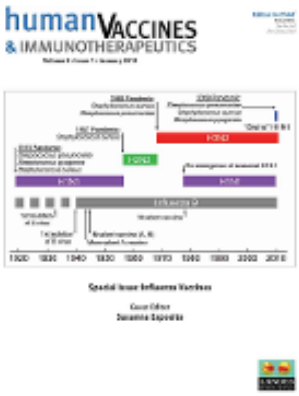

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Economic value of influenza vaccination

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Influenza epidemics are responsible for high mortality and morbidity rates in particular among elderly and high risk groups. This review is aimed at assessing the economic value of vaccination in these groups. A search of full economic evaluations of influenza vaccination in comparison with no interventions was performed on PubMed from January 1990 to May 2011. Only economic evaluations dealing with elderly and high risk groups were considered. The quality of selected articles was assessed through Drummond's checklist. Sixteen cost-effectiveness analyses and four cost-benefit analyses were included: overall, the quality of studies was fairly good. The vaccination was demonstrated to be cost-effective or cost-saving in almost all studies, independently by the perspective and the type of analysis. Influenza vaccination is a worthwhile intervention from the pharmacoeconomic view-point, anyway a standardization of methods should be desirable in order to guarantee the comparability and transferability of results.

Introduction

Influenza infection is an important public health issue representing a major cause of morbidity and mortality worldwide. It affects every year from 5 to 20% of the population resulting in more than 200,000 hospitalizations and 36,000 deaths.[1] Although the whole population is affected, influenza morbidity and mortality rates are particularly high among individuals at increased risk of complications, such as elderly—especially those living in the community—cancer patients or patients with underlying immunosuppressive diseases.[1-3] Both medical expenses, due to resource use, and societal costs, from mortality and loss in productivity, are generated by this highly contagious viral infection. Vaccination for elderly and at high-risk groups is an effective strategy to prevent influenza and reduce epidemics impact and efforts have been focused on vaccine administration in most countries. Age-based immunization programs are targeted to persons over 60, 65 or 70 y old, while risk-based immunization ones to those with pre-existing diseases.[2,4] Providing indirect protection through the vaccination of other population subgroups could be a complementary approach. In fact, vaccination of children as well as of healthcare workers has been showed to produce indirect benefits to the community by reducing mortality and morbidity in other vulnerable categories.[5,6] Moreover, healthy working adults vaccination in Western countries, if considered from the societal perspective, seems to have cost-effectiveness and cost-saving potentials, due to indirect benefits related to avoided absenteeism from work and production losses.[7]

In spite of recommendations to immunize all high-risk subjects, a still low vaccination rate has been registered among some subgroups. Adults below 65 y at increased risk of complications from influenza showed a low influenza immunization rate if compared with that of the elderly population, as well as cancer patients compared with their elderly counterparts.[8,9] Low vaccination coverage among cancer patients may have been influenced by the concern that cancer patients' immune response might be attenuated from the underlying immunosuppressive disease and that cancer therapy effects could compromise vaccine effectiveness.[10,11]

Considered all the above mentioned issues, scientific literature devoted a lot of interest to influenza pharmacoeconomics.[7,12-15] This is also the topic of this study, showing the results of a systematic review concerning the economic value of influenza vaccine with a particular focus on elderly and high risk groups which represent the main target of vaccination campaigns across all European countries.

Results

Study selection. On the whole, 776 articles were retrieved on PubMed. After the evaluation of titles and abstracts 31 papers were considered to be eligible. Of the selected 31 studies, five were excluded from the full text reading[4,16-19] and six because full texts were not available.[20-25] In conclusion, 20 full economic evaluations were included (**Fig. 1**).[1-3,26-42] Of the 20 studies included, six (30%) were conducted in Europe (UK, Italy, France, Germany and Netherlands)[26,34-36,38,41] and 14 (70%)[1-3,27-33,37,39,40,42] in extra-European countries, mainly in the US.

Twelve studies (60%)[2,27,29,31,32,34-39,42] were focused on people aged 65 and above: Maciosek et al.[31] also included people over 50 y, two studies chose only people between 65 and 74 y[34,37] and Turner et al.[35] also addressed high risk adult patients.

