Research Article

Health Economic Evaluation For Seasonal Influenza Vaccination Among Elderly People: A Literature Review

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ABSTRACT

Vaccination is considered to be the most effective way to prevent influenza. The health economic evaluation for seasonal influenza vaccine among elderly people has been studied for a long time in many countries yet a detailed review performance has not been introduced. The objective of the study is to review health economic evaluation studies on seasonal influenza vaccines targeted at elderly people. The search strategy was performed on databases including PubMed, Science Direct, and Cochrane Library. The inclusion criteria were designed to include scholarly articles and published peer-reviewed journal from 1992 until October 2015, with English as its publication language and use of primary or secondary data. Meanwhile, reviewed or methodological articles; the studies focusing on epidemiological aspects; lack of English full text, poster format, oral communications, or conference paper were excluded. In consider of the total 43 studies included, 14 of which were conducted in Europe and 29 others originated from extra-European countries, mainly from the United States. The number of published economic evaluations has gone up considerably between 2006 and 2015. The cost-effectiveness analysis (CEA) was often used to estimate economic impacts. The mixed outcome analysis was showed in most of several studies (37.2%) such as QALY and ICER combined. Costs were commonly computed with the societal perspective in 14 publications. The performance of sensitivity analysis took 86% of the publications. Under certain circumstances, such as in severe pandemics, influenza vaccination among elderly people is found to be cost saving with the higher efficacy and the lower vaccination cost.

Keywords: Elderly, economic evaluation, influenza, review, vaccination.

INTRODUCTION

Influenza is an extremely communicable acute viral disease, which is self-limiting in most cases yet still capable of causing lethal complication or even death [1]. According to the United State Center of Disease Control and the European Influenza Surveillance Scheme, "Influenza-like illness (ILI), known as acute respiratory infection (ARI) and flu-like syndromes or symptoms, is a medical diagnosis of possible influenza or other illness causing a group of conventional symptoms such as fever, dry cough, chills, shivering, malaise, appetite loss, body aches and nausea, usually relating to a rapid commencement of disease. The common cold and Influenza, which is more fatal than normal cold despite its unpopularity are assumed to be the regular causes of ILI [2,3]. Meanwhile, human is susceptible to significant clinical illness rooted from the two major kinds of Influenza virus: influenza A and influenza B. Both of which are capable of partitioning off diverse subtypes [1].

For example, the strains of Influenza A virus undergo categorization by hemagglutinin (H) and neuraminidase (N) antigen, which displays annual minor alterations (antigenic drift) and occasional greater changes to another strain (antigenic shift, resulting in pandemics) with pandemics as the possible outcome. Meanwhile, the similar range of disease as that of Influenza A also appears in the case of Influenza B [4], and severe illness can occur with either influenza A or influenza B[5,6,7]. An estimation made by World Health Organization (WHO) states that the impact of influenza ranges from 5 to 20% [8] and an average number from 3 to 5 million cases of severe influenza illness yearly,, which results in 250,000 to 500,000 deaths in the industrialized countries [7]. The groups with high vulnerability to influenza complication are mostly made of seniors (50 years old and over) and patients diagnosed with cardiovascular, pulmonary disorders, and metabolic disease (e.g., diabetes) [9]. Besides its hazard to public health, Influenza is also known for its yearly significant economic influence, in which healthcare resource utilization by the seniors and groups with high vulnerability to influenza complication is involved [10,11]. In the United States (US), the total economic costs influenza amounted to 29 billion USD annually (adjusted to US dollars in 2010) including the direct medical costs (10.2 billion USD) and the indirect costs (18.8 billion USD in loss of productivity) among the entire US population[12]. Specifically, the medical cost of the seniors have put up a yearly financial burden of 5.5 billion USD (adjusted to US dollars in 2010)[13].

So far, vaccination is considered to be the best way to prevent influenza with the highest sufficiency being vaccination. Due to the major deplete of influenza resulted from the broad use of said vaccine. Furthermore, besides its safety and efficacy, Influenza vaccination is also known for its ability of enhancing social productivity,

reducing suffering and excessive rate of mortality during annual influenza epidemics [14]. Gross et al. have estimated by meta-analysis that the vaccination of the elderly can, on average, prevent 56% of respiratory diseases, 53% of pneumonias, 50% of the hospitalizations and 68% deaths [15]. In the US, as in most European countries, vaccination is encouraged among the elderly and individuals at risk. Nevertheless, in spite of the vaccine' benefits, the current national percentage of yearly influenza vaccination among the seniors is around 60 – 65%, which did not satisfy the goal of 90% set by the Health People in 2010 [16,17]. Considering the elderly, there were statistics of 67.7% Caucasians, 56.1% African-Americans and 66.8% Hispanics reporting to had received influenza vaccination in 2010 [16,17].

