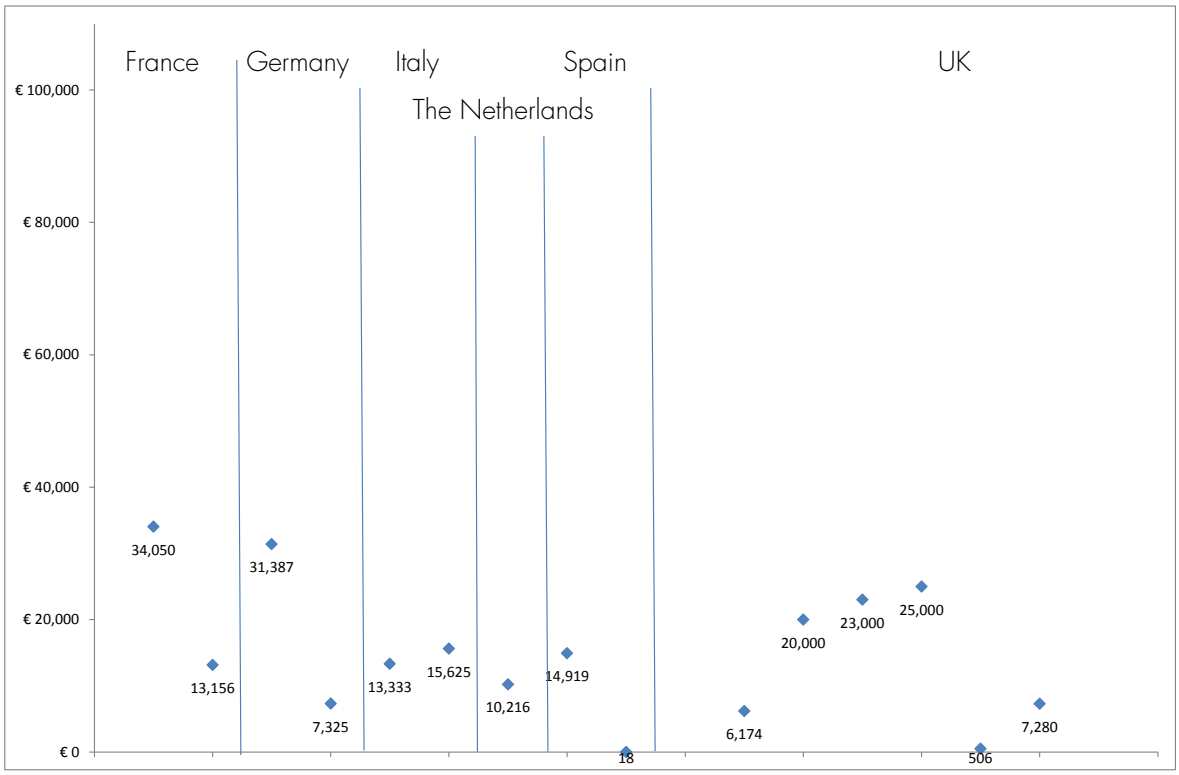
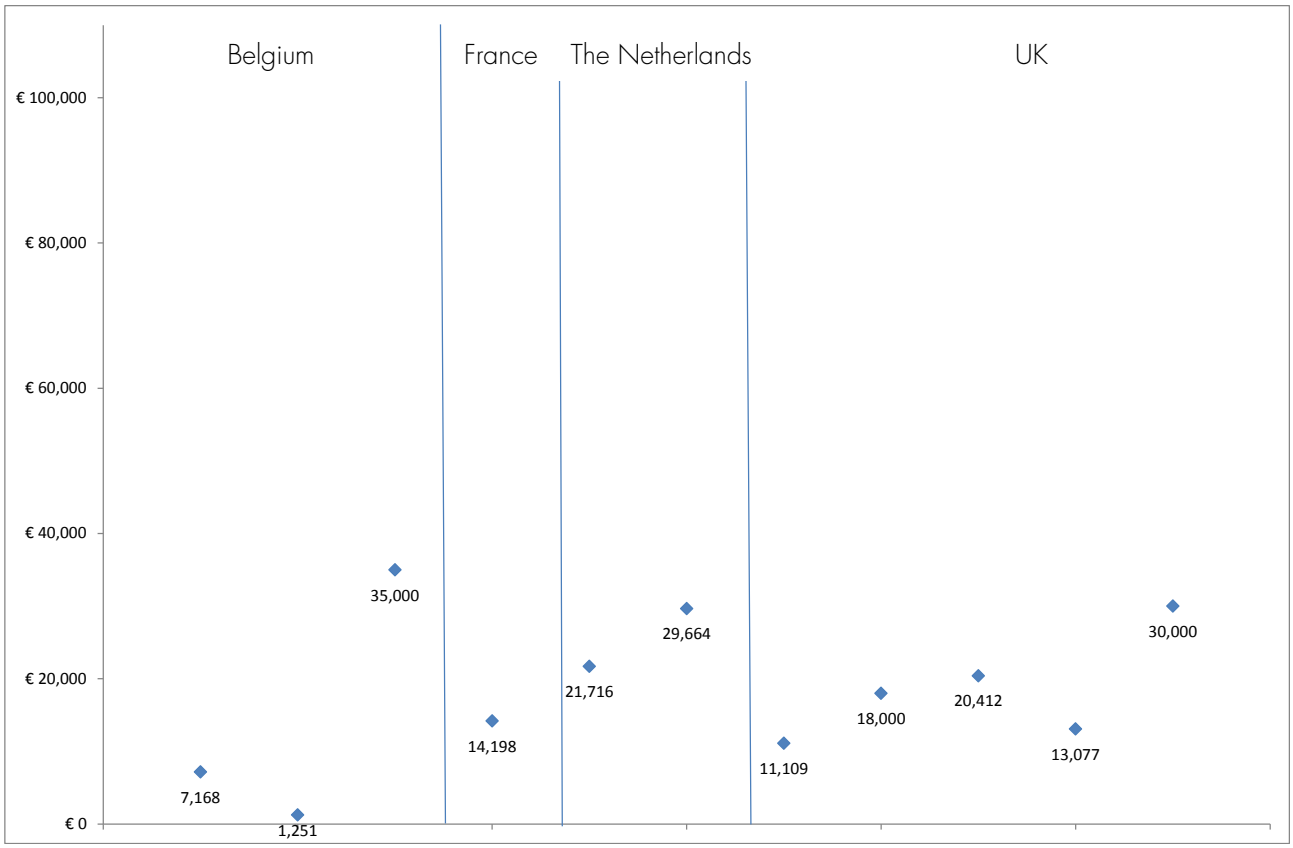


FIGURE 6. ICERs of varicella/herpes zoster vaccination by countries.



to jurisdictions (heterogeneity of screening programmes, vaccinations schedules, medical practices, etc.).

It is however relevant to comment some other issues emerging from the review.

1. Discounting and the current debate: some authors and institutions think that discounting favours short term over long term policies and so discriminates against preventative and other public health programmes. Interestingly, the National Institute for Health and Care Excellence (NICE) has accepted this view suggesting that "treatment effects are both substantial in restoring health and sustained over a very long period -normally at least 30 years-, the Committee should apply a rate of 1.5% for health effects and 3.5% for costs." [97]. On the opposite, the main stream of economic theory does not allow different rates for costs and benefits. Discounting raises the concern that arbitrary variation in study specification leads to arbitrary variation in results. In order to ensure best practice and correct policy choices, the decision makers and the economists would recognise the need for a common standard, i.e. by using the same discount rate, at least at national level.
2. Transparency of models and the current debate: in particular, transparency ("clearly describing the model structure, equations, parameter values and assumptions to enable interested parties to understand the model") [98] needs to be related to the possibility for the public agencies, decision makers for vaccinations campaign, to replicate the models.
3. The societal perspective strongly influenced the results, which were generally cost-effective from this viewpoint (e.g. in the case of rotavirus vaccination).

Finally, clarity is important, as confusion regarding the validity of comparisons with different discount rates, different age-population and different modelling between analyses can only serve to damage cost-utility analyses' credibility with decision makers and others. We acknowledge that this review might be not exhaustive of the eight countries considered, since only two databases were searched and only papers published in English were considered.

CONCLUSIONS

The published literature has shown that vaccination strategies are generally cost-effective in European countries.

High heterogeneity in the results among studies and countries was found.

Competing interests

Both authors received consulting fees from the GSK group of companies for the completion of this study.