For the high risk group of patients, two studies[26,28] dealt with pregnant women, two[1,3] with patients affected with cancer, one[30] with health care workers in close contact with oncological patients and one[41] with people with chronic lung diseases. Two additional studies dealt with children at risk: in the study by Hall et al.[33] they

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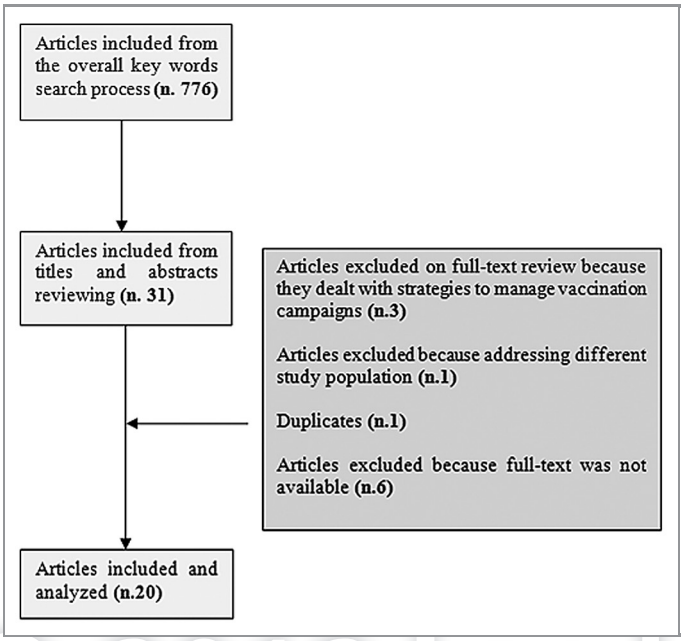

Figure 1. Flowchart of selection of studies.

attended tertiary care and in Dayan et al.[40] they were at risk for different medical conditions (congenital heart disease, asthma, cancer, HIV and insulin-dependent diabetes).

Quality appraisal. The quality of each study was assessed according to Drummond's checklist;[43] **Table 1** shows the overall results. In all studies included, the research question was stated (item 1) and a satisfactory answer to the study question was given (item 33). All but one study[39] reported the primary outcomes (item 11); only three (15%)[30,36,38] did not explain the methods used to assess health status (item 12). Of the 14 papers which clearly explained these methods, 10 (71.4%)[2,3,27,29,33,37,39-42] also provided the details of the subjects from whom evaluations were obtained (item 13). Ten studies (50%)[27-30,34-36,39,41,42] did not report separately the productivity changes (item 14), and in the papers where costs and benefits were not discounted, no explanation was given except for one study[40] (item 25). Only four studies (20%)[2,28,31,36] did not clearly describe the methods followed to estimate resources used and their unit costs (item 17), and eight evaluations (40%)[2,27,28,30,34,37,39,41] did not report them separately (item 16). Anyway, 13 studies (65%)[1,3,26-28,30,34,35,37-41] described the model details (item 20). Although in most studies sensitivity analyses were conducted (item 27), the justification of the choice of the variables included was not always provided (item 28).

Synthesis of results. Table 2 depicts studies included in the review ordered by publication year. Several analyses did not mention all the main features reported in the Table; the absent issues were the perspective, the time horizon, the effectiveness measures and the type of sensitivity analysis. In particular this was the case of Schooling et al.,[2] Chicaìza-Becerra et al.,[30] Wang et al. 2005,[32] Hall et al.,[33] Gasparini et al.,[36] Wang et al. 2002,[39] Hak et al.[41] and Nichol et al. 1994.[42] In relation to alternatives, the main comparison in most part of the studies was between the seasonal influenza vaccination and no vaccination only; two analyses[35,38] included also the chemoprophylaxis for influenza and antiviral treatment. Moreover, two studies[2,38] dealt with two different vaccination programs (opportunistic and comprehensive) in comparison with no vaccination.

