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A systematic review of economic evaluations of seasonal influenza vaccination for the elderly population in the European Union

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Abstract

Objectives: The Council of the European Union (EU) has recommended that action should be taken to increase influenza vaccination in the elderly population. The objective of the study was to systematically review economic evaluations for influenza vaccination in the elderly population in the EU.

Methods: Electronic searches of the NHS Economic Evaluation, Health Technology Assessment, MEDLINE and Embase databases were run to identify full economic evaluations. Two levels of screening were used, with explicit inclusion criteria applied by two independent reviewers at each stage. Pre-specified data extraction and critical appraisal were performed on identified studies. Results were summarised qualitatively.

Results: Of the 326 search results, screening identified 8 relevant studies. Results varied widely, with the incremental cost-effectiveness ratio ranging from dominating (both more effective and cheaper than) no intervention to €459,350 per life-year gained. Cost-effectiveness was most sensitive to variations in influenza strain, vaccination type and strategy, population and modelling characteristics.

Conclusions: The majority of the evidence concludes that vaccination is cost-effective. However, it is difficult to form a strong overall conclusion due to the uncertainty present in the evidence base and the limited sensitivity analysis conducted in studies to explore this. In the future, economic evaluations conducted alongside randomised clinical trials may be particularly useful to fill in many of the data gaps. More advanced modelling techniques (e.g. patient-level simulation) have to potential to characterise the epidemiology of influenza more accurately.

Strengths and limitations of this study

- This study systematically reviewed economic evaluations for influenza vaccination in the elderly population in the EU, a practice that is recommended in policy.
- To the authors' knowledge, this search brings the only previous systematic review of economic evidence for influenza vaccination up to date.
- The study summarises and critically appraises the current evidence base and also discusses potential avenues for future research.
- The review was limited to English-language studies, there is scope to broaden the search to include other languages and identify further papers.

Manuscript

Introduction

Influenza is a highly contagious acute viral infection, with a risk of complications and mortality. It is a serious public health concern, [1–3].

The prevalence of influenza varies each season and is affected by multiple factors (e.g. virus strength and climate). Approximately 10% of the European population have influenza each year, [4]. Symptoms (fever, coughs and headaches) are usually resolved within 2 weeks. Some high-risk groups have an increased risk of complications, such as pneumonia, and can result in hospitalisation, and death, [1,5]. Over 110 million adults in the European Union (EU) are estimated to belong to high-risk groups such as pregnant women and the elderly, [6].

In the elderly population with influenza–like-illness (ILI), hospitalisation risk has been reported to be up to 8.8%, with up to 4.2% admitted cases requiring time in an intensive care unit and a risk of death when admitted to hospital of 3.1% to 13.5%, [5]. Whilst complication rates are lower in the elderly population when compared to other high-risk groups, older people are more likely to fall into multiple high-risk groups, due to the presence of chronic conditions (e.g. heart failure, Parkinson's disease and asthma) [7,8]. In reality the burden may be higher as influenza contributes to more severe illnesses and may therefore be a causal factor of mortality risk despite not being the primary recorded cause of death, [9]. This is partly due to uncommon laboratory testing for the presence of influenza infection is uncommon and as such it is not recorded, [10], In addition, influenza exacerbates existing chronic conditions (e.g. respiratory conditions) and cases secondary infections (such as pneumonia) that are more frequently recorded as the cause of death, [10]. Statistical modelling suggests that influenza may actually be responsible for between 2.5%-8.1% of deaths in the over 75 age group, [10].

Seasonal influenza is important to policy makers because it has a large economic impact, both in terms of costs and population quality of life, [11]. Vaccines are the most commonly used intervention to prevent influenza; they work by simulating infection, provoking the body to create antibodies to protect against infection, [12]. The Council of the EU recommended that by 2014-15 75% of the elderly population should be vaccinated against influenza, [13]. The latest published (2012) figures show that the EU mean vaccination coverage is around 44.7% (range: 1% to 77.4%) of the elderly population, substantially short of the EU target, [14]. Social determinants of seasonal influenza vaccination include gender, marital status, ethnicity, education and housing, [15]. Beliefs also played a role, with previous vaccination experiences, perceived susceptibility and perceived effectiveness of the vaccination impacting whether the population aged 65 and over would receive vaccination, [15]. In patients aged 65 and over strategies were found to be successful in increasing vaccination rates;

including having a lead staff member to identify eligible patients and sending personal invitations to patients, [16]

In the elderly population the primary goal of vaccination is to reduce the risk of complications resulting from influenza, although evidence of effectiveness is limited and uncertain in this population, [12]. In the adult population aged 18-65 influenza efficacy (relative reduction in influenza risk following vaccination) has been reported to have an efficacy rate of 59% [95% CI 51-67] in a pooled analysis of 12 seasons, [17]. As people age the immune system can become compromised and less responsive to vaccination, [18]. When focusing specifically on the elderly population effectiveness appears to be much lower; with an estimate of 23% efficacy in seasons where vaccine matching is good, [19]. In addition, when comparing effectiveness evidence across populations, evidence in the elderly population is much more reliant on low-quality (e.g. non-randomised cohort studies with small samples) [17,19].

In light of the recommendations for influenza vaccination in the elderly population, in an environment with an aging population and the issues discussed above around vaccination effectiveness, relevant economic evaluations are likely to be of interest to policy makers. This study aimed to determine whether influenza vaccination has been demonstrated to be cost-effective, compared to no vaccination and/or alternative interventions, in the elderly population in EU. It also reviewed the strength of the evidence base, to inform policy makers and future research.

Methods

A systematic literature search was conducted to identify economic evaluations looking at influenza vaccinations in the elderly population in the EU.

Search Strategy

Search terms across the databases used included disease-specific terms, e.g. “influenza”; terms for the intervention, e.g. “vaccination” and terms for economic evaluations, e.g. “cost-effectiveness”. Search terms and strategies varied slightly according to the database design and functionality. Free-text and standardised subject terms were used. Alternative spellings were included to capture all potentially relevant citations. The search strategy was piloted to ensure it identified all known studies and all studies identified in a previous review. An example search strategy is provided in the supplementary material.

An initial search was carried out in November 2014. This search used the NHS Economic Evaluation Database (EED) and the Health Technology Assessment (HTA) database via The Cochrane Library. At the time of initial search the EED database was a reliable source for economic evaluations, using a

very precise search over a wide number of databases to capture relevant studies which helps to reduce the number of irrelevant study results, [20]. NHS EED ceased being updated in March 2015 and subsequently in November 2015 searches were updated, with MEDLINE, EMBASE and Econlit databases searched to identify relevant economic evaluations published after this period. Published NHS EED search terms were used to identify economic evaluations [21].

Selection

Identified citations were manually screened against explicit pre-defined inclusion criteria to assess their relevance to the review. To be eligible for inclusion the study sample or modelled population had to be based in the European Union and aged ≥60 or ≥65 years (the definition of elderly used in influenza policies across Europe). The intervention was the seasonal influenza vaccination and comparators could be any alternative intervention intended to reduce the burden of illness associated with influenza (e.g. antiviral treatments) or usual care/no intervention. Studies had to be full economic evaluations; producing an incremental cost-effectiveness ratio using a health outcome. No restriction was placed on publication date. The review was limited to English language articles. Two stages of screening were used, with the same criteria applied for primary screening of abstracts and titles, and secondary screening of full papers.

Two reviewers carried out each stage of screening independently and checked results, with a third reviewer consulted to resolve any disagreements. During screening the primary reason for study exclusion was recorded at each stage.

Data Extraction

Specific data, including information on modelling techniques, parameters and outcomes, were extracted (using pre-defined data extraction tools) from the final evidence base to inform the review. Comprehensive data extraction was undertaken, in line with the NHS EED handbook and with some key additions on modelling technique from a review of economic evaluations of vaccinations, [22,23]. The data extraction form used is provided in the supplementary material. This included extracting information on study methodology, limitations, evidence gaps, results and a quality assessment for critical appraisal. Two reviewers extracted data independently, results were compared and discussion, with any disagreements settled by a third reviewer.

Cost figures were extracted, then converted into 2014 Euros for presentation using the price index for each country and the purchasing power parity conversion factor, [24,25].

Data Synthesis

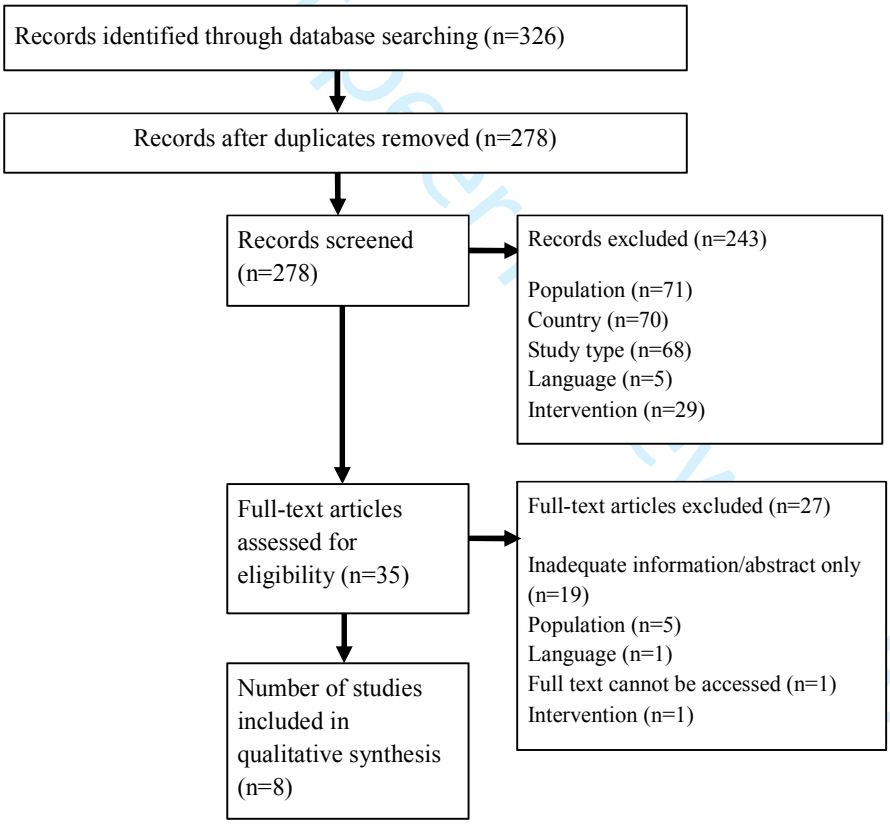
Extracted data were summarised in text and tables. Study characteristics, cost and outcome data were tabulated and summarised. Critical appraisal was qualitatively synthesised with the help of the checklist.

RESULTS

Summary of studies

The search identified 326 results through databases, 35 full-text articles were reviewed, from which eight studies were included in the review (Fig. 1).

Figure 1: flow diagram of search



An overview of study setting, population and intervention/comparator is given in Table 1, Table 2 presents an overview of the study characteristics. A tabular overview of the critical appraisal is provided in the supplementary material.

Table 1: Overview of identified studies

Authors	Population	Country	Intervention/s and comparator/s
Allsup et al (2004), [26]	Low-risk aged 65-74	UK	Standard influenza vaccination versus no intervention
Baio et al (2006), [27]	Unknown risk aged ≥65	Italy	Adjuvanted vaccination or standard vaccination versus no intervention
Brydak et al (2012), [28]	Mixed risk aged ≥65	Poland	Reimbursed vaccination versus no intervention
Lugner et al (2012), [29]	Mixed risk aged ≥65	Germany, Netherlands and UK	Standard vaccination versus no intervention
Meier et al (2015), [30]	Mixed risk aged ≥65	UK	Quadrivalent influenza vaccination versus trivalent influenza vaccination
Piercy et al (2004), [31]	High-risk (suffering from lung or heart disease) elderly people aged ≥65	France	Adjuvanted vaccination versus standard vaccination
Postma et al (1999), [32]	Mixed risk aged ≥65	Netherlands	Standard vaccination versus no intervention
Scuffham & West (2002), [33]	Unknown risk aged ≥65 or 60 (country differences)	England and Wales, France and Germany	Opportunistic vaccination versus no vaccination, comprehensive vaccination versus no intervention

Note: high-risk refers to the elderly population with another condition or circumstance that places them at a greater risk of complications, e.g. respiratory conditions. Low-risk refers to the elderly population, who aside from being older, would not be considered to fall into any high-risk categories.