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APPENDIX

1. HPV VACCINATION

First author, Year	Countries	Vaccine	Comparator	Patient population	Source of vaccine efficacy data	Time horizon	Perspective	Vaccine coverage	Discount rates	Vaccine price (per dose)	Model description	Sensitivity analyses (SAs)	Main cost-effectiveness results (ICUR)	Results of the SAs
Annemans, 2009	Belgium	HPV quadrivalent vaccination + existing screening	cervical screening alone	12-year-old girls	various published studies of non-specified design	lifetime	health care payer	80%	3.0% C 1.5% B	130.22€	Markov model	one- and two-way SAs	The ICUR was 10,546€	The addition of a booster vaccination and the discount rate were influential inputs but ICURs remained below the threshold of 45,000€/QALY
Thiry, 2009	Belgium	HPV quadrivalent vaccination + existing screening	cervical screening alone	12-year-old girls	meta-analysis and RCTs	lifetime	health care payer	84%, booster: 59%	3.0% C 1.5% B	114.5€	Markov model	Deterministic and probabilistic SAs	Compared to no vaccination, the ICUR with vaccination (plus booster at 22 years) was EUR 32,665€ (range: EUR 17,447€ to EUR 68,078€). The ICUR for vaccination at 12 years without booster was €14,382/QALY	The HPV vaccination strategy was dominated by screening alone in the scenario that assumed that screening coverage reduced to 59% (a reduction of 20%) or with a reduction in screening uptake of 10% or more
Demarteau, 2013	Belgium	HPV bivalent vaccination + existing screening	cervical screening alone	12- to 40-year-old females	RCTs	lifetime	health care payer	80%	3.0% C 1.5% B	431€ (full course)	Markov cohort model	one-way and probabilistic SAs	The ICUR of vaccination was 9,171€ at age 12 years, 17,348€ at age 26 years, and 42,847€ at age 40 years.	The discount rate was the most influential parameter in the univariate analyses. The probabilistic sensitivity analysis showed that HPV vaccination would be expected to remain cost-effective for vaccination up to 25–30 years
Bergeron, 2008	France	HPV quadrivalent vaccination + existing screening	cervical screening alone	14-year-old girls	RCTs	lifetime	direct health care costs and third-party payer	80%	3.5% C 1.5% B	€88.10 or €135.60 depending on the payer	Markov model	one-way SAs	The ICUR of vaccination was 13,809€ from the perspective of the direct health care payer and 8,408€ from the perspective of the third-party payer	Vaccination was cost-effective (ICUR<€50,000) in all scenarios
Demarteau, 2011	France	HPV bivalent vaccination + existing screening	cervical screening alone	12-year-old girls	RCTs	lifetime	health care payer	not reported	3.0% C 1.5% B	€133.82	Markov model	deterministic and probabilistic SAs	The ICUR with screening plus vaccination, compared with screening only, was 9,706€.	The discount rate was the most influential parameter in the univariate analyses. The probabilistic sensitivity analysis showed that progression and regression from HPV, CIN1, and CIN2/3 were the most influential parameters
Hillemanns, 2009	Germany	tetravalent HPV vaccination for girls aged 12 years added to existing screening	conventional screening alone	12-year-old girls	RCTs	lifetime	health care payer	80%	4.0% C 1.5% B	€143.8	Markov model of HPV infection and cervical cancer	one-way SAs	The ICUR of vaccination plus screening compared to screening alone was €10,530	ICURs were sensitive to variations in protection duration of less than 20 years and discount rates. Vaccine price did not affect model outcomes.
Schobert, 2012	Germany	quadrivalent HPV vaccination added existing screening	conventional screening alone	girls of 12-17 years	RCTs	lifetime	third-party payer	45% and 55% for the 12–14 and 15–17 respectively	3%	€451.20 (three doses plus administration)	Dynamic transmission model	one-way SAs	The ICUR of vaccination was €5,525	The results were most sensitive to discount rates, duration of vaccine protection and utility scores.
Mennini, 2009	Italy	quadrivalent HPV vaccine added to existing screening	conventional screening	12-year-old girls	RCTs	lifetime	health care provider	80%	3.0% C 1.5% B	€106	Markov model	one-way SAs	The ICUR of vaccination compared to screening only was €9,569	The ICURs ranged from ranged from €2,781 to €48,122. Influential inputs were discount rates and vaccine efficacy duration.
La Torre, 2010	Italy	HPV vaccination (bivalent vaccine) added to existing screening programme	conventional screening alone	12-year-old girls	meta-analysis of RCTs	lifetime	health care payer	not reported	3%	€90.00 (bivalent vaccine)	deterministic mathematical cohort model with a Markov structure	deterministic SAs	The ICUR of vaccination was €22,055	Influential inputs were discount rate and age at vaccination
Favato, 2012	Italy	various cervical cancer screening strategies added to HPV vaccination	screening alone	girls aged 12, 15, 18, and 25 years (depending on the strategy)	RCTs	lifetime	third-party payer (NHS)	Vaccin. register of the Basilicata Region (84.7%)	3.0% C 1.5% B	€69.13	Markov state-transition model	probabilistic SA and EVPI	Compared with no vaccination, the ICUR was €12,013 with the two-cohort strategy, €13,232 with the three-cohort strategy, and €13,890 with the four-cohort strategy.	The EVPI analysis suggested that model findings were subject to limited uncertainty
Coupe, 2009	NED	programme of bivalent HPV vaccination for girls aged 12 years, in addition to cytology-based cervical cancer screening for women	cervical screening alone	12-year-old girls	various published studies of non-specified design	lifetime	not explicitly stated but appears third-party payer	85%	4.0% C 1.5% B	€125	Markov model	deterministic SAs (scenario analyses)	The ICUR of adding vaccination to screening alone was €19,429 (range: €11,000 to €25,000)	variations in assumptions on the waning effect and price of vaccination had the strongest impact on ICURs
de Kok, 2009	NED	HPV bivalent vaccination added to the existing screening programme in women	conventional screening alone	12-year-old girls	not clearly reported	lifetime	society	85%	3%	€118	Microsimul. screening analysis (MISCAN) model	deterministic SAs	Compared to no screening alone, the ICUR of vaccination was €53,500	The threshold price per vaccine dose at which the cost-effectiveness of HPV vaccination would be €20,000 per QALY gained was € 40 under favorable assumptions. Vaccine efficacy and incidence of cervical cancer were also drivers of the model
Bogaards, 2011	NED	HPV vaccination for adult women	no vaccination	women aged 17 to 25 years	RCT	lifetime	society	50%	4.0% C 1.5% B	three prices: €125 (2010 pharmacy price), €65, and €35	individual-based simulation model	one-way SAs	At a vaccine price of €125, the ICUR with vaccination over no vaccination was €48,433 for all 17- to 25-year-olds (€22,526 at a vaccine price of €65 and €9,572 at a vaccine price of €35).	vaccine price was the main cost driver of the model. Other influential inputs were the discount rate and the inclusion of cross-protection
O'Mahony, 2011	NED	HPV vaccination for girls aged 12 years or older combined with existing screening	conventional screening alone	12-year-old girls	not reported (referred to a previous publication)	lifetime	not reported	not reported	4.0% C 1.5% B and also by a common rate of 4%	not reported	MISCAN microsimul. screening analysis model for 1, 10, 20, and 30 birth-cohorts	One-way SAs	The ICUR with vaccination was €101,700 with a discount rate of 4% for both costs and benefits and ranged between €22,100 to €29,900 depending on model assumptions with a discount rate of 4% for costs and 1.5% for benefits.	The ICUR decreases as the number of cohorts increases under differential discounting, but not under equal discounting
Westra, 2011	NED	HPV vaccine for women 12–50 years of age	no vaccination	women 12–50 years of age	RCTs	lifetime	not reported	100%	4.0% C 1.5% B	€105	Markov model	deterministic and probabilistic SAs as well as scenario analyses	The ICURs of vaccination over no vaccination were €19,900 for 12-year-old girls, €52,100 for 30-year-old women, and remained below the threshold of €30,000 for women < 23 years of age.	ICURs were sensitive to variations in vaccine price and assumptions about vaccine efficacy and duration of protection