Type of economic analysis and cost measures. Overall, 16 out of 20 studies (80%)[1-3,26-32,34-37,40,41] were cost-effectiveness analyses (CEA) whereas four (20%)[33,36,39,41] were cost-benefit analyses (CBA). Regarding effectiveness measures, eight studies (40%)[1,26-29,31,34,35] used quality adjusted life years (QALYs), three (15%)[32,34,38] used life years gained (LYG) and all the others chose cases of influenza, hospitalizations, influenza-related complications and deaths averted (**Table 2**). Authors evaluated alternatives from different perspectives with studies taking into consideration also more than one: societal,[1-3,27,28,31,32,34,37,40,41] third party payer/payers,[2,3,26-30,34,35,38,42] individual.[2] In three studies the point of view was not clearly declared.[33,36,39] Economic analyses could include both direct and indirect costs. In this review, all 20 studies included direct medical costs, in that costs referred to the management of the disease, from prevention to treatment of complications. Seven of them[1,3,28,32,35,37,40] and ten of them[2,3,27,28,31,32,34,36,38,41] also considered indirect costs and direct non-medical costs respectively.

The type of direct medical costs mostly taken into account were: costs related to vaccine itself, its administration and the management of adverse events, hospitalizations, general practitioner consultations, drugs administrated to treat influenza-related illness and intensive care.

Regarding direct non-medical costs, the main cost driver was represented by transport to the healthcare facilities, whereas indirect costs were mainly listed as productivity loss and days/hours of work lost for outpatient visit and vaccine administration.

Studies outcomes. Influenza vaccination, compared with no vaccination, appeared to be cost-effective and sometimes cost-saving among elderly. In particular, Maciosek et al.[31] showed that influenza vaccination was cost-effective (Incremental Cost-Effectiveness Ratio-ICER of US$ 980 per QALY gained). According to the study by Gasparini et al.,[36] influenza vaccination was cost-benefit (cost-benefit ratio of 8.22) and produced a net saving of € 110.20 per vaccinated person. In the study performed in 2005, Wang et al.[32] demonstrated the cost-effectiveness of community-based influenza vaccination in terms of death averted and LYG with an ICER of US$ 3,899 and US$ 309 respectively. Another study by the same Authors[39] demonstrated that influenza vaccination produced three times more savings than no vaccination avoiding approximately US$ 57.71 for pneumonia, chronic obstructive pulmonary diseases (COPD) and cardiovascular diseases per each vaccinated subject. Scuffham et al.[38] showed that vaccination strategies were cost-effective in comparison with no vaccination, chemoprophylaxis and antiviral treatment strategies whereas an economic evaluation conducted in the US[37] from the societal perspective showed that influenza vaccination resulted in net cost savings. In a former study, the same author[42] found that vaccination saved an average of US$ 117 per person, by reducing hospitalization due to pneumonia, influenza and COPD and the number of deaths from all causes.

Table 1. Results of the quality appraisal

			Yes	No	Unclear	Inappropriate
Study Design	1	The research question is stated	20			
	2	The economic importance of the research question is stated	17		3	
	3	The viewpoints of the analysis are clearly stated and justified	14	4	2	
	4	The rationale for choosing the alternatives programs or interventions compared is stated	12		8	
	5	The alternatives being compared are clearly described	15	3	2	
	6	The form of economic evaluation used is stated	17	2	1	
	7	The choice of form of economic evaluation is justified in relation to the question addressed	4	8	8	
Data Collection	8	The sources of effectiveness estimates used are stated	13	7		
	9	The details of the design and results of effectiveness study are given (if based on a single study)	6	7	2	5
	10	Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness study)	2	4		14
	11	The primary outcome measures for the economic evaluation are clearly stated	19		1	
	12	Methods to value health status and other benefits are stated	14	3	3	
	13	Details of the subjects from whom evaluations were obtained are given	10	4	6	
	14	Productivity changes (if included) are reported separately	7	10		3
	15	The relevance of productivity changes to the study question is discussed	4	4		12
	16	Quantities of resources are reported separately from their unit costs	11	8	1	
	17	Methods for the estimation of quantities and unit costs are described	16		4	
	18	Currency and price data are recorded	12	5	3	
	19	Details of currency of price adjustment for inflation or currency conversion are given	5	14	1	
	20	Details of any model used are given	13	1	6	
	21	The choice of model used and the key parameters on which it is based are justified	10	4	6	
Analysis And Interpretation Of Results	22	Time horizon of costs and benefits is stated	11	6	3	
	23	The discount rate is stated	10	9	1	
	24	The choices of rates are justified	2	5	2	11
	25	An explanation is given if costs/benefits are not discounted	1	7		12
	26	Details of statistical tests and confidence intervals are given for stochastic data	11	9		
	27	The approach to sensitivity analysis is given	15	5		
	28	The choice of variables for sensitivity analysis is justified	9	4	1	6
	29	The ranges over which the variables are varied are stated	9	5	1	5
	30	Relevant alternatives are compared	20			
	31	Incremental analysis is reported	12	7	1	
	32	Major outcomes are presented in a disaggregated as well as aggregated form	11	9		
	33	The answer to the study question is given	20			
	34	Conclusions follow from the data reported	20			
	35	Conclusions are accompanied by the appropriate caveats	12	5	3	