Table 2: Study design and headline results

Authors	Study design	Evaluation details	Data source/s
Allsup et al (2004), [26]	• Evaluation type: CEA and CUA • Measure of health benefit: deaths averted and QALYs gained	• Type of study: RCT based economic evaluation • Perspective: healthcare provider • Time horizon: lifetime • Price year: NR	The main source of data was a prospective, single-blind, randomised, placebo-controlled clinical trial. Some parameters (e.g. baseline hospitalisation rate) were supplemented with hospital data and/or clinician expert assumptions.
Baio et al (2006), [27]	• Evaluation type: CEA • Measure of health benefit: deaths averted	• Type of study: model based economic evaluation (Bayesian network model) • Perspective: healthcare provider • Time horizon: NR • Price year: NR	Observational study data from 4 GP databases over 3 flu seasons was used for efficacy. The remainder of the evidence sources are unclear (not specified).
Brydak et al (2012), [28]	• Evaluation type: CUA • Measure of health benefit: deaths averted, life-years gained and QALYs gained	• Type of study: model based economic evaluation (decision tree) • Perspective: healthcare provider • Time horizon: lifetime • Price year: 2009	Published data specific to Poland was used to inform the model where possible. It was noted that in some cases Polish data was not available and US data had to be used (e.g. hospitalisations).
Lugner et al (2012), [29]	• Evaluation type: CUA • Measure of health benefit: QALYs gained	• Type of study: model based economic evaluation (dynamic transmission model) • Perspective: healthcare provider and societal • Time horizon: lifetime • Price year: 2008	National data sources were used for demographic, resource use and cost data. Where evidence was not available for Germany and the UK, data from the Netherlands was used (e.g. hospitalisations). Vaccine efficacy was taken from a published review and meta-analysis of studies from multiple countries/influenza seasons.

Meier et al (2015), [30]	• Evaluation type: CEA and CUA • Measure of health benefit: QALYs gained	• Type of study: model based economic evaluation (Markov model) • Perspective: healthcare provider (societal as a secondary analysis) • Time horizon: lifetime • Price year: 2012/13	National data sources were used for incidence, costs, utilities, complications and mortality data. Vaccine efficacy was taken from a published review of studies from multiple countries/influenza seasons. Over-the-counter medication usage was estimated from previous publications.
Piercy et al (2004), [31]	• Evaluation type: CEA • Measure of health benefit: deaths averted and life-years gained	• Type of study: model based economic evaluation (decision tree) • Perspective: healthcare provider • Time horizon: lifetime • Price year: NR	A variety of evidence sources were used, including national data, published literature and expert opinion. When French data could not be sourced (e.g. hospitalisations), data from other European countries was used.
Postma et al (1999), [32]	• Evaluation type: CEA • Measure of health benefit: life years gained	• Type of study: model based economic evaluation (decision tree) • Perspective: healthcare provider • Time horizon: lifetime • Price year: 1995	National data and published literature from the Netherlands were used for parameter values. Vaccine efficacy was taken from a published review and meta-analysis of studies from multiple countries/influenza seasons.
Scuffham & West (2002), [33]	• Evaluation type: CEA • Measure of health benefit: life years gained and morbidity days saved	• Type of study: model based economic evaluation (decision tree) • Perspective: healthcare provider • Time horizon: lifetime • Price year: 2000	Evidence sources included published studies, national databases and expert opinion. In some cases country specific data were not available for all parameters and it was taken from another country in the study (e.g. vaccine efficacy came from a US study).
Key: CEA, cost-effectiveness analysis; CUA, cost-utility analysis; ICER, incremental cost-effectiveness ratio; NR, not reported; QALY, quality-adjusted life-year; RCT, randomised controlled trial.			

Population characteristics

The susceptibility of the population has important implications for the rate of complications; if more people are at risk of complications, vaccination is likely to produce larger health gains. One study considered the low-risk elderly population alone, [26] and another study focused purely on the high-risk population, [31]. Another study compared results between the low and high-risk population, [32]. Among the remaining studies the high-risk proportion varied from 35% to 81% of the population and was variable by country, [28–30,32]. Two studies did not report the proportion at high-risk, [27,33].

Interventions

Influenza vaccination was considered in all studies, with three studies including two vaccine types, [27,30,31]. Influenza vaccination consists of a single dose vaccination given annually to provide resistance to influenza Vaccination intervention arms included vaccinations rates of between 40%-90% (mean 65%). The comparator was almost exclusively no intervention, [26–31,33,34]. Vaccination rates in the no intervention arm varied from 0 to 68% in the high-risk population. One study included anti-viral drugs as a comparator, but did not directly compare it to a vaccination intervention arm, [33,35,36].

Costs and Outcomes

Four studies undertook a cost-effectiveness analysis alone, with the measure of health benefit provided in terms of life years gained or deaths averted, [27,31–33], 2 studies performed a cost-utility analysis with quality-adjusted life-years (QALYs) as the measure of health benefit, [29,30], and 2 studies included both cost-effectiveness and cost-utility analyses, [26,28]. All studies assessed life-years gained as a result of avoiding death related to influenza complications. In the 4 studies reporting cost-utility results, one study accounted for morbidity by applying lost utility related to mortality to estimate QALYs, [26]. The three other studies also accounted for short-term changes in utility as a result of having influenza, [28–30].

Seven out of 8 studies used a one year time horizon for costs, consistent with vaccination covering one season and the short-term/immediate associated costs, therefore discounting costs was not relevant, [26–29,31–33]. The remaining study considered repeat vaccinations and costs each flu season over a lifetime, [30]. Where relevant, studies applied country-specific guidelines for discounting outcomes; ranging from 1.5% to 5% annually.

All studies considered cases of influenza/ILI and associated hospitalisations, mortality, primary care visits and treatments (e.g. painkillers). One study accounted for vaccination side effects, but only in terms of cost (not health), [33].

Six studies used a healthcare payer perspective and considered direct costs alone, [26–28,31–33]. One study also included a societal perspective as a sensitivity analysis, [30]. Indirect societal costs were included in one study in the form of productivity losses, by calculating herd immunity and subsequent benefits in the working age population, [29].

All studies included costs associated with purchasing vaccines, influenza related treatments, primary care visits and hospitalisations. Six studies included administration costs, [26,28,29,31–33]. One study included vaccine side effect costs, [33]. Transportation costs, over-the-counter medication costs and private nursing home costs were considered in the societal perspective of one study, [30]. Production losses arising in the younger population as a result of influenza were included in one study, relevant due to the inclusion of herd immunity effects, [29]. One study included a doctor incentive/promotion fee, to increase the uptake of vaccination in the intervention arm, [26].

Study results

Key study outcomes are given in Table 3.

Table 3: Key study outputs

Study	Intervention and comparator	Net health benefits (per patient)	Net costs (per patient)	Incremental cost-effectiveness ratio*	Headline results
Allsup et al (2004), [26]	Vaccination versus no intervention	0.000007 fewer deaths and 0.000044 additional QALYs	€ 5.37*	€3,576,908 per death avoided, €459,350 per life-year gained and €572,305 per QALY gained	Influenza vaccination was judged not to be cost-effective in the low-risk elderly population.
Baio et al (2006), [27]	Adjuvanted vaccination versus no intervention	NR	-€3.76	Adjuvanted vaccine dominated no intervention (per death averted)	Adjuvanted vaccine was shown to be cost-effective against the standard vaccine and no intervention strategies. Both vaccination types were cost-effective against no intervention.
	Standard vaccination versus no intervention	NR	-€1.91	Standard vaccine dominated no intervention (per death averted)	
Brydak et al (2012), [28]	Reimbursed vaccination versus no intervention	NR	€22.61	€11,790 per QALY gained, €58,981 cost per death avoided and €6,881 per life-year gained	Introducing public funding of influenza vaccination for people aged 65 and over to increase coverage was cost-effective compared to the status quo.
Lugner et al (2012), [29]	Vaccination versus no intervention (Germany)	NR	€13.22	€1,065 per QALY gained (direct costs) and dominant per QALY gained (indirect costs included)	In general, vaccination was shown to be a cost-effective strategy. Early vaccination strategies are more favourable with lower total costs and cost per QALY gained. The inclusion of indirect costs makes the early vaccination strategies dominant in all countries.
	Vaccination versus no intervention (UK)	NR	€17.19	€4,621 per QALY gained (direct costs) and dominant per QALY gained (indirect costs included)	
	Vaccination versus no intervention (Netherlands)	NR	€17.62	€1,338 per QALY gained (direct costs) and dominant per QALY gained (indirect costs included)	

Meier et al (2015), [30]	Quadrivalent influenza vaccination versus trivalent influenza vaccination	NR	NR	£11,998 per QALY	Quadrivalent vaccination is cost-effective compared with trivalent vaccination in the UK.
Piercy et al (2004), [31]	Adjuvanted vaccination versus standard vaccination	0.003397 fewer ILI cases, 0.000043 deaths avoided and 0.000300 LYG	€1.31	€30,503 per death avoided and €6,131 per LYG	Results were mixed according to the different scenarios for the strain of the influenza virus considered.
Postma et al (1999), [32]	Vaccination versus no intervention	NR	NR	€2,468 per LYG (all elderly people), €9,355 per LYG (low-risk) and dominant per LYG (high-risk)	Population-wide influenza vaccination for elderly people was found to be cost-effective. More favourable results were estimated in the high-risk population.
Scuffham and West (2002), [33]	Opportunistic vaccination versus no intervention (England)	0.547400 fewer morbidity days and 0.001040 LYG	-€1.89	Dominated per LYG gained	Vaccination strategies were cost-effective versus no intervention.
	Comprehensive vaccination versus no intervention (England)	1.065400 fewer morbidity days and 0.002020 LYG	-€0.84	Dominated per LYG	
	Opportunistic vaccination versus no intervention (France)	0.822500 fewer morbidity days and 0.001470 LYG	€2.11	€1,437 per LYG	
	Comprehensive vaccination versus no intervention (France)	1.011300 fewer morbidity days and 0.001800 LYG	€6.53	€3,623 per LYG	
	Opportunistic vaccination versus no intervention (Germany)	0.479500 fewer morbidity days and 0.000780 LYG	€2.87	€3,676 per LYG	
	Comprehensive vaccination versus no intervention (Germany)	0.760200 fewer morbidity days and 0.001240 LYG	€8.69	€7,016 per LYG	

Key: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NR, not reported; QALY, quality-adjusted life-year.
* Trial cost only reported (not actual modelled costs).

The total cost of vaccination varied from €8.50 to €35.95 per person. Differences between studies mainly occurred due to variation in administration costs rather than variation in vaccine cost; lower costs were associated with opportunistic vaccination. The overall net cost of intervention was variable as shown in Table 2 but in some cases, the vaccination costs were offset by savings elsewhere.

Vaccination appears to be cost effective throughout the studies for both the primary and sensitivity analyses conducted, with the exception of Allsup et al study (2004) which reported a significantly higher ICER, [26]. This study focused on the low-risk population only. In addition, it applied lower reductions in the risk of hospitalisation from vaccination and lower costs of hospitalisations. It also applied a cost vaccination promotion where the other studies did not, increasing the validity of costs as this is likely to be needed to reach high vaccination levels. This was also the only study completed alongside a randomised controlled trial, the remainder were economic models using secondary data sources.

The two studies that reported probabilistic sensitivity analysis estimated that vaccination would be cost effective in between 68% to 87% cases, [28,30]. Scenario and one-way sensitivity analysis demonstrated key variables to be the incidence of influenza, vaccine efficacy, discount rates and complication rates (mortality and hospitalisation). In general, studies showed that despite parameter uncertainty, the majority of tested scenarios still demonstrated vaccination to be cost effective.