First author, Year	Countries	Vaccine	Comparator	Patient population	Source of vaccine efficacy data	Time horizon	Perspective	Vaccine coverage	Discount rates	Vaccine price (per dose)	Model description	Sensitivity analyses (SAs)	Main cost-effectiveness results (ICUR)	Results of the SAs
Westra, 2011	NED	HPV vaccine for women 12–50 years of age	no vaccination	women 12–50 years of age	RCTs	lifetime	not reported	100%	4.0% C 1.5% B	€105	Markov model	deterministic and probabilistic SAs as well as scenario analyses	The ICURs of vaccination over no vaccination were €19,900 for 12-year-old girls, €52,100 for 30-year-old women, and remained below the threshold of €30,000 for women < 23 years of age.	ICURs were sensitive to variations in vaccine price and assumptions about vaccine efficacy and duration of protection
Coupe, 2012	NED	various cervical cancer screening strategies added to HPV vaccination	conventional screening alone (no vaccination)	women of different ages, depending on the screening strategy		lifetime	society	95%	4.0% C 1.5% B		individual-based simulation model	deterministic SAs	Four times HPV DNA screening between 30 and 60 years was the selected scenario in addition to HPV16/18 vaccination, whether or not cross-protection was conferred (€6,707 and €9,994/QALY, respectively). In the absence of cross-protection, a fifth screening round might be considered (ICUR €22,967/QALY).	If the vaccine-induced type-specific incidence reduction was lowered to 99%, one screen during lifetime was cost-effective even in addition to 13-valent vaccination
Luttjeboer, 2013	NED	bivalent HPV vaccination	conventional screening	12-year-old girls	manufacturer	lifetime	not explicitly stated but appears health care payer	100%	4.0% C 1.5% B	€120	Markov cohort model	deterministic and probabilistic SAs plus scenario analyses	The ICUR with vaccination was €5,815 when including cross-protection and €7,142 when excluding it	The median ICUR was €5,028, the full range of simulations fell between €2,800 and €8,700. vaccine price and discount rate were influential inputs
	NED	bivalent and quadrivalent HPV vaccination	no vaccination	12-year-old girls	studies of unclear design	lifetime	not explicitly stated but appears third-party payer	50%	4.0% C 1.5% B	€105	Markov model	one-way SAs	The ICURs with bivalent and quadrivalent vaccines were €17,600 and 18,900, respectively.	Discount rate for health benefits, duration of protection, and vaccine price were influential inputs
Dasbach, 2008	UK	quadrivalent HPV vaccination for girls aged 12 years or older combined with existing screening	no vaccination	girls aged 12 years or older	RCT	lifetime	third-party payer (NHS)	12–14 years 40%, 15–17 years 30%, 19–24 years 25% in the first year of catch-up	3.5%	£75	previous disease transmission model	one-way SAs and scenario analyses	Routine vaccination of 12-year-olds was weakly dominated. The ICURs over the next non-dominated alternative was: £5,882 with routine vaccination and 12 to 14 year-old catch-up (versus no intervention); £5,971 with routine vaccination and 12 to 17 year-old catch-up (versus 12 to 14 year-old catch-up); and £11,412 with routine vaccination and 12 to 24 year-old catch-up (versus 12 to 17 year-old catch-up)	the two most influential model inputs were health utility values and duration of vaccine protection
Jit, 2008	UK	routine HPV vaccination of 12-year-old girls[2], three doses, and the use of a bivalent vaccine with protection against HPV types 16 and 18 only	no vaccination	12-year-old girls and other age-sex-stratified cohorts	published sources of unclear design	lifetime	health care payer	80%	3.5%	£60 (catalogue price in the USA) and £80.50 (private price in the UK)	transmission dynamic model	deterministic and probabilistic SAs	Compared to no vaccination, the median ICUR with vaccination of 12-year-old girls was £22,474 (95% CI: £13,722 to £32,920).	If vaccine protection lasted for 10 years only, then the ICUR would increase to £33,868. the ICUR with a catch-up programme for girls aged 12 to 18 years was £11,856 (95% CI: cost-saving to £31,107). Vaccination for both girls and boys was not cost-effective.
Kulasingam , 2008	UK	school-based quadrivalent HPV vaccine added to existing screening	conventional screening alone	12-year-old girls	RCT plus assumptions and other studies	lifetime	health care payer	85%	3.5%	£75	Markov model	one- and multi-way Sas	The ICUR of vaccination was £21,059	Results were sensitive to assumptions about the need for a booster, the duration of vaccine efficacy and discount rate
Jit, 2011	UK	bivalent and quadrivalent HPV vaccination	no vaccination	12-year-old girls	RCTs and assumptions	lifetime	health care payer (NHS)	80%	3.5%	£84.50	transmission dynamic model	Probabilistic SAs	Considering various scenarios and assumptions, the ICURs ranged from £12,000 to £22,000 for quadrivalent vaccination and from £16,000 to £41,000 with bivalent vaccination	At a threshold of £30,000 per QALY, the bivalent vaccine needs to be cheaper than the quadrivalent vaccine to be equally cost effective, mainly because of its lack of protection against anogenital warts. The price difference per dose ranged from a median of £19 to £35 across scenarios about vaccine duration, cross protection, and end points prevented.
Rogoza, 2008	UK, NED	HPV vaccination for girls aged 12 years or older combined existing screening	conventional screening alone	12-year-old girls	previous modelling studies and RCTs	lifetime	health care payer (UK) and society (the Netherlands)	100%	3.5% UK; 4% C, 1.5% B NED	€105 in the Netherlands and £84 in the UK	Markov model	One-way SAs	The ICUR of vaccination was €18,472 in the Netherlands and £18,037 in the UK	overall, ICURs remained below commonly used cost-effectiveness thresholds

1.Four strategies were considered: routine vaccination at age 12 years, and routine vaccination at age 12 years combined with temporary catch-up vaccination at ages 12–14, 12–17 and 12–24 years. 2. Various alternative HPV vaccination strategies were as follows: vaccinating girls at ages 13 or 14, vaccinating boys and girls at age 12, a catch-up campaign in the first year of vaccination to vaccinate females from age 12 to ages 14, 16, 18 or 25, achieving a coverage of 70% or 90% for the full.

2. PNEUMOCOCCAL VACCINATION

First author, Year	Countries	Vaccine	Comparator	Patient population	Source of vaccine efficacy data	Time horizon	Perspective	Vaccine coverage	Discount rates	Vaccine price (per dose)	Model description	Sensitivity analyses (SAs)	Main cost-effectiveness results (ICUR)	Results of the SAs
Talbird, 2010	Germany	routine vaccination of infants with a new 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PCV-10)	7-valent pneumococcal conjugate vaccine (PCV-7)	infants and young children	a published study of non-specified design	one year	health care payer	about 90%	Undisc.	not reported but price parity was assumed	steady-state population model	deterministic SAs	In the one-year analysis, PCV-10 dominated (i.e. more effective and less expensive than) PCV-7	base case results were robust. vaccine efficacy and waning were the most influential inputs
Jiang, 2012	Germany	23-valent pneumococcal polysaccharide vaccine (PPV23)	no vaccination	immunocompetent adults; immunosuppressed adults; and elderly people	A recent Cochrane systematic literature review and meta-analysis of ten prospective clinical trials	lifetime	third-party payer and society	not clearly reported	3%	€30.25	population-based Markov model	one-way SAs and probabilistic SAs	The ICUR with vaccination over no vaccination was €17,065 from the perspective of the third-party payer and €25,687 from the societal perspective	The ICUR was sensitive to the vaccine effectiveness against nonbacteremic pneumococcal pneumonia (NBPP), waning function and incidence of NBPP. PPV23 was cost effective in 86.7% of the cases when the willing-to-pay was set at €30,000 per QALY gained, while the rate increased to 98.1% when the willing- to-pay was at €50,000 per QALY gained.
Boccalini, 2013	Italy	various age-based vaccination programmes with 13-valent polysaccharide conjugate vaccine (PCV-13) for elderly people[1]	no vaccination	subjects aged 65 years or over	RCTs	five years	health care payer	50%	3%	PCV-13: €42.50; PCV-23: €16	mathematical population model	univariate and multivariate SAs	Compared to no vaccination, the ICURs were €16,987 with the single-cohort strategy, €19,289 with the two-cohort strategy, and €22,109 with the three-cohort strategy. The ICURs increased to €21,493, €24,443, and €27,866, respectively, including the sequential PCV-13 + PCV-23 immunisation.	Base case results were robust. Rate of community-acquired pneumonia and PCV-13 vaccination coverage rates were influential inputs
Bos, 2003	NED	Universal infant vaccination with the seven-valent pneumococcal conjugate vaccine (PCV-7)	no vaccination	infants	published studies of unclear design	lifetime	society	not reported	4%	€40	decision tree model	univariate SAs	at a vaccine price of €40, the ICUR of vaccination was €71,250 (€79,500 excluding indirect costs)	incidence of infections, vaccine efficacy and vaccine price were the most influential inputs
Hubben, 2007	NED	national infant vaccination programme with the four doses PCV-7	no vaccination	infants	various published studies of non-specified design	10 years	society	not reported	4%	€50 (with administ. costs)	a previous model	deterministic and probabilistic SAs	The ICUR with vaccination compared to no vaccination was €14,000	The sensitivity analysis showed that assumptions on herd immunity and vaccine cost had a strong impact on the cost-effectiveness results. The ICURs ranged from €9,800 to €20,200.
Rozenbaum, Hak, 2010	NED	PCV-13 in the elderly	no vaccination (23PPV only to a few individuals at substantially increased risk)	people aged ≥65 years (both whole population and those at increased risk for pneumonia)	previous cost-effectiveness analyses	lifetime	society	83% among high-risk 65% among low-risk	4.0% costs 1.5% benefits	€50 (assumed)	decision-tree analytic model	alternative scenarios about key inputs of the model	In the base case scenario in the total population, the ICUR of vaccination was €14,416 without indirect effect and €31,055 with indirect effects (€8,547 and ERUR 22,152 in the high-risk population).	The model was sensitive to variations of vaccine efficacy parameters
Rozenbaum, Sanders, 2010	NED	three pneumococcal conjugate vaccines: PCV-7, PCV-10, and PCV-13	no vaccination	infants	RCTs and observational studies	five years	not explicitly stated but appears society	95%	4.0% costs 1.5% benefits	PCV-7: €50; PCV-10: €62.25; PCV-13: €68.56	decision tree model	deterministic and probabilistic SAs	Compared to no vaccination, the ICUR was €113,891 with four-dose PCV-7 (€82,975 with three-dose PCV-7), €52,947 with PCV-10, and €50,042 with four-dose PCV-13 (€35,743 with three-dose PCV-13)	increases in herd protection and reductions in vaccine prices reduced the ICURs. Overall, the likelihood of PCV-7 being cost-effective was low
Rozenbaum, van Hoek, 2010	NED	routine infant vaccination with PCV-7	no vaccination	infants	RCTs	five years	society	not reported but might be 95% as previous model	4.0% costs 1.5% benefits	€50	a published static cohort model	not reported	Compared to no vaccination, the ICUR with PCV-7 was €72,360 without net-indirect effects (herd protection minus serotype replacement) and €16,750 with net-indirect effects	At an ICUR threshold of €50,000, the net-indirect effects of vaccination need to be at least 16% of those observed in the US studies for vaccination to remain cost-effective
Diez-Domingo, 2011	Spain	A three-dose schedule (two doses and a booster) of PCV-13, given in the first year of life	no vaccination	babies in their first year of life	RCTs	lifetime	health care payer	95%	3%	€4,708 (calculation not clear)	decision tree model	one-way SAs and scenario analyses	The ICUR with vaccination over no vaccination was €10,407	assumptions on herd effects and serotype replacement were model driver but in most scenarios the ICUR remained within the cost-effectiveness threshold of €30,000
Bergman, 2008	Sweden	PCV-7 in infants	no vaccination	infants	RCT	lifetime	society	close to 100%	3%	€55.30	a published Markov model	one-way SAs	The ICUR was €29,200 (€5,500 when including herd immunity)	the most influential inputs were discount rate, inclusion of indirect costs, vaccine efficacy against acute otitis media (AOM), incidence of AOM, and vaccine price
By, 2012	Sweden	10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) and 13-valent pneumococcal conjugate vaccine (PCV-13)	no vaccination	infants and young children	a previous cost-effectiveness study	lifetime	society	100%	3%	SEK 518.95	Markov cohort model	one-way SAs	ICURs were not calculated as PHiD-CV resulted in improved health outcomes of 45 QALYS at a cost of 62 million SEK less than PCV-13. Thus PHiD-CV was the dominant strategy (less costly, more effective) over PCV-13.	results were sensitive to changes in the acute otitis media related outcome parameters
Klok, 2013	Sweden	Universal infant vaccination with PCV-10	Universal infant vaccination with the 13-valent pneumococcal conjugate vaccine (PCV-13)	infants	published studies of unclear design plus assumptions	lifetime	health care payer	100%	3.0% C benefits not discounted	SEK 518.95	decision-analytic model	deterministic SAs	PCV-13 was the dominant strategy over PCV-10	base case results were robust in all scenarios
Melegaro, 2004	UK	Universal infant vaccination with the seven-valent pneumococcal conjugate vaccine (PCV-7)	no vaccination	infants	RCTs	lifetime	third-party payer (NHS)	probably 100%	3.5% C 1.5% B	£30	cohort model	deterministic and probabilistic SAs	The ICUR of vaccination over no vaccination was £59,945	the most influential inputs were the incidence of invasive pneumococcal disease, the inclusion of herd immunity effects, and the cost of the vaccine. In the base-case, only 29% of the model simulations resulted in a cost per QALY gained of less than £30,000.