Findings by a Colombian study[29] demonstrated that vaccination reduced costs associated to influenza from US$ 74.2 million to US$ 35.7 million, being cost-saving. On the contrary, Michaelidis et al.[27] reported a moderate cost-effectiveness profile for vaccination if compared with results explained above.

In the two studies focused on children, vaccination was shown to be cost-saving from the societal perspective in the Argentinian CEA[40] and less costly than other preventive measures, with a cost-benefit ratio of 6.4 among high risk children in the study by Hall et al.[33]

Influenza vaccination among high risk groups was cost-effective in all studies considered, but Hak et al.[41] with respect to patients younger than 65. In particular, as far as adult cancer patients are concerned, the vaccination was either cost-effective, with an ICER of US$ 224.00 per QALY[1] gained, or cost-saving, averting costs by US$ 2,107 and US$ 6,338 from the health care and societal perspective respectively.[3]

Type of sensitivity analysis. In this review, all but five economic evaluations[30,32,39,41,42] performed a sensitivity analysis: six[2,26-28,35,37] performed a probabilistic sensitivity analysis and

Table 2. Studies characteristics and results

Reference	Type of analysis	Alternatives	Country	Perspective	Patients	Time horizon	Effectiveness measure	Cost measure (Currency year)	Type of sensitivity analysis	Results
Jit M et al., Vaccine 2011[26]	CEA	**Influenza vaccination vs no vaccination**	England and Wales	Payer (NHS)	Pregnant women (aged 15–44 y)	2 y post vaccination	QALY	Direct medical costs(£ 2008)	Probabilistic sensitivity analysis	**ICER:** £ 23,000 per QALY if it is assumed that infants are partially protected through their mothers. **ICER:** £ 28,000 per QALY gained if infants are not protected. **If some vaccine protection lasts for a second season ICER:** £ 15,000 per QALY gained
Michaelidis CI et al., Vaccine 2011[27]	CEA	**Influenza vaccination vs no vaccination**	US	Society and Third Party Payer	African-American and Hispanic population over age 65	Lifetime	QALY	Direct medical and non-medical costs (US$ 2009)	Probabilistic sensitivity analysis	**ICER: US$ 48,617 per QALY saved from societal perspective and US$ 49,240 from Third Party Payer**
Beigi RH et al., Clin Infect Dis 2009[28]	CEA	**Influenza vaccination vs no vaccination**	US	Society and Third Party Payer	Pregnant women	Influenza season 2009	QALY	Direct medical and non-medical costs and indirect costs (US$ 2009)	Probabilistic sensitivity analysis	**Maternal influenza vaccination is a cost-effective approach** when influenza prevalence ≥ 7.5% and influenza-attributable mortality ≥ 1.05% (consistent with epidemic strains). **At a higher prevalence of influenza (30%)** the **single-dose** strategy is **cost-saving** while the **two-dose strategy** remains **highly cost-effective** (ICER US$ 6,787.77 per QALY)
Lin HH et al., Clin Microbiol Infect 2009[3]	CEA	**Influenza vaccination vs no vaccination**	Taiwan	Health Care and Society	Adult cancer patients aged 20–64 y	1 y	Hospitalizations and deaths averted	Direct medical and non medical costs, indirect costs (US$ 2007)	One-way sensitivity analysis	**Influenza immunization** is **cost-saving: savings of US$ 2,107** and **US$ 6,338 per case averted**, from health-care and societal perspectives, respectively
Porras-Ramirez A et al., Rev salud pùblica 2009[29]	CEA	**Influenza vaccination vs no vaccination**	Colombia	Third Party Payer	Children less than 2 y of age and elderly older than 65	1 y	QALY, deaths, hospitalizations and ambulatory visits averted	Direct medical costs (US$ 2007)	One-way sensitivity analysis	**Elderly (> 65 y) Influenza vaccination is cost saving,** reducing costs related to influenza from **74.2 million** to **35.7 of US$ avoiding 59% of costs of illness**