Adjuvanted vaccination, whilst associated with a higher cost of vaccination, was cost effective when compared to standard vaccination as higher efficacy rates lead to increased health benefits, [27,30,31]. As expected, the vaccination of high-risk individuals was demonstrated to be more cost effective than vaccinating low-risk individuals, as this population is more susceptible to complications, which are costly and negatively impact quality of life, [32]. Passive vaccination strategies were found to be more cost effective than comprehensive/targeted strategies, [30,33]. One model included transmission rates and captured externalities arising from herd immunity, [29].When these indirect effects were included results became more favourable, as it demonstrated cost savings.

Critical appraisal

Studies were critically appraised to determine the overall quality of the evidence base; a summary is given in supplementary data. None of the studies reported all information required for data extraction, or to conform to the WHO guidelines or recommended checklists for economic evaluations, [22,37–39]. In some cases there was a failure to report fundamental assumptions, design and inputs, which means that the risk of bias is difficult to judge. These factors indicate uncertainty about the robustness of the overall result that vaccination is cost-effective.

Measure of health benefit

The robustness of QALY estimates is questionable due to the limited relevant evidence and small study samples of utility studies. A review concluded that no utility studies using robust methods were available for influenza, which was reflected in the cost-utility evaluations identified, [40]. Lugner et al (2012) took utility decrements relating to influenza from an English postal survey of 288 patients with confirmed influenza, using the European Quality of life 5-dimension health questionnaire (EQ-5D), [29,41]. The generalisability of this study to the elderly Dutch population is difficult to assess as patient characteristics were not reported. Meier et al (2015) and Brydak et al (2012) applied utility values taken from a survey of 15 working age healthcare workers in the US with utilities scored using the health utilities index, [28,30,42]. This is arguably not relevant to the elderly population. The WHO guidelines recommend that economic evaluations are cost-utility analyses, however without robust utility data, cost-utility evaluations will have limited validity, [37].

ILI was used in all studies as a proxy for influenza. The severity and subsequent cost of influenza can vary substantially, therefore there are concerns that this outcome is too broad, [43]. However, this is the primary end-point of clinical trials and subsequently studies are restricted by this, [44]. Longer-term outcomes associated with influenza were not considered; likely due to a lack of robust clinical data and the impact of confounding factors in the long-term, [12]. The likely direction of bias caused by excluding long-term outcomes is unclear, it may understate the value of vaccination if it increases a person's health over time, or may overstate the value of vaccination if side effects occur in the long-term.

Costs

The majority of studies considered direct costs only. This approach is justified as indirect costs are less important in a retired population. Societal costs (e.g. transport and over-the-counter drugs) are likely to be minimal due to the nature of the illness. Appropriately, the only study that included productivity losses did so because they considered herd immunity effects in the working age population, [29]. A single study included vaccination side effect costs (by including a GP consultation cost for patients experiencing side effects); however, these are rare and usually require only minimal medical attention, [33]. This was supported by sensitivity analysis demonstrating that the cost of side effects had little impact on results. Only 1 study applied costs to promote vaccination in the intervention arm, [26]. No studies considered the cost of service redesign to increase vaccination (e.g. opening additional clinics) which is likely to be highly relevant for healthcare systems that face an aging population. Thus, the true cost of vaccination is likely to be underestimated across studies.

Model

On the whole, modelling approaches were relatively simple (e.g. static decision tree models), reflecting gaps in the evidence base. One study used a dynamic transmission model and was therefore

able to capture the impact of transmission and herd immunity. This characterises interactions across the population and is therefore more reflective of the spread of disease and the indirect benefit for those not vaccinated, [29]. Other models will underestimate the cost effectiveness of influenza vaccination, however, WHO guidelines recommend that a static model is acceptable as a more conservative approach, [37].

More complex methodologies may capture the nature of the disease more accurately, however given the noted lack of clinical evidence it is unlikely that the current evidence base is sufficient to inform these, [12]. For example, patient-level simulations can also be more precise when modelling population interactions, [45]. Additionally stochastic models, with events occurring randomly, can more realistically model epidemics, as these occur by chance of transmission amongst population interactions, [23].

Methods to address uncertainty

In general, studies did not perform detailed sensitivity analysis, despite many recognising that there are issues with the evidence base. Methods used to analyse uncertainty were varied, such that results are not comparable. The WHO recommend that sensitivity analyses for economic evaluations of vaccines should vary the following 5 parameters as a minimum: discount rates, vaccine efficacy, influenza incidence, influenza complication rates and vaccine price, [37]. None of the studies identified varied all of the recommended parameters. Only 2 studies included probabilistic sensitivity analysis, [28,30]. Most scenarios tested in sensitivity analysis still resulted in favourable cost-effectiveness results for influenza vaccination. However, this is not a robust conclusion due to the lack of thorough investigation and transparency shown when conducting sensitivity analysis and providing ranges for parameters. This restricts our ability to explore transferability of study results to alternative countries, settings and influenza seasons.

Discussion

The majority (7/8) of the identified studies found influenza vaccination to be cost effective in an elderly European population. Results were sensitive to variations in the strain of influenza incidence, vaccination type, efficacy and strategy, population risk and modelling characteristics. This is in alignment with the previous review identified, [34]. However, the robustness of this conclusion is limited due to the evidence gaps and subsequent uncertainty demonstrated in the literature base, as well as the limited investigation into this uncertainty. Robust, transparent studies are needed to reduce parameter uncertainty, focusing on clinical evidence (health benefits and side effects), utilities and resource use data. Once the data available to inform economic models are more robust, then complex modelling methods can be utilised to suitably reflect the disease and wider outcomes. Increasing this evidence base could lead policy makers to revaluate current recommendations.

The review focused on the elderly population, which is one of many high-risk groups. To prioritise the right groups to target for vaccination, due to cost and resource constraints, decision makers are likely to need to conduct further reviews of the economic evidence for other high-risk groups. For example, these analyses might focus on groups with chronic conditions, pregnant women or children. This would produce a more balanced judgement of where to prioritise intervention.

The original search for studies used a single database (NHS EED), increasing the chance of missing papers that could change the conclusions of the review. However, at the time NHS EED was comprehensive, searching a wide range of databases, and was regularly updated. The updated search included more databases. The review included English language articles only, which risks language bias. Searches were limited to published journal articles. Widening the searches to the grey literature or unpublished reports may have been more likely to identify studies with inconclusive or negative cost-effectiveness results. The generalisability of some of the results of this review to other settings (outside the EU) may be limited, due to inevitable differences resource use, treatment pathways and population characteristics.

This review highlights several areas that would benefit from additional research. Parameter uncertainty affected the strength of economic evaluations, largely because many of the trials for vaccine efficacy are underpowered, non-randomised and susceptible to bias, [12]. A number of the evaluations used the same effectiveness data to estimate model parameters, this will over-represent a limited evidence base. Without more and stronger quality data to inform parameters economic evaluations will always be subject to a high degree of uncertainty. Trials for the vaccination cover the influenza season, typically a 6-month period over winter, [12]. A predominance of short term evidence in the literature prevented the identified studies from including longer-term outcomes. There was also a lack of evidence for each country, with studies relying on external data sources with questionable relevance to their population. Moreover, this evidence gap meant that many studies used the same sources for certain inputs, potentially over-representing the results of a small and low quality evidence base. Work to ensure that robust country-relevant data inputs are available would increase the validity of future evaluations.

Future economic evaluations should follow good practice guidelines and ensure that they are transparently reported to assist reviewers in the future. Economic evaluations conducted alongside a long-term RCT would be particularly helpful to address evidence gaps. In the future, if the evidence base expands, more complex modelling techniques may become feasible. These would be able to capture the epidemiology of the illness, include longer-term outcomes and include the impact of herd immunity, providing a more accurate assessment of the benefits of vaccination.

Contributors

GE Shields and J Elvidge conducted the literature search with oversight from LM Davies. G Shields wrote the first draft of the manuscript, J Elvidge and LM Davies contributed to the final writing of the paper.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

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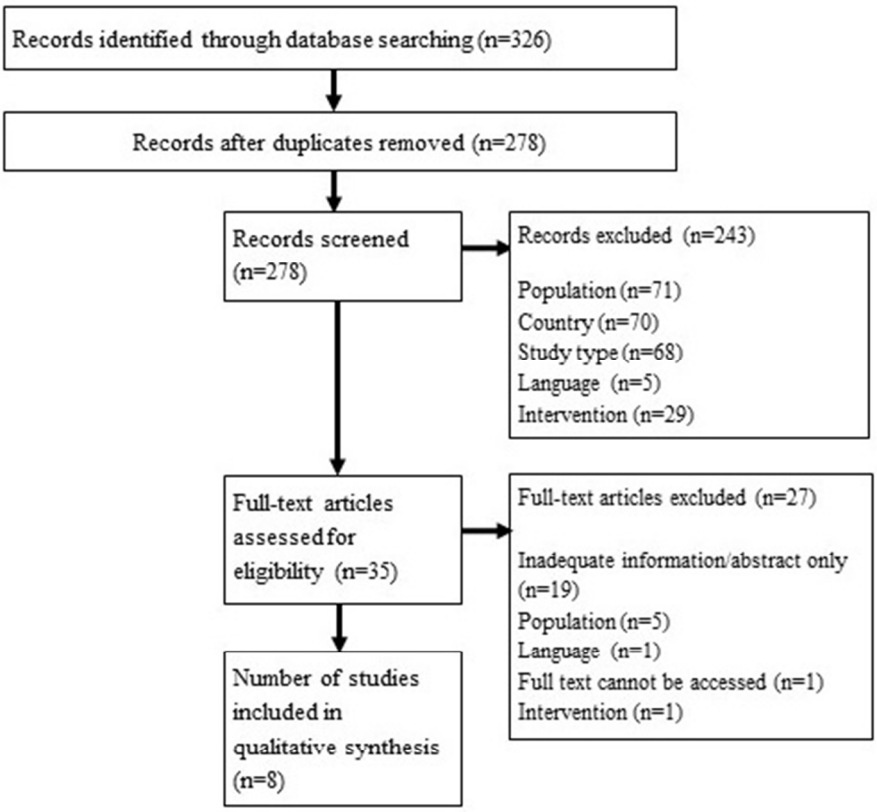

Figure 1: flow diagram of search

143x125mm (96 x 96 DPI)

Supplementary material

Example search strategy

1 Influenza, Human/
2 influenza/
3 flu/
4 influenza virus/
5 seasonal flu/
6 1 or 2 or 3 or 4 or 5
7 Vaccination/
8 vaccine/
9 7 or 8
10 Economics/
11 exp "costs and cost analysis"/
12 Economics, Dental/
13 exp economics, hospital/
14 Economics, Medical/
15 Economics, Nursing/
16 Economics, Pharmaceutical/
17 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
18 (expenditure$ not energy).ti,ab.
19 value for money.ti,ab.
20 budget$.ti,ab.
21 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 ((energy or oxygen) adj cost).ti,ab.
23 (metabolic adj cost).ti,ab.
24 ((energy or oxygen) adj expenditure).ti,ab.
25 22 or 23 or 24
26 6 and 9 and 21
27 26 not 25
28 letter.pt.
29 editorial.pt.
30 historical article.pt.
31 28 or 29 or 30
32 27 not 31
33 exp animals/ not humans/
34 32 not 33
35 limit 34 to yr="2014 -Current"

Blank data extraction form: key study attributes and critical appraisal

Subject of the study	
Health technology	
Disease	
Type of intervention	
Hypothesis and/or study question	
Key elements of the study	
Economic study type	
Study population	
Modelling and statistical extrapolation	
Setting	
Dates to which data relate	
Link between effectiveness and cost data	
Clinical evidence	
Clinical and epidemiological data	
Parameter value	
Data sources	
Methods to obtain data	
Economic analysis	
Summary measure of health benefit reported	
Type of measure of health benefit	
Utility or WTP benefit measures - method of valuation	
Discount rate for utility or WTP	
Economic analysis	
Whose direct cost	
Which direct costs	
Source of resource use	
How prices estimated	
Costs discounted	