First author, Year	Countries	Vaccine	Comparator	Patient population	Source of vaccine efficacy data	Time horizon	Perspective	Vaccine coverage	Discount rates	Vaccine price (per dose)	Model description	Sensitivity analyses (SAs)	Main cost-effectiveness results (ICUR)	Results of the SAs
Knerer, 2012	UK	the pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV), which is a 10-valent pneumococcal conjugate vaccine was compared to 13-valent pneumococcal conjugate vaccine (PCV-13)	no vaccination	newborns and young children	published sources of unclear design supplemented by expert opinion	lifetime	not explicitly stated but appears third-party payer	100%	not reported	£27.60	Markov cohort model	deterministic and probabilistic SAs	PHiD-CV vaccination was found to be dominant (more effective and less costly) over PCV-13	acute otitis media-related outcome parameters were drivers of the model. the probability that PHiD-CV was dominant over PCV-13 was 95%
Rozenbaum, 2012	UK	13-valent pneumococcal conjugate vaccine (PCV-13) added to the 23-valent polysaccharide vaccination, for those at high risk, and the usual infant vaccination programme	no PCV-13 vaccination (usual care consisting of the 23-valent polysacc. vaccination, for those at high risk, and the usual infant vaccination programme)	people at high risk aged two years or older	an expert panel of five members	lifetime	health care payer (NHS)	risk-groups (100%)	3.5%	£49.10	cohort decision model	deterministic and probabilistic SAs	The ICUR of the vaccination programme was estimated to be £183,680, assuming no impact on non-bacteraemic pneumonia. Only vaccination of one risk group, those with chronic liver disease, resulted in a ratio of cost per QALY that was below £30,000.	When an impact on non-bacteraemic pneumonia was assumed, the ICURs for the individual risk groups ranged from £10,825 to £37,686. Vaccine efficacy and predicted herd effects of the infant programme were influential inputs.
van Hoek, 2012	UK	13-valent pneumococcal conjugate vaccine (PCV-13)	discontinuing PCV-7	infants	previous modelling study	30 years	NHS	not reported	3.5%	£49.60	dynamic infectious disease model	probabilistic Sas and scenario analyses	Using a threshold of £30,000 per QALY gained, introducing PCV- 13 is cost-effective in 100% of parameter combinations sampled if non-invasive disease outcomes are included, but only 33% if they are not.	vaccine price and discount rate were influential inputs
Ament, 2000	Spain Sweden Belgium France UK	pneumococcal vaccination in people aged 65 years or over to prevent both pneumococcal pneumonia and invasive pneumococcal disease	no vaccination	people aged 65 years or over	a published case-control study	Lifetime	society	probably 100%	3%	Belgium: €19; France: €13.8; Scotland: €14.3, Spain: €11.5; Sweden: €10.2	not specified	one- and two-way SAs	to prevent invasive pneumococcal disease, the ICUR was €25,907 for Belgium, €19,182 for France, €14,892 for Scotland, €10,511 for Spain, and €32,675 for Sweden. To prevent pneumococcal pneumonia, the ICUR was €2,126 for France, €242 for Scotland, and dominant for Belgium, Spain, and Sweden.	key drivers of the model were vaccine administration costs, incidence of disease, and mortality rate of invasive disease
Evers, 2007	Italy Spain Sweden Germany Belgium France NED, UK	pneumococcal vaccination with 14- and 23-valent pneumococcal polysaccharide vaccine in the elderly	no vaccination	people older than 65 years of age	a published case-control study	lifetime	not explicitly stated but appears third-party payer	probably 100%	3%	Bel: €17.9; UK, SPA €14.4; Fra: €13.6; GER: €27.1; ITA: €25.8; NED €17.5; SCO: €14.4; SWE: €7.5	cohort model	one- and two-way SAs	In the cohort of 65-year-olds, the ICUR of vaccination over no vaccination was €22,847 in Belgium, €17,228 in England and Wales, €17,444 in France, €17,093 in Germany, €16,544 in Italy, €13,740 in the Netherlands, €13,920 in Scotland, €12,027 in Spain, and €23,657 in Sweden	results were sensitive to variation in the incidence and mortality of invasive pneumococcal disease, administration costs of the vaccine and vaccine effectiveness.
Strutton, 2012	Netherlands Germany	13-valent pneumococcal conjugate vaccine (PCV-13) in the paediatric national immunisation programme	7-valent and 10-valent PCVs (PCV-7 and PCV-10)	infants and young children	RCTs and assumptions	Lifetime	third-party payer	80% Germany; 95% Netherlands	5% Germany; 4% costs, 1.5% outcomes NED	GER: €49 for PCV-7 and PCV-13, EUR39.90 for PCV-10. NED: €57.13 for PCV-7 and PCV-10 and €68.56 for PCV-13	decision tree model	scenario analyses	Compared to PCV-7, PCV-13 was dominant in Germany and had an ICUR of €38 in the Netherlands. Compared to PCV-10, PCV-13 was dominant both in Germany and in the Netherlands.	The scenario analysis showed that PCV-13 remained the preferred strategy (dominant or cost-effective at a threshold of €50,000 per QALY) over PCV-10 in all scenarios except when PCV-10 direct effects were adjusted for immunogenic response and neither the 13-valent nor the 10-valent vaccine incurred indirect effects.

1. immunization of 65 y-old subjects (single-cohort strategy), simultaneous vaccination of people aged 65 and 70 y (double-cohort strategy) and, lastly, simultaneous immunization of subjects aged 65, 70 and 75 y (triple-cohort strategy). The additional impact of administration of a PPV23 dose, one year after PCV13, was evaluated