Table 2. Studies characteristics and results (continued)

Reference	Type of analysis	Alternatives	Country	Perspective	Patients	Time horizon	Effectiveness measure	Cost measure (Currency year)	Type of sensitivity analysis	Results
Schooling CM et al., Hong Kong Med J 2009[2]	CEA	"**No intervention**" scenario compared with: **(1) Comprehensive vaccination program** (2)**Opportunistic vaccination program**	China	Society, Personal or Individual, Government or publicly funded health care	People aged 65 y and above	1 y	N.A.	Direct medical and non-medical costs	Probabilistic sensitivity analysis	**Vaccination is cost-saving from the** societal point of view only. **Vaccination** could be **cost-saving** from governmental perspective if the cost of vaccinating each person was HK$ 39.6 or less
Chicaíza-Becerra RA ett al., Rev. salud pública 2008[30]	CEA	**Influenza vaccination vs no vaccination**	Colombia	Payer	Health workers in close contact with oncological patients	N.A.	Day of hospitalization saved	Direct medical costs	N.A.	Cost savings for vaccination of US$ 1,324 per day of stay saved
Avritscher ett al., Cancer 2007[1]	CEA	**Influenza vaccination vs no vaccination**	US	Society	Working age cancer patient 20–64 y	1 y	QALY	Direct medical costs and indirect costs (US$ 2005)	One way and two way sensitivity analysis	**The ICER of vaccination is** US$ 224.00 per QALY gained
Maciosek MV et al., Am J Prev Med 2006[31]	CEA	**Influenza vaccination vs no vaccination**	US	Society	Birth cohort of 4 million (Age $<$ 50; Age 50–64; Age $\geq$ 65)	Lifetime	QALY	Direct medical and non medical costs (US$ 2000)	One-way sensitivity and multi-way sensitivity analysis	**$\geq$ 65 age group** ICER US$ 980 per QALY saved (US$ 17 per person vaccinated without non-medical direct costs)
Wang ST et al., Vaccine 2005[32]	CEA	**Influenza vaccination vs no vaccination**	Taiwan	Society	Elderly people aged 65 y and above	1 y	Death averted and LYG	Direct medical and non-medical costs and indirect costs (US$ 2001)	N.A.	ICER: US$ 3,899 per death averted and US$ 309 per LYG
Hall JL et al., J Pediatr 2005[33]	CBA	**Influenza vaccination vs no vaccination**	US	N.A.	Children aged 6 to 23 mo with and without risk factors for influenza	Influenza season 2002	Hospitalizations avoided	Direct medical costs	Sensitivity analysis performed but not specified in details	**Benefit-Cost ratio: 6.4** for high risk children

Table 2. Studies characteristics and results (continued)

Reference	Type of analysis	Alternatives	Country	Perspective	Patients	Time horizon	Effectiveness measure	Cost measure (Currency year)	Type of sensitivity analysis	Results
Allsup et al., Vaccine 2004[34]	CEA	**Influenza vaccination vs placebo**	UK	Payer (NHS) and Society	People aged 65–74 y in 2001 based on 1998 projections	influenza season 1999–2000	GP consultations, hospital admissions and deaths avoided, LYG and QALY	Direct medical costs and non-medical costs	One-way sensitivity analysis	**Incremental NHS cost per GP consultation avoided:** £ 2,000 (approximately). **Incremental NHS cost per hospital admission avoided**: £ 61,000 (approximately). **Incremental NHS cost per death averted:** £ 1,900,000 (approximately). **Incremental NHS cost per LYG:** £ 244,000 (approximately). **Incremental NHS cost per QALY gained:** £ 304,000 (approximately).
Turner et al., HTA 2003[35]	CEA	Prophylaxis models comparing **eight strategies**: (1) no prophylaxis, (2) vaccination, (3) amantadine, (4) oseltamivir, (5) zanamivir, (6) vaccination + amantadine, (7) vaccination + oseltamivir, (8) vaccination + zanamivir	UK	Payer (NHS)	Healthy adults, high-risk adults, children and residential care elderly (> 65 y)	21 d	QALY	Direct medical costs and indirect costs (for sensitivity analysis) (£2001)	Probabilistic sensitivity analysis	**High-risk adults** Vaccination generates the low mean ICER (£ 2333 per QALY gained) compared with no intervention and dominates all other independent strategies. **Residential care elderly** In this patient group, vaccination is a cost-saving strategy and dominates the three alternative prophylactic strategies
Gasparini et al., Vaccine 2002[36]	CBA	**Influenza vaccination vs no vaccination**	Italy	N.A.	People aged 65 y and above	6 mo	N.A.	Direct medical and non medical costs (€ 2000)	Sensitivity analysis performed but not specified in details	**CBR** is 8.2 Net saving per vaccinated person: € 110.20
Nichol KL et al., Vaccine 2002[37]	CEA	**Influenza vaccination vs no vaccination**	US	Society	Healthy people between 65 and 74 y	6 mo	Hospitalizations and number of deaths prevented	Direct medical costs and indirect costs (US$ 1996)	Probabilistic sensitivity analysis	**Vaccination** resulted in **net cost savings** at each of the levels of vaccination costs studied