Date of price data	
Marginal or average costs	
Resource use separately reported	
Costs adjusted for inflation and how	
Costs excluded	
Adjustments to costs	
Budget impact (yes or no)	
Currency	
Economic analysis	
Why include/exclude productivity costs	
Source of cost and quantity data	
Were costs and quantities separately reported	
When resources measured	
Discounted? Why? Relevant?	
Statistical analysis cost	
Point estimates used (yes or no)	
Descriptive statistics used	
Statistical tests used	
Parameters tested	
Study powered to detect differences?	
Analysis uncertainty	
Parameter uncertainty investigated (yes or no)	
How parameter uncertainty investigated	
Uncertainty investigated all parameters (yes or no)	
If not all parameters, which investigated	
Methods or rationale for deterministic analysis	
Probabilistic analysis were distributions defined	
Was structural uncertainty assessed	
Was variability in data investigated	

Estimated benefits	
Total benefits for each intervention	
Duration of benefits	
Were side effects/adverse events included	
Net (incremental benefit) of intervention-comparator	
Statistical test of differences in benefit	
Sensitivity analysis of benefits only	
Cost results	
Net (incremental) cost) of intervention-comparator	
Statistical test of differences in cost	
Sensitivity analysis of costs only	
Results of any currency conversion	
Synthesis	
Was synthesis reported (yes or no)	
If no, was rationale for no synthesis reported	
ICER	
Net benefit	
Probability cost effective	
Cost acceptability curve (yes or no)	
Sub-group analysis or sensitivity analysis (yes or no)	
Type of sub group or parameters varied in sensitivity analysis	
ICER	
Net benefit	
Probability cost effective	
Cost acceptability curve (yes or no)	
Authors conclusions	
Conclusions	
Choice of comparators	
Was the choice of intervention explicitly justified (yes or no)	

Was the choice of intervention implicitly justified (yes or no)	
Key reasons for choice of intervention	
Was the choice of comparator explicitly justified (yes or no)	
Does the choice of intervention or comparator affect the	
Modelling	
Model structure/technique clearly reported	
Input data clearly reported	
Input data sources clearly reported	
Uncertainty investigated (yes or no)	
Methods used to assess uncertainty	
Results of uncertainty assessments clear (yes or no)	
Other positive or negative comments on model	
Assessment of validity of model - robust? - biased?	
Validity effectiveness	
Sources of data for model parameters	
Were data combined to estimate parameters (yes or no)	
If yes, were methods clearly reported (yes or no)	
If yes, what methods used to combine data	
How were data identified for inclusion	
What inclusion criteria	
Justification for choice of data (yes or no)	
If yes, what was justification	
What was quality of evidence used to derive parameter estimates	
Validity of health benefit	
Summary measure of benefit (yes or no)	
If yes, how derived	
How were utility values measured or identified	
To what extent does the measure of benefit cover all relevant	
Overview of costs	

Were all relevant costs included for perspective (yes or no)	
If no, what omitted	
For each cost category, were all relevant cost items included (yes	
If no, what omitted	
Do any omissions affect results or authors conclusions (yes or no)	
Cost details	
Sources of resource use, price and cost data	
Price adjustments (yes or no)	
If yes, what price adjustments	
Costs discounted (yes or no)	
If no, appropriate	
Were any resource use, price or cost data stochastic (yes or no)	
If yes, any statistical analysis	
Cost data adequately reported yes/no	
If no, why	
Other cost issues	
Costs valid (unbiased) (yes or no)	
If no, why	
Costs generalisable (yes or no)	
If no, why	
Other issues	
Comparisons with other studies (yes or no)	
If yes, results of comparison	
Generalisability addressed (yes or no)	
If yes, how	
Selective reporting of results (yes or no)	
If yes, in what ways	
Conclusions reflect scope/data	
Authors report the limitations (yes or no)	

If yes, what	
Any other shortcomings yes/no	
If yes, what	
Implications	
Authors recommendations	
Recommendations suggested by abstractor	
Implications reported by authors	
Implications suggested by abstractor	
Related publications	
Related publications	
Important to review for model	
Important to review for systematic review paper	
Focus on key model attributes	
Static or dynamic	
Stochastic or deterministic	
Aggregate or individual	
Discrete or continuous	
Key: ICER, incremental cost-effectiveness ratio; WTP, willingness to pay threshold.	

Adapted from: [22,23]

Table summary of critical appraisal

Study	Studies reporting clearly
Research question	100% [26–33]
Study design	25% [29,30]
Perspective	87.5% [26–28,30–33]
Intervention	100% [26–33]
Comparators	100% [26–33]
Study population	100% [26–33]
Method of economic evaluation	87.5% [26–33]
Data collection	
Source(s) of effectiveness estimates	87.5% [26,28,30–33]
Methods of synthesis used to source effectiveness estimates (if applicable)	37.5% [26,30,33]
Methods used to value health states and benefits	87.5% [26,28–33]
Quantities of resource use and costs reported separately	62.5% [26,28,29,31,33]
Methods for resource use and unit costs	87.5% [26,28,29,31,33]
Price year	62.5% [28–33]
Price adjustments for inflation or currency conversion	12.5% [29]
Analysis and interpretation of results	
Time horizon	87.5% [26,28–33]
Discount rate (if applicable)	100% [28–33]
Explanation given if cost or benefits were not discounted (if applicable)	100% [26,27]
Statistical test(s) and confidence intervals given for stochastic data	12.5% [26]
Sensitivity analysis methods	100% [26–33]
Choice of variables for sensitivity analysis	87.5% [26,28–33]
Ranges used in sensitivity analysis	100% [26–33]
Appropriate comparisons	100% [26–33]
Incremental analysis reported	100% [26–33]
Outcomes presented disaggregated and aggregated	25% [28,33]
Study question answered	100% [26–33]
Conclusions relevant to study	100% [26–33]
Limitations	62.5% [26,28–30,33]
Generalisability issues	25% [28,29]
Comparisons to other studies	37.5% [26,28,30]

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4/5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 and supplementary material
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5 and supplementary material
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	14 and supplementary material
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14-16 and supplementary material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14-16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

A systematic review of economic evaluations of seasonal influenza vaccination for the elderly population in the European Union

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Secondary Subject Heading:	Immunology (including allergy), Health policy, Geriatric medicine, Infectious diseases, Public health
Keywords:	HEALTH ECONOMICS, GERIATRIC MEDICINE, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Public health < INFECTIOUS DISEASES

A systematic review of economic evaluations of seasonal influenza vaccination for the elderly population in the European Union

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Abstract

Objectives: The Council of the European Union (EU) has recommended that action should be taken to increase influenza vaccination in the elderly population. The aims were to systematically review and critically appraise economic evaluations for influenza vaccination in the elderly population in the EU.

Methods: Electronic searches of the NHS Economic Evaluation, Health Technology Assessment, MEDLINE and Embase databases were run to identify full economic evaluations. Two levels of screening were used, with explicit inclusion criteria applied by two independent reviewers at each stage. Pre-specified data extraction and critical appraisal were performed on identified studies. Results were summarised qualitatively.

Results: Of the 326 search results, screening identified 8 relevant studies. Results varied widely, with the incremental cost-effectiveness ratio ranging from being both more effective and cheaper than no intervention to costing €459,350 per life-year gained. Cost-effectiveness was most sensitive to variations in influenza strain, vaccination type and strategy, population and modelling characteristics.

Conclusions: Most studies suggest that vaccination is cost-effective (7/8 studies identified at least one cost-effective scenario). All but one study used economic models to synthesise data from different sources. The results are uncertain due to the methods used and the relevance and robustness of the data used. Sensitivity analysis to explore these aspects was limited. Integrated, controlled prospective clinical and economic evaluations and surveillance data are needed to improve the evidence base. This would allow more advanced modelling techniques to characterise the epidemiology of influenza more accurately and improve the robustness of cost-effectiveness estimates.

Strengths and limitations of this study

- This study systematically reviewed economic evaluations for influenza vaccination in the elderly population in the EU, a practice that is recommended in policy.
- To the authors' knowledge, this search brings the only previous systematic review of economic evidence for influenza vaccination up to date.
- The study summarises and critically appraises the current evidence base and also discusses potential avenues for future research.

- The review was limited to English-language studies, there is scope to broaden the search to include other languages and identify further papers.

Manuscript

Introduction

Seasonal influenza is a highly contagious acute viral infection, with a risk of complications and mortality. It is important to policy makers because it has a large economic impact, both in terms of costs and population quality of life, [1]. The prevalence of influenza varies each season and is affected by multiple factors (e.g. virus strength and climate). It is a serious public health concern generally and particularly for high-risk groups such as older people, [2–7]. In the European Union the elderly population makes up 18.9% of the population, over 96 million people (2015 figures), [8].

In the elderly population with influenza–like-illness (ILI), hospitalisation risk has been reported to be up to 8.8%, with up to 4.2% admitted cases requiring time in an intensive care unit and a risk of death when admitted to hospital of 3.1% to 13.5%, [5]. Whilst complication rates are lower in the elderly population compared to other high-risk groups, older people are more likely to have chronic conditions and fall into multiple high-risk groups, (e.g. heart failure, Parkinson's disease and asthma), [6,7]. In addition, influenza exacerbates existing chronic conditions (e.g. respiratory conditions) and causes secondary infections (such as pneumonia) that are more frequently recorded as the cause of death, [9]. These factors mean that influenza may contribute to more severe illnesses and be a causal factor of increased mortality risk, rather than the primary recorded cause of death (laboratory testing for the presence of influenza infection is uncommon), [9,10]. Statistical modelling suggests that influenza may be responsible for between 2.5%-8.1% of deaths in the over-75 age group, [9].

Vaccines are the most commonly used intervention to prevent influenza; they work by simulating infection, provoking the body to create antibodies to protect against infection, [11]. Two types are available; trivalent which protects against three viruses, and quadrivalent which protects against four viruses. Vaccines can also contain squalene-based adjuvants (e.g. MF59) which aim to improve the efficacy of vaccines. The Council of the EU recommended that by 2014-15, 75% of the elderly population should be vaccinated against influenza, [12]. The latest published (2012) figures show that the EU mean vaccination coverage is around 44.7% (range: 1% to 77.4%) of the elderly population, substantially short of the EU target, [13].

In the elderly population the aims of vaccination are to reduce the rate of influenza and to decrease the burden of complications (morbidity and mortality) resulting from influenza, although evidence of protection is limited and uncertain in this population, [11,14]. In the adult population aged 18-65, influenza (relative reduction in influenza risk following vaccination) has been reported to have an efficacy rate of 59% [95% CI 51-67] in a pooled analysis of 12 seasons, [14]. As people age the immune system can become compromised and less responsive to vaccination, [15]. When focusing

specifically on the elderly population effectiveness appears to be much lower; with one study reporting 23% efficacy for elderly individuals living in care homes in seasons where vaccine matching (the degree of similarity between the circulating virus and strain in the vaccine) is good, [16]. For individuals living in the community the same study noted that vaccines were not statistically significantly effective at preventing influenza, although well matched vaccines provided benefits in reducing related admissions to hospital and pneumonia, [16]. In addition, when comparing effectiveness evidence across populations, evidence in the elderly population is much more reliant on low-quality studies (e.g. non-randomised cohort studies with small samples), [14,16].

It is important that intervention strategies, such as vaccination programmes, provide value for money in budget-constrained health care systems. As such, in light of the recommendations for influenza vaccination in the elderly population, and in an environment with an aging population and the issues discussed above around vaccination effectiveness, relevant economic evaluations are likely to be of interest to policy makers.

This study had two aims, Firstly, to determine whether influenza vaccination interventions were demonstrated to be cost-effective in older people in the EU. The second aim was to critically appraise the methods and data to evaluate the validity and robustness of the study findings, to inform policy makers and future research.

Methods

A systematic literature search and narrative review was conducted to identify economic evaluations of influenza vaccinations in the elderly population in the EU.

Search Strategy

Search terms across the databases used included disease-specific terms, e.g. “influenza”; terms for the intervention, e.g. “vaccination” and terms for economic evaluations, e.g. “cost-effectiveness”. Search terms and strategies varied slightly according to the database design and functionality. Free-text and standardised subject terms were used. Alternative spellings were included to capture all potentially relevant citations. The search strategy was piloted to ensure it identified all known studies and all studies identified in a previous review. An example search strategy is provided in the supplementary material.