3. ROTAVIRUS VACCINATION

First author, Year	Countries	Vaccine	Comparator	Patient population	Source of vaccine efficacy data	Time horizon	Perspective	Vaccine coverage	Discount rates	Vaccine price (per dose)	Model description	Sensitivity analyses (SAs)	Main cost-effectiveness results (ICUR)	Results of the SAs
Blicke, 2009	Belgium	universal (fully reimbursed) childhood rotavirus vaccination with either two-dose Rotarix or three-dose RotaTeq	no vaccination and the current pattern of care in Belgium (partial reimburses. of the two-dose Rotarix or the three-dose RotaTeq)	infants	RCTs	7 years	health care payer and society	98%	3.0% costs 1.5% benefits	Rotarix €56; RotaTeq €37	deterministic static model	deterministic and probabilistic SAs	Compared with no vaccination, fully funded universal rotavirus vaccination would cost €51,030 per QALY gained with Rotarix and €65,767 with RotaTeq (for society, €7,572 and €30,227 per QALY, respectively). Fully funded universal vaccination dominated partially funded private vaccination because the former is cheaper per vaccinated person and at least as effective as the latter.	ICURs are most influenced by the uncertainty regarding the annual probability to die due to rotavirus and waning of efficacy against rotavirus episodes of any severity (health care payer perspective) and the number of days of work absence for non-hospitalised rotavirus cases (societal perspective)
Melliez, 2008	France	routine childhood vaccination against rotavirus (with Rotarix and RotaTeq that were not considered separately)	no vaccination	infants	RCTs	three years	society	75%	3%	€150 per course	Markov model	one- and two-way SAs	The ICUR with vaccination over no vaccination was €138,693 (€98,000 using Rotarix at €114 per course and €151,000 using RotaTeq at €161 per course)	the most influential model inputs were disease incidence, mortality rates, and vaccine price
Standaert, 2008	France	two-dose vaccine against rotavirus infection	no vaccination	infants	RCT	lifetime	limited social perspective (no indirect costs)	85%	3.0% C 1.5% B	€57	Markov model	univariate and multivariate SAs	The ICUR of routine vaccination was €44,583	influential inputs were the probabilities of moving from diarrhoea to severe diarrhoea, of seeking medical advice and of going to an emergency clinic; the utility scores for diarrhoea versus in children and infants; the rate of non-rotavirus-related hospitalizations; the discount rate applied to the effect measure; and the hospitalization cost. Overall, 94% of the ICURs were under an informal threshold of €50,000 per QALY
Panatto, 2009	Italy	a programme of universal vaccination (Rotarix) against rotavirus for newborns	no vaccination	newborns	RCTs	five years	health care payer and society	90%	4.0% C 1.5% B	€40	a published state-transition Markov model	not reported	In comparison with no vaccination, the ICUR with vaccination was €9,186 from the perspective of the health care payer. Vaccination was dominant from the viewpoint of the society	not reported
Goossens, 2008	NED	mass vaccination strategy with the human live-attenuated oral vaccine Rotarix (RIX4414) for the active immunisation of infants from the age of six weeks	no vaccination	children from birth to 4 years of age	the European 036 study, which included 3,994 patients	lifetime	society	100%	4.0% C 1.5% B	€100	Markov model	deterministic and probabilistic SAs	The ICUR with vaccination over no vaccination was €28,488 (€21,900 at a vaccine price of €90 and €35,076 at a vaccine price of €110)	The probability of being hospitalised was the main driver of the model. at a willingness to pay of €50,000 per QALY, the probability of being cost-effective for mass vaccination was around 83%
Mangen, 2010	NED	two rotavirus vaccines, namely RotaTeq and Rotarix, added to the national immunisation programme for infants	no vaccination	infants (under one year of age)	recently published European cost-effectiveness analyses (no clear details were reported)	20 years	health care payer and society	97%	4.0% C 1.5% B	Rotarix €45; RotaTeq €28	discrete-event model	one-way SAs	ICURs were reported only in a graph, which showed lower (i.e. more favourable) ratios for Rotarix than RotaTeq but either vaccines were around or above the figure of €50,000 per QALY.	Vaccine-related costs, annual epidemic-size, and indirect protection are the major factors that determine cost-effectiveness of rotavirus vaccination
Rozenbaum , 2011	NED	Routine rotavirus vaccination of infants (Rotarix and RotaTeq were assumed to be interchangeable)	no vaccination	infants	RCTs	five years	society	95%	4.0% C 1.5% B	€75 (ranging from €50 to €100)	decision-tree model	deterministic and probabilistic SAs	The ICUR of vaccination was €46,717 at a vaccine price of €75 per child and €85,468 at a vaccine price of €100 per child.	at a cost of €75 per child vaccinated, influential inputs were costs of hospitalisations, potential herd immunity protection effects and mortality in hospitalised cases. The probability of rotavirus vaccination being cost-effective was 74% at a threshold of €50,000 per QALY and 14% at a threshold of €20,000 per QALY
Bruijning-Verhagen, 2013	NED	targeted rotavirus vaccination of high-risk infants and universal vaccination	no vaccination	infants	vaccine trials	20 years	health care payer and society	88%	3%	universal vaccine: €75; targeted vaccine: €100	age-structured stochastic multi-cohort model	univariate and multivariate SAs	compared to no vaccination, from a health care payer perspective, the ICUR was €2,600 with targeted vaccination and €60,200 with universal vaccination (€162,000 with universal versus targeted vaccination)	at a threshold of €35,000 per QALY, the probability of being cost-effective from the perspective of the health care payer was 6% with universal vaccination and 100% with targeted vaccination (71% and 100%, respectively from the societal perspective). the key model driver was the mortality rate.
Tu, 2013	NED	Routine rotavirus vaccination of infants	no vaccination	infants	RCTs	five years	society	95%	4.0% C 1.5% B	€75 (ranging from €50 to €100)	decision-tree model	deterministic and probabilistic SAs	The ICUR of routine vaccination was €15,600 (no herd immunisation) and €3,800 with herd protection in children up to 5 years	not reported
Perez-Rubio, 2011	Spain	vaccination for rotavirus with RotaTeq or Rotarix	no vaccination	infants	RCTs	five years	health care payer and society	100%	5%	€69.50 (RotaTeq) and €93.66 (Rotarix)	decision tree model	one-way SAs of vaccine price	With RotaTeq, the ICUR of vaccination compared with no vaccination was €74,958 from the healthcare payer perspective and €45,624 from the societal perspective. With Rotarix, the ICUR of vaccination compared with no vaccination was €52,603 from the healthcare payer perspective and €23,435 from the societal perspective.	reductions in vaccine price were required for the vaccination strategies being cost-effective

First author, Year	Countries	Vaccine	Comparator	Patient population	Source of vaccine efficacy data	Time horizon	Perspective	Vaccine coverage	Discount rates	Vaccine price (per dose)	Model description	Sensitivity analyses (SAs)	Main cost-effectiveness results (ICUR)	Results of the SAs
Jit, 2007	UK	three-dose RotaTeq and two-dose Rotarix	no vaccination	infants	RCTs	5 years	health care payer	95%	3.5%	Rotarix £35, RotaTeq £25	cohort model	deterministic and probabilistic SAs	Compared with no vaccination, the ICUR was £79,905 with RotaTeq and £60,928 with Rotarix.	When including the economic value of work lost by caregivers, the ICURs improved to £74,000 for RotaTeq and £54,500 for Rotarix. At the base case vaccine prices, neither vaccination strategy was cost-effective. Influential inputs were the QALYs lost by caregivers per episode, the cost of the vaccine and, for RotaTeq only, and vaccine efficacy against non-hospitalised cases.
Martin, 2009	UK	universal infant rotavirus vaccination	no vaccination	infants	RCT	lifetime	health care payer and society	88%	3.5%	£41.38	Markov model	deterministic and probabilistic SAs	The ICUR of vaccination compared with no vaccination was £23,298 from the NHS perspective, and £11,459 from the societal perspective	the cost of hospitalisation and the number of GP visits were the most influential variables. Vaccination, compared with no vaccination, had over 90% probability of an ICUR below £30,000 per QALY.
Jit, 2009	Belgium, UK, France, the NED	Rotarix (and RotaTeq)	no vaccination	infants	RCTs	lifetime	health care provider (and society)	70%	3%	**Rotarix:** €56 for Bel, €54 for UK, €62 for Fra and €45 for NED. **RotaTeq:** €37 for Bel, €44 for UK, €48 for Fra and €28 for NED.	age structured cohort model	deterministic SAs and scenario analyses	At a threshold of €30,000 per QALY, rotavirus vaccination was not cost-effective in the four countries from the perspective of the health care payer and not including indirect effects. Ratios were only displayed in graphs.	A key input was the discount rate. Vaccination became cost-effective when considering indirect protection and societal costs. Rotavirus vaccination is unlikely to be cost effective in any of the five countries studied if the vaccines are supplied at their market price.