Table 2. Studies characteristics and results (continued)

Reference	Type of analysis	Alternatives	Country	Perspective	Patients	Time horizon	Effectiveness measure	Cost measure (Currency year)	Type of sensitivity analysis	Results
Scuffham PA et al., Vaccine 2002[38]	CEA	"**No intervention**" scenario compared with: (1) **opportunistic vaccination program** (passive recruitment), (2) **comprehensive vaccination** program (active recruitment), (3) 4 weeks **chemoprophylaxis** course using **neuraminidase inhibitors (NIs)**, (4) 4 weeks **chemoprophylaxis** course using **ion-channel inhibitors (ICIs)**, (5) **early treatment with NIs**, **(6) early treatment with ICIs**	England and Wales, France, Germany	Healthcare Financer	People aged 65 y and above	6 mo	LYG, deaths and hospitalizations averted	Direct medical and non-medical costs(€ 2000)	One-way sensitivity analyses	**Opportunistic and comprehensive vaccination** is **cost effective compared with other strategies**
Wang CS et al., Vaccine 2002[39]	CBA	**Influenza vaccination vs no vaccination**	Southern Taiwan	N.A.	People aged 65 y and above	6 mo	Hospitalizations due to COPD, pneumonia and cardiovascular diseases averted	Direct medical costs	N.A.	**Influenza vaccination** produces **3 times more benefit than non-vaccination**, with a **saved cost** for pneumonia, COPD and cardiovascular diseases of about **US$ 57.71 for each vaccinated person**
Dayan GH et al., Vaccine 2001[40]	CEA	**Influenza vaccination vs no vaccination**	Argentina	Society	High risk children aged 6 mo to 15 y	1 y	Influenza episodes averted	Direct and indirect costs (US$ 1998)	One-way sensitivity analysis	**Vaccination** would lead to a **net saving of US$ 11,894,870 per vaccinated cohort** (US$ 10.04 per vaccinated child)

Table 2. Studies characteristics and results (continued)

Reference	Type of analysis	Alternatives	Country	Perspective	Patients	Time horizon	Effectiveness measure	Cost measure (Currency year)	Type of sensitivity analysis	Results
Hak E et al., J Epidemiol Community Health 1998[41]	CBA	**Influenza vaccination vs no vaccination**	Netherlands	Society	Patients of all ages with chronic lung disease (excluding patients < 18)	Influenza season 1995–6	Deaths and hospitalizations averted due to respiratory tract illness and cardiac diseases	Direct medical and non medical costs	N.A.	No effectiveness of immunization was established in patients 18–64 y, after controlling for baseline prognosis. **Elderly patients** Economic benefit of £ 50 per elderly vaccinee, suggesting that in Netherlands immunization of elderly patients with chronic lung disease is **effective and cost-saving**
Nichol KL et al., NEJM 1994[42]	CEA	**Influenza vaccination vs no vaccination**	US	Institution	People aged 65 y and above	3 influenza seasons (1990–1, 1991–2, 1992–3)	Hospitalizations, hospitalization costs and mortality	Direct medical costs	N.A.	**Vaccination** was associated with a **reduction of hospitalization rate for pneumonia and influenza** and for **all acute and chronic respiratory conditions**. **Direct savings** per **year averaged US$ 117** per person vaccinated with a **cumulative savings of nearly US$ 5 million**