An initial search was run in November 2014, using the NHS Economic Evaluation Database (EED) and the Health Technology Assessment (HTA) database (via The Cochrane Library). At the time of initial search the EED database was a reliable source for economic evaluations, using a very precise search over a wide number of databases to capture relevant studies which helps to reduce the number

of irrelevant study results, [17]. NHS EED ceased being updated in March 2015 so the updated search (November 2015), included the MEDLINE, EMBASE and Econlit databases. The NHS EED search terms were used to identify economic evaluations, [18].

Selection

Identified citations were manually screened to identify potentially relevant papers to include in the review, using explicit pre-defined inclusion criteria: the study sample or modelled population had to be (i) based in the European Union (ii) aged ≥60 or ≥65 years (the definition of elderly used in influenza policies across Europe). Studies did not need to exclusively look at this age group, but had to present the results for the elderly population separately to other populations if they did consider wider populations. Studies had to compare the seasonal influenza vaccination intervention to a comparator intended to reduce the burden of illness associated with influenza (e.g. an alternative form of vaccination or antiviral treatments) or usual care/no intervention. This meant that the comparator arm could also include a proportion of people who were vaccinated against influenza. A fourth inclusion criteria was that studies had to be full economic evaluations; producing an incremental cost-effectiveness ratio using a health outcome. No restriction was placed on publication date. The review was limited to English language articles. After screening of titles and abstracts, full papers were retrieved and screened using the same inclusion criteria.

Two reviewers independently screened citations and full papers, with a third reviewer consulted to resolve any disagreements. The primary reason for study exclusion was recorded at each stage.

Data Extraction

Comprehensive data extraction was undertaken, in line with the NHS EED handbook and with some key additions on modelling technique from a review of economic evaluations of vaccinations, [19,20]. Pre-defined data extraction and quality assessment forms (see supplementary material) were used to extract information on study methodology, results, limitations, evidence gaps and quality for critical appraisal. Two reviewers extracted data independently, results were compared and discussion, with any disagreements settled by a third reviewer.

Cost figures were converted into 2014 Euros for presentation using the price index for each country and the purchasing power parity conversion factor to facilitate comparison between studies in different EU countries, [21,22].

Data Synthesis

Extracted data were summarised in text and tables. Study characteristics, cost and outcome data were tabulated and summarised. Critical appraisal was qualitatively synthesised with the help of the

checklist. The key aspects assessed included the reporting of key information (e.g. study design and how parameters were identified), methods used and the validity of cost and health benefits used.

RESULTS

Summary of studies

Figure 1 summarises the flow of studies identified and selected for review.

An overview of study setting, population and intervention/comparator is given in Table 1, Table 2 presents an overview of the study characteristics. A tabular overview of the critical appraisal is provided in the supplementary material.

Table 1: Overview of identified studies

Authors	Population	Country	Intervention/s and comparator/s	Vaccination coverage in paper and actual reported vaccination coverage, [13]		
				Intervention	Comparator	Reported vaccination coverage rate, [13]
Comparison of vaccination types						
Baio et al (2006), [23][a]	Unknown risk aged ≥65	Italy	MF59 adjuvanted vaccination versus standard non-adjuvanted vaccination	100%	100%	63%
Meier et al (2015), [24]	Mixed risk aged ≥65 (48% high-risk)	UK	Quadrivalent influenza vaccination versus trivalent influenza vaccination	71.3%	71.3%	76%
Piercy et al (2004), [25]	High-risk (suffering from lung or heart disease) elderly people aged ≥65	France	MF59 adjuvanted vaccination versus standard non-adjuvanted vaccination	61%	61%	53%
Comparison of vaccination strategies						
Allsup et al (2004), [26]	Low-risk aged 65-74	UK	Inactivated influenza vaccination versus no intervention	60%	20%	76%
Baio et al (2006), [23][a]	Unknown risk aged ≥65	Italy	MF59 adjuvanted vaccination or standard non-adjuvanted vaccination versus no intervention	100%	0%	63%
Brydak et al (2012), [27]	Mixed risk aged ≥65 (50% high-risk)	Poland	Reimbursed vaccination versus no intervention	40%	13.5%	12%
Lugner et al (2012), [28]	Mixed risk aged ≥65 (73-100% high-risk)	Germany, Netherlands and UK	Vaccination versus no intervention	90%	0%	56% Germany 74% Netherlands 76% UK
Postma et al (1999), [29]	Mixed risk aged ≥65 (35% high-risk)	Netherlands	Vaccination versus no intervention	83% high risk 65% low-risk	68% high risk 27% low risk	74%
Scuffham	Unknown	England	Opportunistic	53%	0%	76% UK

& West (2002), [30]	risk aged ≥65 or 60	and Wales, France and Germany	vaccination versus no vaccination, comprehensive vaccination versus no intervention	opportunistic vaccination 65-75% comprehensive vaccination		53% France 56% Germany

Note: high-risk refers to the elderly population with another condition or circumstance that places them at a greater risk of complications, e.g. respiratory conditions. Low-risk refers to the elderly population, who aside from being older, would not be considered to fall into any high-risk categories.

[a] Note that the study by Baio et al (2006) directly compared vaccination types, as well as comparing both vaccination types to no vaccination, [23].

Table 2: Study design and headline results

Authors	Study design	Evaluation details	Data source/s
Comparison of vaccination types			
Baio et al (2006), [23][a]	• Evaluation type: CEA • Measure of health benefit: deaths averted	• Type of study: model based economic evaluation (Bayesian network model) • Perspective: healthcare provider • Time horizon: NR • Price year: NR	Observational study data from 4 GP databases over 3 flu seasons was used for efficacy. The remainder of the evidence sources are unclear (not specified).
Meier et al (2015), [24]	• Evaluation type: CEA and CUA • Measure of health benefit: QALYs gained	• Type of study: model based economic evaluation (Markov model) • Perspective: healthcare provider (societal as a secondary analysis) • Time horizon: lifetime • Price year: 2012/13	National data sources were used for incidence, costs, utilities, complications and mortality data. Vaccine efficacy was taken from a published review of studies from multiple countries/influenza seasons. Over-the-counter medication usage was estimated from previous publications.
Piercy et al (2004), [25]	• Evaluation type: CEA • Measure of health benefit: deaths averted and life-years gained	• Type of study: model based economic evaluation (decision tree) • Perspective: healthcare provider • Time horizon: lifetime • Price year: NR	A variety of evidence sources were used, including national data, published literature and expert opinion. When French data could not be sourced (e.g. hospitalisations), data from other European countries was used.
Comparison of vaccination strategies			
Allsup et al (2004), [26]	• Evaluation type: CEA and CUA • Measure of health benefit: deaths averted and QALYs gained	• Type of study: RCT based economic evaluation • Perspective: healthcare provider • Time horizon: lifetime • Price year: NR	The main source of data was a prospective, single□blind, randomised, placebo□controlled clinical trial. Some parameters (e.g. baseline hospitalisation rate) were supplemented with hospital data and/or clinician expert assumptions.

Brydak et al (2012), [27]	• Evaluation type: CUA • Measure of health benefit: deaths averted, life-years gained and QALYs gained	• Type of study: model based economic evaluation (decision tree) • Perspective: healthcare provider • Time horizon: lifetime • Price year: 2009	Published data specific to Poland was used to inform the model where possible. It was noted that in some cases Polish data was not available and US data had to be used (e.g. hospitalisations).
Lugner et al (2012), [28]	• Evaluation type: CUA • Measure of health benefit: QALYs gained	• Type of study: model based economic evaluation (dynamic transmission model) • Perspective: healthcare provider and societal • Time horizon: lifetime • Price year: 2008	National data sources were used for demographic, resource use and cost data. Where evidence was not available for Germany and the UK, data from the Netherlands was used (e.g. hospitalisations). Vaccine efficacy was taken from a published review and meta-analysis of studies from multiple countries/influenza seasons.
Postma et al (1999), [29]	• Evaluation type: CEA • Measure of health benefit: life years gained	• Type of study: model based economic evaluation (decision tree) • Perspective: healthcare provider • Time horizon: lifetime • Price year: 1995	National data and published literature from the Netherlands were used for parameter values. Vaccine efficacy was taken from a published review and meta-analysis of studies from multiple countries/influenza seasons.
Scuffham & West (2002), [30]	• Evaluation type: CEA • Measure of health benefit: life years gained and morbidity days saved	• Type of study: model based economic evaluation (decision tree) • Perspective: healthcare provider • Time horizon: lifetime • Price year: 2000	Evidence sources included published studies, national databases and expert opinion. In some cases country specific data were not available for all parameters and it was taken from another country in the study (e.g. vaccine efficacy came from a US study).

Key: CEA, cost-effectiveness analysis; CUA, cost-utility analysis; ICER, incremental cost-effectiveness ratio; NR, not reported; QALY, quality-adjusted life-year; RCT, randomised controlled trial.

[a] Note that the study by Baio et al (2006) directly compared vaccination types, as well as comparing both vaccination types to no vaccination, [23].

Study results

Key study outcomes are given in Table 3.

Table 3: Key study outputs

Study	Population	Intervention and comparator	Net health benefits (per patient)[a]	Net costs (per patient)	Incremental cost-effectiveness ratio*	Headline results
Comparison of vaccination types						
Baio et al (2006), [23][c]	Unknown risk aged ≥65	Adjuvanted vaccination versus standard vaccination	NR	-€1.95	Adjuvanted vaccine dominated standard vaccination (per death averted)	Adjuvanted vaccine was shown to be cost-effective against the standard vaccine.
Meier et al (2015), [24]	Mixed risk aged ≥65 (48% high-risk)	Quadrivalent influenza vaccination versus trivalent influenza vaccination	NR	NR	€11,751 per QALY	Quadrivalent vaccination is cost-effective compared with trivalent vaccination in the UK.
Piercy et al (2004), [25]	High-risk elderly people aged ≥65	Adjuvanted vaccination versus standard vaccination	0.003397 fewer ILI cases, 0.000043 deaths avoided and 0.000300 LYG	€1.31	€30,503 per death avoided and €6,131 per LYG	Results were mixed according to the different scenarios for the strain of the influenza virus considered.
Comparison of vaccination strategies						
Allsup et al (2004), [26]	Low-risk aged 65-74	Vaccination versus no intervention	0.000007 fewer deaths and 0.000044 additional QALYs	€ 5.37[b]	€3,576,908 per death avoided, €459,350 per life-year gained and €572,305 per QALY gained	Influenza vaccination was judged not to be cost-effective in the low-risk elderly population.
Baio et al (2006), [23][c]	Unknown risk aged ≥65	Adjuvanted vaccination versus no intervention	NR	-€3.76	Adjuvanted vaccine dominated no intervention (per death averted)	Both vaccination types were cost-effective against no intervention.
		Standard vaccination versus no intervention	NR	-€1.91	Standard vaccine dominated no intervention (per death averted)	

Brydak et al (2012), [27]	Mixed risk aged ≥65 (50% high-risk)	Reimbursed vaccination versus no intervention	NR	€22.61	€11,790 per QALY gained, €58,981 cost per death avoided and €6,881 per life-year gained	Introducing public funding of influenza vaccination for people aged 65 and over to increase coverage was cost-effective compared to the status quo.
Lugner et al (2012), [28]	Mixed risk aged ≥65 (73-100% high-risk)	Vaccination versus no intervention (Germany)	NR	€13.22	€1,065 per QALY gained (direct costs) and dominant per QALY gained (indirect costs included)	In general, vaccination was shown to be a cost-effective strategy. Early vaccination strategies are more favourable with lower total costs and cost per QALY gained. The inclusion of indirect costs makes the early vaccination strategies dominant in all countries.
		Vaccination versus no intervention (UK)	NR	€17.19	€4,621 per QALY gained (direct costs) and dominant per QALY gained (indirect costs included)	
		Vaccination versus no intervention (Netherlands)	NR	€17.62	€1,338 per QALY gained (direct costs) and dominant per QALY gained (indirect costs included)	
Postma et al (1999), [29]	Mixed risk aged ≥65 (35% high-risk)	Vaccination versus no intervention	NR	NR	€2,468 per LYG (all elderly people), €9,355 per LYG (low-risk) and dominant per LYG (high-risk)	Population-wide influenza vaccination for elderly people was found to be cost-effective. More favourable results were estimated in the high-risk population.
Scuffham and West (2002), [30]	Unknown risk aged ≥65 or 60 (country differences)	Opportunistic vaccination versus no intervention (England)	0.547400 fewer morbidity days and 0.001040 LYG	-€1.89	Dominated per LYG gained	Vaccination strategies were cost-effective versus no intervention.
		Comprehensive vaccination versus no intervention (England)	1.065400 fewer morbidity days and 0.002020 LYG	-€0.84	Dominated per LYG	
		Opportunistic vaccination versus no intervention (France)	0.822500 fewer morbidity days and 0.001470 LYG	€2.11	€1,437 per LYG	

		Comprehensive vaccination versus no intervention (France)	1.011300 fewer morbidity days and 0.001800 LYG	€6.53	€3,623 per LYG	
		Opportunistic vaccination versus no intervention (Germany)	0.479500 fewer morbidity days and 0.000780 LYG	€2.87	€3,676 per LYG	
		Comprehensive vaccination versus no intervention (Germany)	0.760200 fewer morbidity days and 0.001240 LYG	€8.69	€7,016 per LYG	

Key: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NR, not reported; QALY, quality-adjusted life-year.