Regarding all the issues mentioned above, the health economic evaluation for seasonal influenza vaccine among elderly people has been studied for a long time in many countries on the world without providing a detailed review performance. Hence, a systematic review of health economic evaluation studies on seasonal influenza vaccines targeted at elderly people (50 years old and over) was conducted. Therefore, our aim was to conduct a systematic review of health economic evaluation studies on seasonal influenza vaccines targeted at elderly people (aged from 50 years old and older). In particular, in our review, not only the methodological features, and even their limitations, but also the economic assessment caused by selected published studies. This review would be explored a better contribution for policymakers to allocate vaccine safely and effectively.

MATERIALS AND METHODS

Study design

A systematic review of economic evaluation, which related articles of seasonal influenza and published from 1992 until October 2015, was executed with subjects being elderly people.

Search strategy

The search strategy, was performed on electronic databases including PubMed, Science Direct, and Cochrane Library. Specifically, in these databases, different search strategies were conducted by combining and using the following keywords: ('health economic evaluation', 'economic evaluation', 'cost effectiveness', 'cost benefit', 'cost utility'), ('flu pandemic*', 'influenza*', 'influenza in human', 'human influenza').

Inclusion criteria

An article which was considered to be eligible had to satisfy the following criteria: It had to relate to pharmacoeconomic and/or health economic evaluation of influenza vaccination; the targeted group includes the elderly whose ages are 50 years and older; all included studies should have been published in a peer-reviewed journal with English as its publication language and from 1992 to until October 2015. The publications would be selected if they used primary or secondary data.

Exclusion criteria

Studies would be rejected if they were editorial, reviewed or methodological articles. Whenever available, they could be put into use as either a guide or reference for our systematic review. Due to the fact that some articles only concentrated on epidemiological and clinical facets and disregarded both costs and outcomes of interventions, or if they were non-economic evaluation analysis, were not in health sector, and were not human studies, they were excluded. Furthermore, in cases of lack of English full text, poster format, oral communications, or conference paper, studies were not accepted in this review.

Study selection

Searching process was continued until no new articles were found. Duplicate records were removed, then titles, abstracts, and full-text were read and screened by two researchers independently. As a matter of fact, the identification of included articles as well as other works was under the control of corresponding author.

The structure of data extraction characteristic was composed of 20 main categories (1) namely authors, (2) the major type of correspondent or first authors, (3) country, (4) year of publication, (5) publication language, (6) intervention, (7) type of intervention, (8) currency of reported results, (9) methodology of health economic evaluation, (10) type of study design, (11) type of perspective, (12) target population, (13) time horizon, (14) type of data used, (15) type of cost included, (16) type of outcome, (17) discount rate, (18) type of sensitive analysis, (19) software, and (20) primary funding resource.

Based on the inclusion and exclusion criteria mentioned above, **43** articles were selected after screening steps described in Figure 1.

Preliminarily, the search strategy identified 1,383 original studies, of which the titles and abstracts were perused. Follow this first investigation, 1,263 papers were excluded due to their lack of qualification to the inclusion criteria. Later on, a check for duplicates was executed, which resulted in 60 studies got excluded for being mentioned in more than one database. Other exclusion criteria were: unavailability of the full text (3 studies), no provision in English (14 studies). Finally, only 43 studies were qualified to be included in this systematic review.

Table 1 illustrates the amount of publication from 1992 to 2015. The number of published economic evaluations has gone up considerably between 2006 and 2015. With the total of 43 publications, of which the largest number of article (n=15) was published in the period of 2001 – 2005. As shown in this table, the number of papers increased between 1992 and 2005, then decreased in the 2005 –

2010 period and later on surged back during the 2011 – 2015 with 11 papers.