4. INFLUENZA

First author, Year	Countries	Vaccine	Comparator	Patient population	Source of vaccine efficacy data	Time horizon	Perspective	Vaccine coverage	Discount rates	Vaccine price (per dose)	Model description	Sensitivity analyses (SAs)	Main cost-effectiveness results (ICUR)	Results of the SAs
Livartowski, 1996	France	Vaccine against Haemophilus influenzae type b (Hib)	no vaccination	children aged under five years	published sources of unclear design	10 years	health care payer (national health insurance system) and families (co-payments)	100%	6%	about FF 108.50 per injection (difference between the pentavalent and the quadrivalent vaccines)	not specified	one-way SAs	The ICUR of vaccination compared with no vaccination was FF 34,050 from the perspective of the French national health insurance system and FF 64,688 when considering the patients' families financial burden	The most influential inputs in terms of cost per life-year gained were incidence of meningitis, meningitis mortality rate, number of vaccine doses needed to assure efficacy, and discount rate
Marchetti, 2007	Italy	two strategies for childhood influenza vaccination: vaccination of all children aged 6 to 60 months versus vaccination of all children aged 6 to 24 months	the current strategy of vaccination of children at high-risk	healthy children aged 6 to 60 months	meta-analysis of RCTs plus two Italian RCTs	5 years	health care payer and society	30%	3%	€5.50	decision tree model plus Markov model	deterministic and probabilistic SAs	from the perspective of the third-party payer and in comparison with the current strategy, the ICUR was €13,333 with the vaccination of 6- to 24-month-old children and €10,000 with the vaccination of 6- to 60-month-old children. From the perspective of society, both vaccination strategies were dominant.	ICURs were generally robust. From the perspective of the health care system, influenza vaccination of children aged 6 to 60 months and of children aged 6 to 24 months had probabilities of 86% and 74%, respectively, of costing less than €50,000 per QALY gained over current vaccination. From the perspective of society, the two vaccination strategies had 89% and 80% probability, respectively, of being cost-effective.
Abellán, 2007	Spain	routine influenza vaccination for all adults aged 50–64 years	current policy of vaccinating only those aged 50–64 years who are at high risk of complication from influenza and healthcare/social workers	people over 50 years of age	a systematic Cochrane review of 10 RCTs and a meta-analysis of 20 cohort studies in elderly persons	lifetime	third-party payer and society	31.31% high-risk/eligible 21.04% low-risk/non-eligible	3%	€3.42	probabilistic decision analytic model	deterministic and probabilistic SAs	The ICUR of vaccination was €14,919 from the perspective of the third-party payer and €4,149 from a societal perspective	The most influential variable was the attack rate. The ICURs never exceeded €50,000 and in few cases were higher than €20,000. At a threshold of €50,000 per QALY gained, the probability of the new policy being cost-effective was 93% from the third-party payer perspective, and 97% from the societal perspective.
Navas, 2007	Spain	universal influenza vaccination of children	no vaccination	preschool and school aged children (i.e. 3 to 14 years)	a prospective cohort study in healthy children aged 3 to 14 years attending private paediatric clinics in Barcelona, Spain, during 2004/2005	6 months	health care payer and society	probably 100%	not necessary	€4.35	decision tree analytic model	One-way SAs	Vaccination had an ICUR of €18.26 from the perspective of the health care payer and was dominant from a societal viewpoint	vaccine price and cost of work absenteism were model drivers
Allsup, 2004	UK	Influenza vaccination for healthy people aged 65 to 74 years	no vaccination (placebo)	community-dwelling people between the ages of 65 and 74 years, without any of chronic illnesses for influenza vaccine	RCT	one year	third-party payer (NHS)	60%	not necessary	£3.30	modelling was used to extrapolate the clinical and economic outcomes of the trial to the population of 65- to 74-year-olds in England	one-way SAs	The ICUR from the perspective of the NHS was £304,000 (approximately)	only in the best scenario, the ICUR approached £50,000 per QALY, but in many scenarios was higher than £300,000 per QALY
Turner, 2006	UK	adult influenza vaccination	no vaccination	healthy adults aged between 50 and 64 years	Cochrane review	unclear	health care payer and society	not reported	not applied	£5.40	decision tree model	deterministic and probabilistic SAs	The ICUR with vaccination was £6,174 from the perspective of the NHS and £10,766 from the perspective of the society	The cost per QALY remained below £30,000 in all sensitivity analyses
Baguelin, 2010	UK	various H1N1v influenza vaccination strategies were considered	no vaccination	depending on the vaccination strategy	RCTs of seasonal influenza vaccines plus authors' assumptions	lifetime	health care payer	70% high-risk 40% low-risk	3.5%	£10 (not included in the base case analysis)	deterministic transmission dynamic model	Probabilistic SAs and regression analysis	ICURs of the vaccination strategies were not reported. If the cost of vaccine purchase itself is treated as a sunk cost, vaccinating risk groups very likely to be cost-effective, since most ICURs lie below the £20,000 per QALY gained threshold.	The most influential parameter is the overall size of the epidemic without vaccination, followed by QALY loss per case, hospitalisation rates and costs, and case-fatality ratios
Jit, 2010	UK	Seasonal influenza vaccination for women in their second or third trimester of pregnancy	no vaccination	pregnant women	a 2007 Cochrane review that pooled the results of several RCTs	two years	third-party payer (NHS)	45%	3.5%	£6.04	decision tree model	deterministic and probabilistic SAs	In the base case (infants partially protected and no vaccine efficacy after the first season), the ICUR was £23,000 (95% CI: £10,000 to £140,000). The ICUR was £28,000 assuming no infant protection and £15,000 when infants and mothers were protected for the second season.	The most influential inputs were the quality of life lost with clinically apparent influenza and the cost of vaccine administration. The probability of vaccination being cost-effective was 69% at a threshold of £30,000 per QALY (54% in the scenario without infant protection and 87% in the scenario with second season protection).
Baguelin, 2012	UK	the current influenza vaccination programme for clinical risk groups and for those aged 65 years or older	no vaccination	people aged 65 years or over and clinical risk groups (people of all ages with chronic respiratory, heart and renal diseases, diabetes, and immunosuppression due to disease or treatment)	a published study of non-specified design	lifetime	not explicitly stated but appears third-party payer	20%	3.5%	£6.04	a published age-structured dynamic model of influenza transmission	deterministic and probabilistic SAs	At the accepted willingness-to-pay threshold of between £20,000 to £30,000 per QALY gained, vaccination was likely to be cost-effective in all scenarios, except when the influenza strain was mild and the vaccine was poorly matched to that strain	influential inputs were strain severity and match to vaccine, QALY loss for case, proportion of febrile cases, and vaccine administration costs

First author, Year	Countries	Vaccine	Comparator	Patient population	Source of vaccine efficacy data	Time horizon	Perspective	Vaccine coverage	Discount rates	Vaccine price (per dose)	Model description	Sensitivity analyses (SAs)	Main cost-effectiveness results (ICUR)	Results of the SAs
Pitman, 2013	UK	paediatric influenza vaccination using two vaccines (either live attenuated influenza vaccine LAIV or trivalent inactivated influenza vaccine TIV) and different age groups[2]	no vaccination	children	RCTs	lifetime	third-party payer (NHS)	50%	3.5%	£5.81 for both vaccines	dynamic transmission model	deterministic and probabilistic SAs	the current vaccination policy was cost-saving over no vaccination. After excluding dominated strategies, the ICUR were £506 with current policy plus LAIV in 2-10 year olds and £298 with current policy plus LAIV in 2-18 year olds	vaccinating 2–18 year olds with LAIV was invariably the policy with the highest probability of being cost-effective. Influential inputs were vaccine uptake and changes in the basic reproductive number of the virus.
Abalos, 2007	Italy Germany France	vaccination for all individuals aged 50 to 64 years	(current) vaccination only for people aged 50 to 64 years at high-risk of complications	people aged 50 to 64 years	systematic review of 10 RCTs	one year	third-party payer and society	70%	3%	Brazil: R$4.74; France: €6.28; Germany: €7 eligible patients and €17.28 non-eligible patients; Italy: €12.77 pharmacy and €4.98 under contract	probabilistic analytic decision model	deterministic and probabilistic SAs	The ICUR from the perspective of third-party payer was €13,156 in France, €31,387 in Germany, and €15,652 in Italy. From the societal perspective, universal vaccination was dominant in Germany and Italy, while the ICUR was €7,989 in France.	The most influential parameters were attack rate, size of high-risk population, and death rates after consultation for ILI. The CEAC showed that the probability of the ICUR being below the threshold of €50,000/QALY was 94% in France, 89% in Italy, and 72% in Germany from a third-party payer perspective (95%, 99%, and 100% from a societal perspective)
Lugner, 2012	Germany UK NED	three strategies for vaccination against influenza, in a pandemic: vaccination for the whole population, vaccination of people 65 years old or older, and vaccination of people with a high transmission rate (those aged five to 19 years)	no vaccination	whole population, elderly, or those aged 5 to 19 years (depending on the immunisation strategy)	published sources of unclear design	lifetime	not explicitly stated but appears third-party payer	90%	Benefits: Germany 5%, the NED 1.5%, UK 3.5%. Costs: not discounted (short-term analysis)	€10	age-structured model of influenza transmission	deterministic SAs	All vaccination strategies were cost-effective compared to no vaccination. In scenarios where the vaccine became available at the peak of the pandemic and there was pre-existing immunity among elderly people, the ICUR for vaccinating high transmitters was €7,325 in Germany, €10,216 in the Netherlands, and €7,280 in the UK.	When including productivity losses, all vaccination strategies were dominant or highly cost-effective in all countries and in most scenarios

1. only high-risk groups (those with chronic respiratory, heart, kidney, liver neurological disease, diabetes, and immunosuppression, pregnant women and household contacts of immunocompromised individuals); risk groups and the following age groups: 0-4 years, 5-14 years, over 65 years, 0-14 years, and 0-14 years plus over 65 years. 2. (pre-school 2-4 years of age, pre and primary school children 2-10 years of age, or all children 2-18 years of age) or current practice of vaccinating those at increased risk of influenza associated morbidity, including everyone of 65 years of age and over, with TIV