[a] Note that net benefit per person was calculated by the author where the total net benefits across the population and total population figures were provided by studies. This may mean that there appear to be differences between the ICER value calculated by the study and the value calculated using the net benefit above, likely due to rounding differences.

[b] Trial cost only reported (not actual modelled costs).

[c] Note that the study by Baio et al (2006) directly compared vaccination types, as well as comparing both vaccination types to no vaccination [23].

Vaccination type comparisons

Three studies including two vaccine types, [23–25]. Adjuvanted vaccination, whilst associated with a higher cost of vaccination, was cost effective when compared to standard vaccination as higher efficacy rates increased health benefits, [23,25]. Though the two studies focusing on adjuvanted vaccination identified it as being cost-effective, the ICER results were very different (dominant versus a cost per QALY gain). It is difficult to assess where the difference in the result arose from, due to a lack of reporting incremental health benefits and net costs. However, there were some key differences in the studies that could have affected this, including; modelling characteristics (decision tree versus Bayesian network model), the population risk level, sources of effectiveness evidence and in particular the influenza attack rate. The latter in particular stands out as being very different between studies; Piercy et al (2004) assumed a rate of 5% (author's assumptions) whereas Baio et al (2006) used estimates from the literature, with a mean of 16%, [23,25].

Quadrivalent vaccination was cost-effective when compared to trivalent vaccination in the base case scenario modelled by Meier et al (2015), [24]. However, this study does not make it clear whether the data used to inform efficacy of the vaccination for the base case results was specific to the elderly. The study also considered two scenarios (a best-matching season and a worst-matching season) but did not report the results separately for the elderly population.

Two studies which compared vaccination types included probabilistic sensitivity analysis. Baio et al (2006) estimated that adjuvanted vaccination was over 90% likely to be cost-effective compared to standard vaccination, [23]. Meier et al (2015) included probabilistic sensitivity analysis, [24]. The authors found that quadrivalent vaccination was estimated to be cost-effective in between 68% to 87% of scenarios compared to trivalent across the total modelled population. However, this was not restricted to the elderly population sub-group thus it is impossible to draw conclusions from this study about the uncertainty around estimates that are specific to the elderly population.

Vaccination strategy comparisons

Vaccination intervention (i.e. strategies that increase the level of vaccination within a population) appears to be cost effective throughout the studies for both the primary and sensitivity analyses conducted, with the exception of Allsup et al study (2004) which reported a significantly higher ICER, [26]. As previously noted, studies included different levels of vaccination in their intervention/comparator arms, however this does not appear to cause any systematic differences in results.

Allsup et al (2004) is noted to have significantly different results to the other studies. This study focused on the low-risk population only. In addition, it applied lower reductions in the risk of

hospitalisation from vaccination and lower costs of hospitalisations. It also applied a cost of vaccination promotion where the other studies did not, increasing the validity of costs as this is likely to be needed to reach high vaccination levels. This was also the only study completed alongside a randomised controlled trial (RCT); the remainder were economic models using secondary data sources. Studies conducted within RCT have high internal validity and this study appeared to be robust and was overall well-reported. However, Jit et al (2013) noted that there are some issues when relying on one single trial for an economic evaluation has problems, [31]. In particular, a lack of external validity as the vaccine efficacy changes each season, it is possible that the study was conducted in a season in which vaccine matching was poor, [31].

The susceptibility of the population has important implications for the rate of complications; if more people are at risk of complications, vaccination is likely to produce larger health gains. One study compared results between the low and high-risk population, [29]. As expected, the vaccination of high-risk individuals was demonstrated to be more cost effective than vaccinating low-risk individuals, as this population is more susceptible to complications, which are costly and negatively impact quality of life, [29]. This trend seems to be reflected in the other studies identified, for example with Brydak et al (2012) and Lugner et al (2012), as the latter has a greater proportion of high-risk individuals has a more favourable ICER per QALY gained (in the same countries), [27,28].

A passive vaccination strategy was found to be more cost effective compared to no intervention than a comprehensive/targeted strategy, [30]. Comprehensive strategies are associated with greater health benefits but the passive strategy has reduced costs as they avoids the additional consultation costs, only vaccinating when people present at the GP for other reasons.

One model included transmission rates and captured externalities arising from herd immunity, [28]. When these indirect effects were included results became more favourable (from an ICER that was judged to be below cost-effective thresholds to dominant), as it demonstrated cost savings. The inclusion of herd immunity has important implications for the vaccination coverage in the intervention and comparator arm. Herd immunity means that the impact of increasing vaccination levels is not linear, e.g. an equal change in the coverage rate between studies could have very different results depending on what the comparator/usual care coverage rate is, as the scope for benefits from herd immunity will be different. Whilst this does not affect this review because only one study included herd immunity, it is an important point for future researchers looking to compare study results as more studies including herd immunity become available in the future.

It would be expected that different countries have comparatively different cost-effectiveness results, due to differences in healthcare service design and population differences that may affect the attack rate and complication rates. However, there does not seem to be a clear pattern demonstrated across

the studies included. For example, three studies included the UK but results are very different; one found vaccination to be cost saving and more effective (dominant), another found it to be cost increasing but cost-effective, and another found it to be cost-increasing and not cost-effective, [26,28,30]. Some of this difference can be explained by assumptions made about the vaccination cost, and other study differences (e.g. susceptibility of the population). However, one key issue when interpreting results across countries is a lack of evidence specific to each population (discussed further in the critical appraisal section).

One study which compared vaccination to no intervention include probabilistic sensitivity analysis and determined that vaccination was 79.93% likely to be cost effective (below the threshold of 3 GDP per capita), [27]. Across all studies (irrespective of intervention and comparator) scenario and one-way sensitivity analysis demonstrated key variables to be the incidence of influenza, vaccine efficacy, discount rates and complication rates (mortality and hospitalisation). In general, studies showed that despite parameter uncertainty, the majority of tested scenarios still demonstrated vaccination to be cost effective. Further detail on sensitivity analysis conducted is provided in an overview table in the supplementary material.

Critical appraisal

Studies were critically appraised to determine the overall quality of the evidence base; a summary is given in supplementary data. None of the studies reported all information required for data extraction, or to conform to the WHO guidelines or recommended checklists for economic evaluations, [19,32–34]. In some cases there was a failure to report fundamental assumptions, design and inputs, which means that the risk of bias is difficult to judge. In particular, it is difficult to assess the quality of the data used (and therefore the validity of study results), due to the lack of reporting around this, including how parameters were identified. These factors indicate uncertainty about the robustness of the overall result that vaccination is cost-effective.

Intervention and comparator

Three studies directly compared two vaccine types and found that the cost effectiveness of vaccination varied by type of vaccine [23–25]. Six studies included a comparison of a strategy to vaccinate older people to no vaccination strategy [23,24,26–30]. Of these studies the comparator arm included a proportion of participants who would be vaccinated which ranged from 0-27% in low or mixed risk populations and 68% in a high risk population. The reported coverage rates for the countries included in the studies ranged from 12% to 76%. The data indicate that practice varies between countries and that the decision to implement or change a vaccination strategy for older people needs to take the underlying coverage rate into account. Two studies considered a vaccination level very similar to reality, improving the validity of these studies, [24,27]. One study included anti-

viral drugs as a comparator, but did not directly compare them to a vaccination intervention arm and so results are not presented, [30].

Four studies, which synthesised evidence from multiple sources within an economic model, did not report vaccination type (e.g. adjuvant, quadrivalent, etc.), [24,28–30]. As there are different vaccination types available it would be more robust if evaluations focused on a specific type, in these cases it is not known whether data may have been synthesised from studies for different vaccination types, reducing validity.

Effectiveness data

One study was conducted alongside a RCT, [26]. This was single-blinded only as double-blinding was not feasible due to the intervention type (injection), which may introduce bias. One study identified the efficacy inputs from prospective cohort studies which were not randomised or blinded to intervention, increasing the risk of bias [23]. The authors did not report detailed information about the cohort study design or participants so it is not possible to assess the validity and robustness of the data and analyses used in the economic model. The remaining studies synthesised data about vaccine efficacy/effectiveness from several sources. None of these economic evaluations reported the methods used to identify and select studies to estimate effectiveness data inputs. Most of the authors reported that they needed to supplement data on vaccine efficacy with evidence from other countries, or apply the same efficacy values across different countries in the same study, [24,25,27–30]. This means that it is not possible to assess the validity and robustness of the vaccine efficacy/effectiveness data used in the economic models. For example, Scuffham and West (2004) used the same efficacy source for 3 countries and many of the papers use the same network meta-analysis for effectiveness of the influenza vaccination, [30]. This reduces the validity of study results and suggests that the studies may be over-representing a limited evidence base.

Measure of health benefit

Four studies undertook a cost-effectiveness analysis alone, with the measure of health benefit provided in terms of life years gained or deaths averted, [23,25,29,30], 2 studies performed a cost-utility analysis with quality-adjusted life-years (QALYs) as the measure of health benefit, [24,28], and 2 studies included both cost-effectiveness and cost-utility analyses, [26,27]. All studies assessed life-years gained as a result of avoiding death related to influenza complications. In the 4 studies reporting cost-utility results, a single study accounted for morbidity by applying lost utility related to mortality to estimate QALYs, [26]. The other studies also accounted for short-term changes in utility as a result of having influenza, [24,27,28].

The robustness of QALY estimates is questionable due to the limited relevant evidence and small study samples of utility studies. A review concluded that no utility studies using robust methods were available for influenza, which was reflected in the cost-utility evaluations identified, [35]. Lugner et al (2012) took utility decrements relating to influenza from an English postal survey of 288 patients with confirmed influenza, using the European Quality of life 5-dimension health questionnaire (EQ-5D), [28,36]. The generalisability of this study to the elderly Dutch population is difficult to assess as patient characteristics were not reported. Meier et al (2015) and Brydak et al (2012) applied utility values taken from a survey of 15 working age healthcare workers in the US with utilities scored using the health utilities index, [24,27,37]. This is arguably not relevant to the elderly population. The WHO guidelines recommend that economic evaluations are cost-utility analyses, however without robust utility data, cost-utility evaluations will inevitably have limited validity, [32].

ILI was used in all studies as a proxy for influenza. The severity and subsequent cost of influenza can vary substantially, therefore there are concerns that this outcome is too broad, [38]. However, this is the primary end-point of clinical trials and subsequently studies are restricted by this, [38]. Longer-term outcomes associated with influenza were not considered; likely due to a lack of robust clinical data and the impact of confounding factors in the long-term, [11]. The likely direction of bias caused by excluding long-term outcomes is unclear, it may understate the value of vaccination if it increases a person's health over time, or may overstate the value of vaccination if side effects occur in the long-term.