CEA, cost-effectiveness analysis; CBA, cost-benefit analysis; UK, United Kingdom; US, United States; NHS, National Health Service; QALY, quality adjusted life years; LYG, life years gained; GP, general practitioner; COPD, chronic obstructive pulmonary disease; CBR, cost-benefit ratio; N.A., not available.

seven[1,3,29,31,34,38,40] a one-way or a multi-way sensitivity analysis by varying only one or few parameters each time in order to assess the robustness of the base case results. In two economic evaluations[33,36] the type of sensitivity analysis was not specified.

Discussion

Our review focused on influenza vaccination in elderly and high risk groups and demonstrated that vaccination can be considered a valuable public health intervention because of its cost-effective or cost-saving potentials. The conclusion drawn by our study is consistent with past literature[44] on the topic and with current literature on different subgroups of population. In fact, influenza vaccination has been demonstrated to be cost-effective or cost-saving also in people from 50 to 64 y old and in healthy workers.[6,7,45] Postma et al.,[7] in the discussion of their paper, stated that the favorable cost-effectiveness and cost-saving potentials are appreciable taking into consideration the societal perspective. Anyway, if indirect benefits and costs are not considered, cost-saving potentials are lacking.[7] In fact, the vaccination of specific groups of population could be beneficial because of the indirect impact of vaccination on further subgroups and because of indirect costs avoided. The viewpoint of the analysis stands out as a fundamental element able to determine and influence the results of an economic analysis.[46] In particular, from a public health viewpoint, a societal perspective in evaluating intervention is worthwhile because of the specific aim of public health itself: to maintain and improve the health status of the whole population. This means that indirect costs should be always considered as well as indirect benefits in order to better define the impact of an intervention on the whole population. As far as the indirect benefits are concerned, one of the main characteristics of vaccines is to allow the protection of people who do not receive the vaccination. This phenomenon, known as herd immunity, is not often taken into consideration in economic evaluations also for the problems arising in quantifying it. Also the papers included in this review did not consider herd immunity and only in some cases commented on it in the discussion section to describe the limits of the analysis.[27,32]

Anyway, notwithstanding the pitfalls of each economic evaluation included in this review and the heterogeneity between studies, the value of influenza vaccination in elderly and high risk group is strongly supported. In fact, influenza vaccination has been demonstrated cost-effective or cost-saving in elderly in all cases but Michaelidis[27] and Allsup[34] which anyway took into account only medical and non-medical direct costs. Furthermore, vaccination showed a very good economic profile in pregnant women[26,28] and high risk groups of children[33,40] and of adult patients.[1,3,30,35] These results were demonstrated from both the societal and the health care/third part payer perspective and, as far as children are concerned, were achieved considering the need for two doses in unprimed children. On the other hand, results in adult patients under 65 y with chronic lung disease were not positive in comparison to those obtained in patients ≥65 y with the same risk factors in the study by Hak et al.;[41] anyway, the same Authors discussed the potential for an underestimation of the effectiveness of vaccination in younger individuals in their observational study. On the whole, results can be judged highly consistent among different kinds of economic evaluation, distinct perspectives and different ways to compute costs and report outcomes. Furthermore, in agreement with previous systematic reviews,[7] it appears that studies which considered not only direct medical costs yielded better results than the others.

Our work has anyway several weaknesses: first of all, it is not meant to be a comprehensive systematic review of all the literature available on the topic because only one electronic database was searched, being selection bias not excluded. This last is moreover plausible because in the selection process only papers provided with an abstract clearly dealing with high risk groups of patients or elderly have been selected. This could have led to the exclusion of papers addressing different groups of population, both healthy and at high risk, if in the abstract it was not explicitly specified. Furthermore studies were deeply heterogeneous in terms of type of analysis, perspective, assumptions and effectiveness/benefits measures, being indeed not immediately comparable each others. Anyway, at the same time, this represents also a strength of this work because, although the heterogeneity, results are consistent among studies.