5. VARICELLA/HERPES ZOSTER

First author, Year	Countries	Vaccine	Comparator	Patient population	Source of vaccine efficacy data	Time horizon	Perspective	Vaccine coverage	Discount rates	Vaccine price (per dose)	Model description	Sensitivity analyses (SAs)	Main cost-effectiveness results (ICUR)	Results of the SAs
Annemans, 2010	Belgium	vaccination against herpes zoster (HZ) and post-herpetic neuralgia (PHN) in individuals aged 60 years and older	no vaccination	individuals aged 60 years and older	RCT (the Shingles Prevention Study)	lifetime	third-party payer (only direct healthcare costs covered by the Belgian National Institute for Health and Disability Insurance), health care payer (plus patient co-payments), and society	20%	3.0% C 1.5% B	€141.18	Markov model	deterministic and probabilistic SAs	The ICURs of vaccination were €6,799, €7,168, and €7,137 from the perspectives of the third-party payer, the health care payer, and the society, respectively	In the univariate SAs, the ICUR ranged from €4,959 to €19,052. The most influential input was the duration of vaccine efficacy. At a threshold of €30,000 per QALY, the probability of vaccination being cost-effective was 94%
Bilcke, 2012	Belgium	vaccination of all or subgroups of adults aged 60 to 85 years against herpes zoster	no vaccination	adults aged over 60 years	RCT	lifetime	health care payer	30%	3.0% costs 1.5% benefits	€90	static cohort model	one- and multi-way SAs. Worst and best case scenarios were presented depending on the assumptions most and least in favour of vaccination efficacy	For the scenario most in favour of vaccination, the ICUR ranged from €1,251 per QALY at 60 years to €5,498 per QALY at 85 years. For the scenario least in favour of vaccination, the ICURs ranged from €48,978 per QALY at 60 years to €303,705 per QALY at 85 years.	the most influential inputs were age at vaccination, assumptions about vaccine efficacy, and vaccine price
Bilcke, 2013	Belgium	universal childhood varicella-zoster vaccination programme[1]	no universal vaccination	infants, children	not reported (referred to a previous publication)	lifetime	health care payer	95%-80%	3.0% C 1.5% B	€43.46 (€90 booster vaccine)	age-structured transmission -dynamic model	deterministic and probabilistic SAs	the values of ICURs were not reported. Assuming no exogenous boosting, all childhood VZV vaccination programmes cost less than €35,000 per QALY gained for any time horizon up to 100 y when only the impact on chickenpox disease is included. ICURs of vaccination at age 1 and 11 years or at 1 and 4 years were very similar: €5,564–€32,850 compared with €5,781–€35,240.	various scenarios were considered in the base case analyses
Bresse, 2013	France	herpes zoster (HZ) and post-herpetic neuralgia (PHN) vaccination in elderly patients	no vaccination	people aged over 65 years and people aged between 70 and 79 years	RCT (Shingles Prevention Study, SPS)	lifetime	third-party payer and health care payer (including also private insurances and patient copayments)	20%	4%	€125	Markov model	deterministic and probabilistic SAs	from the perspective of the third-party payer, the ICUR was €9,513 with vaccination of people aged 70-79 years and €12,304 when vaccinating people aged over 65 years. From the perspective of the health care payer, the corresponding ICURs were €14,198 and €18,385, respectively.	The most influential inputs were the pain classification used and the vaccine price, as well as utilities and values of discount rates used. (multivariate) sensitivity analysis confirmed that HZ vaccination is cost effective when considering both the 70–79-year-old people and all people over the age of 65 years.
van Lier, 2010	NED	herpes zoster vaccination	no vaccination	elderly people	RCT	lifetime	society	75%	4.0% costs 1.5% benefits	€77	Markov cohort model	univariate and multivariate SAs	ICURs were €38,519 in 60-year-olds, €31,228 in 65-year-olds, €21,716 in 70-year-olds, €24,336 in 75-year-olds, and €34.449 in 80-year-olds	discounting rate, vaccine price and duration of protection of the vaccine have the greatest impact on the ICURs
de Boer, 2013	NED	Routine VZV vaccine in the elderly	no vaccination	elderly people	RCT (the Shingles Prevention Study) plus other studies	lifetime	health care payer and society	25%,	4.0% C 1.5% B	€87	cohort model	one-way SAs and scenario analyses	From a societal pespective, the ICUR of vaccination at age 60 years was €35,555 (€29,664 at age 70 years). From a health care payer pespective, the ICUR of vaccination at age 60 years was €42,004 (€29,881 at age 70 years).	The most influential parameters were vaccine price, incidence ratios of herpes zoster, vaccine efficacy at the vaccine uptake, the duration of protection and the QALY weight of mild pain
Edmunds, 2001	UK	mass adult vaccination against zoster	no vaccination	individuals aged 45 years or older	assumption	lifetime	health care payer	60%	3%	£20	decision analysis model	one-way SAs	In the cohort of 65-year-olds, the ICUR was £11,109 with life-long vaccine, £22,845 with 10 years of protection, and £65,961 with 2.5 years of protection and low vaccine efficacy. The corresponding figures with high vaccine efficacy were £27,255 (life-long), £8,684 (10 years) and £3,560 (2.5 years).	ICURs were particularly sensitive to the cost of the vaccine and to the parameters related to morbidity due to post-herpetic neuralgia
Brisson, 2003	UK	three vaccination strategies: infant strategy (routine mass infant vaccination at 90% coverage), catch-up strategy (infant strategy with catch-up targeted at susceptible 2- to 11-year-olds in the first year; and adolescent strategy (routine vaccination of 11-year-olds who are susceptible)	no vaccination	infants and children up to 11 years	RCTs	lifetime	health care payer and society	90%-80%	3%	£240 (per vial)	transmission dynamic model	deterministic and probabilistic SAs	Infant vaccination and catch-up vaccination produced an overall loss of 54,000 and 68,000 discounted QALYs over 80 years and resulted in a net cost from both the health provider and the societal perspectives. The adolescent strategy had an ICUR of approximately £ 18,000 from the perspective of the health care, while it was dominant from the societal perspective.	vaccine efficacy and the duration of immunity to zoster after exposure to varicella zoster virus were key inputs for the infant and catch-up strategies. Many parameters affected the ICUR of the adolescent strategy but most values remained below £25,000/QALY. These results were confirmed in the probabilistic SAs.

First author, Year	Countries	Vaccine	Comparator	Patient population	Source of vaccine efficacy data	Time horizon	Perspective	Vaccine coverage	Discount rates	Vaccine price (per dose)	Model description	Sensitivity analyses (SAs)	Main cost-effectiveness results (ICUR)	Results of the SAs
van Hoek, 2009	UK	routine vaccination with a herpes zoster (HZ) vaccine for the elderly	no vaccination	people aged 65 years or over	RCT and other publications and assumptions	lifetime	health care payer (NHS)	not reported	3.5%	£55	Markov cohort model	Deterministic and probabilistic SAs	In the 65-year-old cohort, compared to no vaccination, the ICUR of vaccination was £20,412.	the ICUR was most sensitive to vaccine cost and efficacy parameters, as well as the estimated incidence of zoster and parameters that described the QALYs lost from HZ. At a maximum willingness-to-pay for a QALY gained of £30,000, the probability of vaccination being cost-effective was 87% at 65 years and 98% at 70 years (assuming that the vaccine provided additional protection against post herpetic neuralgia).
Moore, 2010	UK	vaccination programme against herpes zoster (shingles) and post-herpetic neuralgia (PHN)	no vaccination	people aged 50-year-old or over	RCT	lifetime	health care payer and society	40%	3.5%	£95	Markov state-transition	deterministic and probabilistic SAs	The ICUR with vaccination was £13,077 from the perspective of the health care payer and £11,417 from the societal perspective	results were sensitive to the duration of vaccine efficacy, the discount rate, the utility estimates, and the pain severity level distribution at diagnosis. The ICUR from the perspective of the health care payer was below £30,000 in 92.7% of simulations
van Hoek, 2012	UK	childhood varicella vaccination alone, varicella vaccination in children and herpes zoster vaccination of the elderly and herpes zoster vaccination of the elderly alone	no vaccination	children and elderly populations	RCT (the Shingles Prevention Study)	lifetime	neatth care payer (NHS)	90% first dose 80% second dose	3.5%	£31	age-structured transmission dynamic model	probabilistic SA and selected one-way SAs	The synthesis of costs and QALYs was presented using cost-effectiveness acceptability curves CEACs. When compared with no vaccination the probability that childhood varicella vaccination alone was cost-effective at a £30,000 per QALY gained was 50%, for herpes zoster vaccination of the elderly alone was 98% and for varicella vaccination in children and herpes zoster vaccination of the elderly was 70%.	The results were found to be very sensitive to the time-frame of analysis. Childhood varicella vaccination was unlikely to be cost-effective if evaluated 30 to 50 years post vaccination

1. Two additional scenarios were as follows: combining a primary varicella zoster virus (VZV) vaccination in children with VZV booster vccine to prevent herpes zoster in adults; using a second dose of primary VZV vaccine at age 6 or 11.