Costs

Seven out of 8 studies used a one year time horizon for costs, consistent with an influenza season and the short-term/immediate associated costs, therefore discounting costs was irrelevant, [23,25–30]. The remaining study considered repeat vaccinations and costs each flu season over a lifetime, [24]. Where relevant, studies applied country-specific guidelines for discounting outcomes; ranging from 1.5% to 5% annually.

The majority of studies considered direct costs only. This approach is justified as indirect costs are less important in a retired population. Societal costs (e.g. over-the-counter drugs) are likely to be minimal due to the nature of the illness. Appropriately, the only study that included productivity losses did so because they considered herd immunity effects in the working age population, the study also included a scenario in which only direct costs were considered, [28]. All studies included costs associated with purchasing vaccines, influenza related treatments, primary care visits and hospitalisations. Six studies included administration costs, [25–30]. The total cost of vaccination varied from €8.50 to €35.95 per person, differences between studies mainly occurred due to variation in administration costs rather than variation in vaccine cost; lower costs were associated with opportunistic vaccination. Transportation costs, over-the-counter medication costs and private nursing

home costs were considered in the societal perspective of one study, [24]. A single study included vaccination side effect costs; in the short-term these are rare and usually require only minimal medical attention, [30]. The inclusion of side effect costs did not have a significant effect on total costs or overall ICER results in this study (supported by a sensitivity analysis), [30]. Longer-term evidence is lacking, with the majority of studies in the elderly population having short time-horizons, hence data on longer-term side effects would not be identified and could not have been included by studies, in the future if studies expand their time horizons this may have implications on results, [1,11]. Only 1 study applied costs to promote vaccination, [26]. No studies considered the cost of service redesign to increase vaccination (e.g. opening additional clinics) which may be relevant for healthcare systems with restraints on resources available (e.g. in the case of an aging population). Thus, the true cost of vaccination is likely to be underestimated across studies depending on the healthcare setting.

Model design

On the whole, modelling approaches were relatively simple (e.g. static decision tree models), reflecting gaps in the evidence base and the short time horizon captured in effectiveness studies. As the main outcomes of the vaccination occur over a single influenza season and occur once only during this time (i.e. influenza infection or no infection), decision trees are a clear and logical structure for the model and are likely to be sufficient to capture the majority of health outcomes and costs. One study used a dynamic transmission model and was therefore able to capture the impact of transmission and herd immunity, [28]. This characterises interactions across the population and is therefore more reflective of the spread of disease and the indirect benefit for those not vaccinated. Overall, this model was reported well and seemed to be robust, but it did require more data than the simpler model approaches. The authors in this case had access to data on population interactions, but this may not be available in every country. Models that exclude herd immunity are likely to underestimate the cost-effectiveness of influenza vaccination, however, WHO guidelines recommend that a static model is acceptable as a conservative approach, [32].

More complex methodologies may capture the nature of the disease more accurately, however given the noted lack of clinical evidence it is unlikely that the current evidence base is sufficient to inform these, [11]. For example, patient-level simulations can also be more precise when modelling population interactions, [39]. Additionally stochastic models, with events occurring randomly, can more realistically model epidemics, as these occur by chance of transmission amongst population interactions, [20].

Methods to address uncertainty

Most scenarios tested in sensitivity analysis still resulted in favourable cost-effectiveness results for influenza vaccination. However, there were limitations to the range of sensitivity analyses reported,

given that many of the studies recognised there are issues with the evidence base. Methods used to analyse uncertainty were varied, such that results are not comparable. The WHO recommend that sensitivity analyses for economic evaluations of vaccines should vary the following 5 parameters as a minimum: discount rates, vaccine efficacy, influenza incidence, influenza complication rates and vaccine price, [32]. None of the studies identified varied all of the recommended parameters and because of this, we cannot fully assess the robustness of the results. One of the studies performed a comprehensive one-way sensitivity analysis; presenting a resulting tornado diagram, [27]. One study did not perform any one-way/scenario analysis, [23]. The remaining studies chose to vary a limited selection of key variables, but did not explain the rationale for these, [24–26,28–30]. Three studies provided and justified ranges used in sensitivity analyses, [24,25,27]. The remainder detailed the ranges but did not provide justification, which means that validity cannot be assessed, [26,28–30]. Three studies included probabilistic sensitivity analysis, but one did not report the results restricted to the elderly population alone, [23,24,27]. This lack of thorough investigation and transparency restricts our ability to assess the robustness of the results or to explore the transferability of study results to alternative countries, settings and influenza seasons.

Discussion

The majority (7/8) of the identified studies found influenza vaccination to be cost effective in an elderly European population. The studies indicated some differences what vaccination strategy may be cost-effective. Adjuvant or quadrivalent vaccinations had more favourable results compared to standard vaccinations. Vaccination targeted to high risk groups of older people were generally more cost-effective and passive vaccination strategies appeared more cost-effective than opportunistic strategies. Decision makers using this evidence would need to check which papers are most relevant to their research question.

Most scenarios tested in sensitivity analysis still resulted in favourable cost-effectiveness results for influenza vaccination. In addition, the studies that conducted probabilistic sensitivity analysis concluded that the likelihood of cost-effectiveness given parameter uncertainty was high. Results were sensitive to variations in the strain of influenza incidence, vaccination type, efficacy and strategy, population risk and modelling characteristics. Review findings are in alignment with the previous review identified, [40].

Limitations of the evidence base

The robustness of conclusions about the cost effectiveness of vaccination in older people is limited due to the evidence gaps and subsequent uncertainty demonstrated in the literature base, as well as the limited investigation into this uncertainty. Studies did not report all of the information needed to assess the internal and external validity of results. Robust economic evaluations require high quality

evidence of effectiveness, service use and health benefit. In the studies reviewed here, the data used is uncertain and in the case of the effectiveness data reliant on underpowered trials. Most of the studies reported limited information about the methods used to identify and select effectiveness data, the relevance of the data to the elderly population or the quality of the data used to estimate effectiveness parameters. In addition, the evidence base is small, especially considering the number of questions decision makers could have. Many of the conclusions about cost-effectiveness rely on the results of single studies, [24,30].

The studies reported limited sensitivity analyses to test the robustness of the conclusions to the assumptions made or uncertainty in the data used. There was also a lack of reporting on key items such as the rationale for the data ranges used in sensitivity analysis. Detailed and clearly justified sensitivity analysis with robust ranges is needed to identify the level of uncertainty and draw evidence based conclusions, [11]. Further investigation into uncertainty, in particular probabilistic sensitivity analysis that includes all parameters, is needed to estimate the level of certainty of the cost-effectiveness results.

Limitations of this review

The review focused on the elderly population, which is one of many high-risk groups. To prioritise the right groups to target for vaccination, due to cost and resource constraints, decision makers are likely to need to conduct further reviews of the economic evidence for other high-risk groups. For example, these analyses might focus on groups with chronic conditions, pregnant women or children. This would produce a more balanced judgement of where to prioritise intervention.

The original search for studies used a single database (NHS EED), increasing the chance of missing papers that could change the conclusions of the review. However, at the time NHS EED was comprehensive, searching a wide range of databases, and was regularly updated. The updated search included more databases. The review included English language articles only, which risks language bias. Searches were limited to published journal articles. Widening the searches to the grey literature or unpublished reports may have been more likely to identify studies with inconclusive or negative cost-effectiveness results, [41]. The generalisability of some of the results of this review to other settings (outside the EU) may be limited, due to inevitable differences resource use, treatment pathways and population characteristics.

Future research

This review highlights several areas that would benefit from additional research. Parameter uncertainty affected the strength of economic evaluations, largely because many of the trials for vaccine efficacy are underpowered, non-randomised and susceptible to bias, [11], and deterministic

scenarios were not explored in thorough scenario analyses. A number of the evaluations used the same effectiveness data to estimate model parameters; this will over-represent a limited evidence base. Without more and stronger quality data to inform parameters economic evaluations will always be subject to a high degree of uncertainty. Trials for the vaccination cover the influenza season, typically a 6-month period over winter, [11]. A predominance of short term evidence in the literature prevented the identified studies from including longer-term outcomes. There was also a lack of evidence for each country, with studies relying on external data sources with questionable relevance to their population. Moreover, this evidence gap meant that many studies used the same sources for certain inputs, potentially over-representing the results of a small and low quality evidence base. Work to ensure that robust country-relevant data inputs are available would increase the validity of future evaluations. Increasing this evidence base could lead policy makers to revaluate current recommendations.

The body of economic evidence suggest that influenza vaccination of elderly populations may be cost effective, but data, methodological transparency and exploration of uncertainty are lacking. Baguelin et al developed a complex epidemiological model to explore the relative cost effectiveness of vaccination in different low and high risk groups, [36,42]. Whilst these evaluations give an indication of the value of complex models, both studies also faced limitations in data about the effectiveness of vaccines and estimates of service use and health benefits, [36,42].

Future economic evaluations should follow good practice guidelines and ensure that they are transparently reported to assist reviewers in the future. Economic evaluations integrated into long-term, prospective, controlled studies (e.g. observational cohort studies or RCTs) or prospective study in elderly populations would help to address the evidence gaps around effectiveness, service use and health benefit. Since the influenza virus mutates each season and differences in vaccine matching each season, a combination of multiple studies and those conducted over several influenza seasons are needed. Improvements in the evidence base would support the development and analysis of more sophisticated modelling techniques. Such models could then characterise the epidemiology of influenza and complications in elderly people, incorporate the impact of herd immunity within the elderly population and between age groups. Robust data about service use and health benefits would allow more detailed estimates of the potential for different vaccination strategies for older people to be cost-effective in different settings.

Contributors

GE Shields and J Elvidge conducted the literature search with oversight from LM Davies. G Shields wrote the first draft of the manuscript, J Elvidge and LM Davies contributed to the final writing of the paper.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

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Data Sharing

No additional data available

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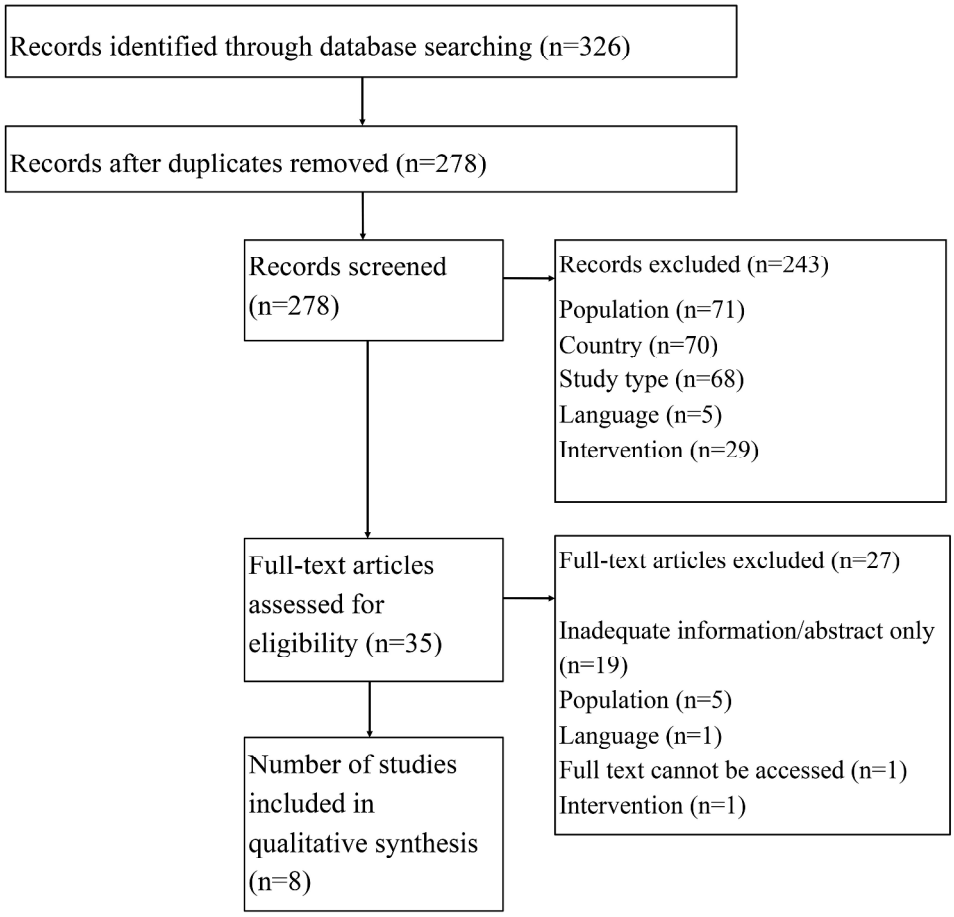