Another important issue pointed out by our review is that, even though a bulk of papers on the economic value of influenza vaccination is available, a standardization of methods should be pursued in order to make assessments more comparable. First of all, according to international guidelines "the QALY is considered to be the most appropriate generic measure of health benefit that reflects both mortality and health related quality of life effects":[47] indeed, the cost-utility analysis should be considered the best way to appreciate the economic value of health intervention also in the view of allowing comparability across countries. Furthermore, the analysis should be performed from both the health service/third payer and societal perspective in order to take into consideration indirect benefits and costs. Finally, even if the quality of studies was generally good, there are some issues which need to be implemented, such as the justification of choices and assumptions as well as the quality and comprehensiveness of reporting. The thorough reporting of sources of data and results could strengthen the comparison across countries and the transferability of results. A specific concern arises for the sensitivity analysis: in fact, the ISPOR Guidelines[47] suggests that sensitivity analyses should be as extensive as possible in order to assess the uncertainty of model input parameters and results. Even if sensitivity analysis has been implemented throughout the years, as suggested also by the lack of this kind of evaluation in early papers, the probabilistic approach should be anyway implemented in order to check the robustness of results. Alongside to the standardization of methods, future research should be focused on the evaluation of economic impact of wider risk-based immunization strategies involving several groups of the population at the same point in time as well as to the assessment of combined age-based and risk-based immunization campaigns. Furthermore, it would be worthwhile to look at all the implications of vaccination campaigns from the organizational point of view and with respect to the budget impact: in fact, being the cost-effectiveness of vaccination

demonstrated, the strategies to achieve a good coverage and to monitor side effects could be meaningful for decision-makers as well as the cost of different vaccines which are available and its impact on national budget.

In conclusion, two considerations can be drawn from our review. First of all, since the reliability and consistency of our results, it is possible to conclude that influenza vaccination in elderly and high risk group is a worthwhile Public Health intervention which has to be continuously implemented in order to achieve good vaccination coverage. Furthermore, albeit the amount of available publications, some efforts should be made in order to improve the comparability of results through the standardization of methods and the development in quality of analyses.

Methods

Study selection. A bibliographic search was performed on PubMed in order to find out articles on the economic evaluation of influenza vaccination from January 1st 1990 until May 30th 2011. The search was restricted by language (Italian, English, French and Spanish) and to Humans and the algorithm was as follows: ("Influenza, Human"[Mesh] OR Flu OR Influenza) AND ("Influenza Vaccines"[Mesh] OR vaccine OR vaccination) AND ("Cost-Benefit Analysis"[Mesh] OR "Cost Savings"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR cost OR cost-effectiveness OR cost-efficacy OR cost-benefit). The search was limited to articles provided with an abstract.

Potential eligible studies were identified in agreement with the following inclusion criteria:

- Target group represented by elderly or high risk patients independently by age (study population);
- Assessment of influenza vaccine alone, without co-somministration (intervention);
- Comparison with no intervention (comparison);
- Complete economic evaluation (cost-effectiveness, cost-benefit and cost-utility analyses) assessing both benefits and costs of influenza vaccination (outcome and study design).

Economic evaluations on pandemic influenza vaccination were not included in the review as well as analyses published on national reports but not on peer-review journals.

In order to identify other potential studies of interest, the electronic search was supplemented by manual examination of the reference lists of found articles.

The identification of eligible articles was performed by two researchers independently (CdW and SC) on the basis of titles and abstracts of articles yielded by the search; the full text of all the potential papers was retrieved and read in order to identify the final works to be considered in the review.

Quality appraisal. Quality appraisal of included studies was performed through the application of the British Medical Journal (BMJ) Drummond's checklist[43] by two independent researchers (CC and MAV). Discrepancies between the two investigators were solved by oral discussion and consensus with a senior investigator (SC). The BMJ Drummond's checklist is composed of 35 items grouped into 3 sections: study design (7 items), data collection (14 items) and analysis and interpretation of results (14 items). Each item could be completely satisfied (yes) or not (no) or not clearly reported (not clear) or not applicable (not appropriate).

Synthesis of results. The following data were extracted independently by two researchers (CC and MAV) and summarized in a Table: type of economic analysis, alternatives, Country, perspective, target population, time horizon, effectiveness and cost measures—including costing year and currency of the studies if available—type of sensitivity analysis and results. Disagreements between the two researchers were solved with the involvement of a third assessor (CdW) and a senior investigator (SC).

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