6. OTHER VACCINATIONS

First author, Year	Countries	Vaccine	Comparator	Patient population	Source of vaccine efficacy data	Time horizon	Perspective	Vaccine coverage	Discount rates	Vaccine price (per dose)	Model description	Sensitivity analyses (SAs)	Main cost-effectiveness results (ICUR)	Results of the SAs
Luyten, 2012	BEL	Hepatitis A vaccine (Havrix) in adults	two comparators: no vaccination and screen-and-vaccine)	adults in general as well as specific risk groups (health care workers, teachers, soldiers or frequent travellers)	not clear but presumably based on RCTs	long-term	health care payer and society	95%	3.0% C 1.5% B	€45.66	Markov cohort model	Deterministic and probabilistic SAs	From the perspective of the health care payer, the median ICUR of vaccination was €185,000 versus no vaccination and €223,000 over screen-and-vaccine. From the societal perspective, the ICURs were approximately €10,000 lower.	The model was most sensitive to the 'probability to die from HAV in the age group above 30'. Overall, ICURs did not change substantially.
Maugtani, 1995	UK	three hepatitis B vaccination strategies: universal infant vaccination, universal pre-adolescent vaccination, and selective vaccination of high-risk groups	no vaccination	infants, pre-adolescents, or high-risk groups (depending on the vaccination strategy)	not clearly reported	long-term	not explicitly stated but appears third-party payer	92%	6%	adult dose: £9.82; infant and pre-adolescent dose: £7.36	not specified	deterministic SAs	Compared to no vaccination, the ICURs were £8,388 with selective vaccination, £2,515 with universal infant vaccination and £2,776 with pre-adolescent vaccination.	In the cost-effectiveness analysis (cost per LY gained), use of discounting was the most influential parameter. adding vaccination in infancy or at pre-adolescence to a selective policy cost £1,537 or £1,658 per year of life gained. Discounting years gained in the future at 6% per annum, however, made pre-adolescent vaccination more cost effective than infant or selective vaccination.
Siddiqui, 2011	UK	three universal or selective infant or adolescent hepatitis B virus (HBV) vaccination programmes	no vaccination	infants and adolescents	published studies of unclear design, including a Cochrane review	lifetime	health care payer (NHS)	90%	3.5%	£9 for infants and £12 for adolescents	Markov model	deterministic and probabilistic SAs	Compared to no vaccination, the ICUR was £263,000 (£172,000 for male infants and £554,000 for female infants) with universal infant vaccination, £493,000 (£352,000 for males and £829,000 for females) with the adolescent immunisation programme, and £90,000 with selective infant vaccination	vaccine price, duration of vaccine-induced immunity, and discount rate were influential inputs
Bos, 2001	NED	universal vaccination with hexavalent meningococcal B outer-membrane vesicle (OMV) vaccine administered in four doses at the age of 2, 3, 4 and 11 months	no vaccination	newborns	RCTs	lifetime	society	75%	4%	€10 (conservat. assumption)	decision tree model	one-way SAs	The ICUR of vaccination versus no vaccination was Euro 15,721	vaccine price, the coverage rate and the quality of life were the most influential inputs
Oostenbrink, 2002	NED	*S. pneumoniae* (SP) or *Neisseria meningitidis*(NM) vaccination	no vaccination	children	unclear	long-term	society	not reported	4%	not reported	decision tree model	deterministic SAs	Compared to no vaccination, the ICUR was €401,965 with routine SP vaccination (three doses) and €22,635 with routine NM vaccination (four doses)	not reported for the vaccination strategies
Bos, 2006	NED	a combined 9-valent meningococcal B and pneumococcal vaccine	no vaccination	newborns	RCTs and other clinical studies	lifetime	society	67%	4%	€40 (EUE 20 to €60)	Markov model	univariate and multivariate SAs	The ICUR of combined vaccination was €17,700 at vaccine price of €40 (€3,160 at vaccine price of €20 and €22,170 at vaccine price of €60)	influential inputs were disease incidence, vaccine price and duration of protective efficacy
Pouwels, 2013	NED	routine infant vaccination (following a 2, 3, 4=11 mo schedule) against serogroup B meningococcal (MenB) disease	no vaccination	infants	published studies of unclear design plus assumptions	lifetime	society	95%	4.0% C 1.5% B	€40	Markov model	one-way and scenario analyses	The ICUR of vaccination was €243,778	The vaccine price per dose including administration costs would need to be as low as €4.70 to remain below the threshold of €20,000 per QALY. For a threshold of €50,000 per QALY this would be €10.35. When alternative vaccine schedules were considered, similar ICURs were achieved. Only variations in incidence levels reduced the ratios
Trotter, 2006	UK	Six alternative meningococcal serogroup C conjugate (MCC) vaccination "introductory" strategies (that combined routine and catch-up vaccination at different ages) and three future MCC vaccination strategies	no vaccination	children (depending on the vaccination strategy)	a published study of non-specified design	lifetime	health care payer (NHS)	not reported	3%	£12	age-structured transmission model	deterministic SAs	Compared to no vaccination, the most attractive "introductory" strategy was the one in which children are routinely vaccinated at 12 months and there is a catch-up campaign for all under 18 years old, with an ICUR of £2,760 over no vaccination. As concerns future strategies, vaccination schedules that reduce the number of doses are generally more cost-effective than current vaccination.	When excluding herd immunity, vaccination at 12 months and no catch up immunisation was the most cost-effective strategy (ICUR of £15,723 over no vaccination). Discount rate and vaccine price were influential inputs.
Hepkema, 2013	NED	quadrivalent conjugate vaccine against serogroup A, C, W135 and Y disease (MenACWY) in 14-month-old children and MenACWY+MenACWY for vaccinating at 14 months and 12 years	routine vaccination with meningoc. serogroup C conjugate (MenC) vaccine	14-month-old children and 12-year-old children	studies of unclear methodology and assumptions	lifetime	society	95.9% (14 months); 94% (12 years)	4.0% C 1.5% B	€42.72 for MenACWY; €55.11 for MenC	decision tree analytic model	one- and two-way SAs plus probabilistic SAs	Vaccinating with MenACWY at 14 months was dominant over MenC. The ICUR of implementing an additional vaccination with MenACWY at 12 years of age was €635,334 compared to MenC. Comparing this booster-dose strategy with MenACWY at 14 months produced an ICUR of €988,490.	Assuming lifelong protection after vaccination at 12 years or using the most recent disease incidence figures resulted in lower ICURs, but the ICURs for vaccination at 12 years of age were still too high to be considered cost-effective. The incidence of serogroup A,C,W135,Y disease had a high impact on the ICUR. Nevertheless, in the scenario showing the prevention of a decline in herd immunity, 95% of simulations comparing MenACWY+MenACWY with MenACWY at 14 months were found below €1,750 per QALY and 100% below €15,800 per QALY.
de Vries, 2010	NED	universal adolescent pertussis vaccination	no vaccination	12-year-olds	RCTs and observational data	long-term	society	96%	4.0% costs 1.5% benefits	€18.30	discrete event simulation model	one-way SAs	The ICURs of vaccination were €4,418 and €6,371 respectively, for the 8- and 15-year protection scenarios	influential inputs were quality of life weights used for pertussis disease

First author, Year	Countries	Vaccine	Comparator	Patient population	Source of vaccine efficacy data	Time horizon	Perspective	Vaccine coverage	Discount rates	Vaccine price (per dose)	Model description	Sensitivity analyses (SAs)	Main cost-effectiveness results (ICUR)	Results of the SAs
Westra, 2010	Netherlands	3 new pertussis immunization strategies for possible addition to the current national immunization program[2]	standard national pertussis immunisation programme	infants, their parents, or pregnant women	Dutch incidence data and other studies of unclear design	8 years	health care payer and society	96%	4.0% costs 1.5% benefits	€18.30	decision tree model	deterministic and probabilistic SAs	From the health care payer perspective, the ICURs were €329,900 with at-birth immunisation, €4,600 with cocooning, and €3,500 with maternal immunisation. Compared to maternal immunisation, the ICUR of cocooning was €6,300. From the societal perspective, the ICUR of at-birth immunisation was 330,100, while cocooning and maternal immunisation were cost-saving	Base case results were generally robust
Rozenbaum, De Cao, 2012	NED	three extended pertussis booster vaccinations[3]	the current pertussis vaccination programme (with doses provided at 2, 3, 4 and 11 months and 4 years)	children and adults	previous studies (already included in this review)	25 years	society	not reported (but little impact)	4.0% C 1.5% B	€21.18	transmission dynamic model	deterministic SAs	The ICUR of the adolescent booster programme was €4,200. The ICUR with the combination strategy was below €10,000. The ICUR of the every-10-year-booster strategy was €16,872.	influential inputs were vaccine efficacy, QALY losses associated with un-notified pertussis cases and the vaccine price
Lee, 2008	GER	one-time vaccination with a single dose of acellular pertussis vaccine (Tdap); vaccination with Tdap boosters every ten years	no vaccination	adults aged between 20 and 64 years	published sources of unclear design	lifetime	society	not reported	3%	€12 (incremental Tdap vaccine vs conventional Td vaccine)	Markov model	one-way SAs	In comparison with no vaccination, the ICUR was €5,800 with one-time vaccination and €7,200 with vaccination every 10 years	influential inputs were disease incidence, vaccine cost, and initial vaccine efficacy
Stevenson, 2002	UK	pre-school booster pertussis vaccination	no vaccination	children aged 4 to 5 years	authors' assumptions based on published studies	five years	not explicitly stated but appears third-party payer	94%	6%	£6 (marginal cost above that of DT)	Markov model	one-way SAs	The ICUR with vaccination was £35,000 or £14,500 depending on the assumption on vaccine efficacy	Beside vaccine efficacy assumptions, influential inputs were the percentage of natural acquired protected individuals and the level of prior protection within the community

1. a three-dose infant vaccination programme that was administered with other routine vaccinations before the age of six months; a two-dose programme for all adolescents at age 12 years; and a selective vaccination programme for infants of intermediate- or high-risk ethnic origin or living in high-incidence locations. 2. immunization of the infant at birth, immunization of the parents immediately after birth of the child (cocooning), and maternal immunization during the third trimester of pregnancy. 3. single adolescent booster administered at the age of 12 years; combining an adolescent booster dose at the age of 10 with an adult (18–30 years) booster dose; every 10 year booster dose