Figure 1: flow diagram of search

333x333mm (300 x 300 DPI)

Supplementary material

Example search strategy

1 Influenza, Human/
2 influenza/
3 flu/
4 influenza virus/
5 seasonal flu/
6 1 or 2 or 3 or 4 or 5
7 Vaccination/
8 vaccine/
9 7 or 8
10 Economics/
11 exp "costs and cost analysis"/
12 Economics, Dental/
13 exp economics, hospital/
14 Economics, Medical/
15 Economics, Nursing/
16 Economics, Pharmaceutical/
17 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
18 (expenditure$ not energy).ti,ab.
19 value for money.ti,ab.
20 budget$.ti,ab.
21 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 ((energy or oxygen) adj cost).ti,ab.
23 (metabolic adj cost).ti,ab.
24 ((energy or oxygen) adj expenditure).ti,ab.
25 22 or 23 or 24
26 6 and 9 and 21
27 26 not 25
28 letter.pt.
29 editorial.pt.
30 historical article.pt.
31 28 or 29 or 30
32 27 not 31
33 exp animals/ not humans/
34 32 not 33
35 limit 34 to yr="2014 -Current"

Blank data extraction form: key study attributes and critical appraisal

Subject of the study	
Health technology	
Disease	
Type of intervention	
Hypothesis and/or study question	
Key elements of the study	
Economic study type	
Study population	
Modelling and statistical extrapolation	
Setting	
Dates to which data relate	
Link between effectiveness and cost data	
Clinical evidence	
Clinical and epidemiological data	
Parameter value	
Data sources	
Methods to obtain data	
Economic analysis	
Summary measure of health benefit reported	
Type of measure of health benefit	
Utility or WTP benefit measures - method of valuation	
Discount rate for utility or WTP	
Economic analysis	
Whose direct cost	
Which direct costs	
Source of resource use	
How prices estimated	
Costs discounted	

Date of price data	
Marginal or average costs	
Resource use separately reported	
Costs adjusted for inflation and how	
Costs excluded	
Adjustments to costs	
Budget impact (yes or no)	
Currency	
Economic analysis	
Why include/exclude productivity costs	
Source of cost and quantity data	
Were costs and quantities separately reported	
When resources measured	
Discounted? Why? Relevant?	
Statistical analysis cost	
Point estimates used (yes or no)	
Descriptive statistics used	
Statistical tests used	
Parameters tested	
Study powered to detect differences?	
Analysis uncertainty	
Parameter uncertainty investigated (yes or no)	
How parameter uncertainty investigated	
Uncertainty investigated all parameters (yes or no)	
If not all parameters, which investigated	
Methods or rationale for deterministic analysis	
Probabilistic analysis were distributions defined	
Was structural uncertainty assessed	
Was variability in data investigated	

Estimated benefits	
Total benefits for each intervention	
Duration of benefits	
Were side effects/adverse events included	
Net (incremental benefit) of intervention-comparator	
Statistical test of differences in benefit	
Sensitivity analysis of benefits only	
Cost results	
Net (incremental) cost) of intervention-comparator	
Statistical test of differences in cost	
Sensitivity analysis of costs only	
Results of any currency conversion	
Synthesis	
Was synthesis reported (yes or no)	
If no, was rationale for no synthesis reported	
ICER	
Net benefit	
Probability cost effective	
Cost acceptability curve (yes or no)	
Sub-group analysis or sensitivity analysis (yes or no)	
Type of sub group or parameters varied in sensitivity analysis	
ICER	
Net benefit	
Probability cost effective	
Cost acceptability curve (yes or no)	
Authors conclusions	
Conclusions	
Choice of comparators	
Was the choice of intervention explicitly justified (yes or no)	

Was the choice of intervention implicitly justified (yes or no)	
Key reasons for choice of intervention	
Was the choice of comparator explicitly justified (yes or no)	
Does the choice of intervention or comparator affect the	
Modelling	
Model structure/technique clearly reported	
Input data clearly reported	
Input data sources clearly reported	
Uncertainty investigated (yes or no)	
Methods used to assess uncertainty	
Results of uncertainty assessments clear (yes or no)	
Other positive or negative comments on model	
Assessment of validity of model - robust? - biased?	
Validity effectiveness	
Sources of data for model parameters	
Were data combined to estimate parameters (yes or no)	
If yes, were methods clearly reported (yes or no)	
If yes, what methods used to combine data	
How were data identified for inclusion	
What inclusion criteria	
Justification for choice of data (yes or no)	
If yes, what was justification	
What was quality of evidence used to derive parameter estimates	
Validity of health benefit	
Summary measure of benefit (yes or no)	
If yes, how derived	
How were utility values measured or identified	
To what extent does the measure of benefit cover all relevant	
Overview of costs	

Were all relevant costs included for perspective (yes or no)	
If no, what omitted	
For each cost category, were all relevant cost items included (yes	
If no, what omitted	
Do any omissions affect results or authors conclusions (yes or no)	
Cost details	
Sources of resource use, price and cost data	
Price adjustments (yes or no)	
If yes, what price adjustments	
Costs discounted (yes or no)	
If no, appropriate	
Were any resource use, price or cost data stochastic (yes or no)	
If yes, any statistical analysis	
Cost data adequately reported yes/no	
If no, why	
Other cost issues	
Costs valid (unbiased) (yes or no)	
If no, why	
Costs generalisable (yes or no)	
If no, why	
Other issues	
Comparisons with other studies (yes or no)	
If yes, results of comparison	
Generalisability addressed (yes or no)	
If yes, how	
Selective reporting of results (yes or no)	
If yes, in what ways	
Conclusions reflect scope/data	
Authors report the limitations (yes or no)	

If yes, what	
Any other shortcomings yes/no	
If yes, what	
Implications	
Authors recommendations	
Recommendations suggested by abstractor	
Implications reported by authors	
Implications suggested by abstractor	
Related publications	
Related publications	
Important to review for model	
Important to review for systematic review paper	
Focus on key model attributes	
Static or dynamic	
Stochastic or deterministic	
Aggregate or individual	
Discrete or continuous	
Key: ICER, incremental cost-effectiveness ratio; WTP, willingness to pay threshold.	

Adapted from: [22,23]

Table summary of critical appraisal

Study	Studies reporting clearly
Research question	100% [26–33]
Study design	25% [29,30]
Perspective	87.5% [26–28,30–33]
Intervention	100% [26–33]
Comparators	100% [26–33]
Study population	100% [26–33]
Method of economic evaluation	87.5% [26–33]
Data collection	
Source(s) of effectiveness estimates	87.5% [26,28,30–33]
Methods of synthesis used to source effectiveness estimates (if applicable)	37.5% [26,30,33]
Methods used to value health states and benefits	87.5% [26,28–33]
Quantities of resource use and costs reported separately	62.5% [26,28,29,31,33]
Methods for resource use and unit costs	87.5% [26,28,29,31,33]
Price year	62.5% [28–33]
Price adjustments for inflation or currency conversion	12.5% [29]
Analysis and interpretation of results	
Time horizon	87.5% [26,28–33]
Discount rate (if applicable)	100% [28–33]
Explanation given if cost or benefits were not discounted (if applicable)	100% [26,27]
Statistical test(s) and confidence intervals given for stochastic	12.5% [26]
Sensitivity analysis methods	100% [26–33]
Choice of variables for sensitivity analysis	87.5% [26,28–33]
Ranges used in sensitivity analysis	100% [26–33]
Appropriate comparisons	100% [26–33]
Incremental analysis reported	100% [26–33]
Outcomes presented disaggregated and aggregated	25% [28,33]
Study question answered	100% [26–33]
Conclusions relevant to study	100% [26–33]
Limitations	62.5% [26,28–30,33]
Generalisability issues	25% [28,29]

Comparisons to other studies	37.5% [26,28,30]

Summary of sensitivity analysis

Study	Description	Key results (€, 2014)
Allsup et al (2004)	• One-way sensitivity analyses conducted on: target coverage, hospitalisation risk, mortality risk, vaccine efficacy, incident rates, promotion costs, hospitalisation costs and life expectancy	• Vaccination was judged to be not cost effective under any scenario when compared with no intervention. • The most influential parameters were vaccine efficacy, influenza hospitalisation and the risk of complications. • ICER ranged from €73,342 to €2,646,693 (life-year)
Baio et al (2006)	• The use of an object-oriented influence model Bayesian network model accounts for uncertainty implicitly.	• Pairwise comparisons demonstrated that the adjuvanted vaccine was over 90% likely to be cost-effective versus standard vaccine at a willingness to pay threshold of €0. At the same threshold adjuvanted was over 75% cost-effective versus no vaccination and standard vaccine was over 80% cost-effective versus no vaccination.
Brydak et al (2012)	• One-way sensitivity analysis (all parameters except vaccine price) • Probabilistic sensitivity analysis	• One-way sensitivity analysis stated that all scenarios (for reimbursed vaccination versus no intervention) were cost effective (below a WTPT 3 GDP per capita). • Probabilistic sensitivity analysis concluded that reimbursed vaccination was 79.93% likely to be cost effective (below the threshold of 3 GDP per capita). • The most influential parameters were vaccine efficacy against death, population utilities, outcome discount rate and the influenza attack rate. • ICER ranged from €9,070 to €21,107 (QALY).
Lugner et al (2012)	• One-way sensitivity analysis was conducted on vaccination cost, influenza transmissibility, coverage and pre-existing immunity	• The vast majority of tested scenarios had ICERs below €15,000 for vaccination versus no intervention. The least cost effective scenario occurred when there was high pre-existing immunity, low transmissibility, direct costs alone were considered and there was a higher vaccine cost. • The most influential parameter was the pandemic scenario (which influences transmissibility/incidence). The other main influential parameters differed according to country.

		• ICER ranged from dominated to €43,006.
Meier et al (2015)	• One-way sensitivity analysis was conducted on the discount rate, vaccine efficacy (degree of matching), influenza incidence and influenza complication rates • Probabilistic sensitivity analysis	• All scenarios indicated that vaccination would be cost-effective under a threshold of £30,000/QALY. • Probabilistic sensitivity analysis concluded that a total of 68% of the simulations were below a threshold of £20,000/QALY, and 87% were below a threshold of £30,000/QALY. • The most influential parameters were circulation of influenza A and the degree of matching between the trivalent vaccine and the circulating influenza B lineages. • ICER ranged from dominant to €25,483 (QALY).
Piercy et al (2004)	• One-way sensitivity analysis was conducted on the discount rate, life expectancy and the influenza incidence rate	• The adjuvanted vaccination was judged to be cost effective (versus standard vaccination) under all scenarios tested. • ICER ranged from dominated to €26,383 (life-year).
Postma et al (1999)	• One-way sensitivity analysis was conducted on pneumonia related hospitalisation rates, mortality risk and hospitalisation bed days, vaccine efficacy and the discount rate	• All tested scenarios resulted in cost effectiveness results (below €12,500 ICER per life-year gained). • The most influential parameters for the net cost were risk of complications (hospitalisation and mortality). • Broken down ICER results were not provided for sensitivity analysis.
Scuffham and West (2002)	• One-way sensitivity analysis was conducted on vaccination effectiveness, side effects, vaccine price, years per life lost, discount rate, coverage and the attack rate	• The majority of tested scenarios were cost saving when vaccination was compared to no intervention. With the exception of a vaccination price increase. • The most influential parameters were vaccine price, vaccine effectiveness and the discount rate for outcomes. • Broken down ICER results were not provided for sensitivity analysis (only net costs).
Key: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year; WTPT, willingness to pay threshold.		

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4/5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 and supplementary material
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5 and supplementary material
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	17-19 and supplementary material
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	17-19 and supplementary material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	17-19
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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