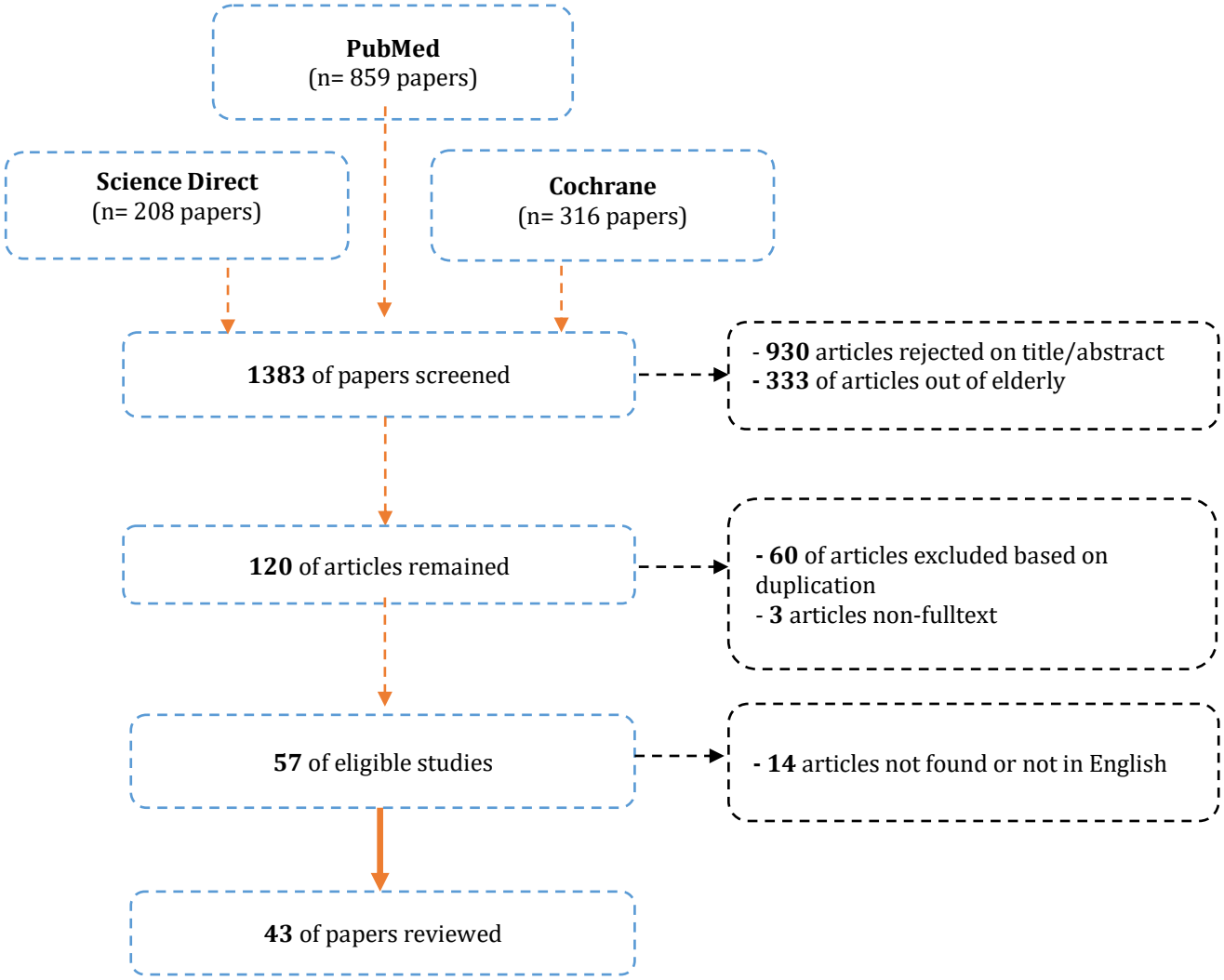

Figure 1: Flow chart of the systematic review results

RESULTS

Table 1: Summary of the main characteristics of economic evaluation studies

Study design	Features	n	%	Study design	Features	n	%
Year of publication	1992-1995	3	7.0	Country	United States	17	39.5
	1996-2000	5	11.6		United Kingdom	4	9.3
	2001-2005	15	34.9		Italy	3	7.0
	2006-2010	9	20.9		Multi-countries	4	9.3
	2011-2015	11	25.6		Other countries	15	34.9
	Total	**43**	**100**		**Total**	**43**	**100**
Type of outcome	QALY	5	11.6	Type of economic evaluation			
	ICER	6	14.0		CEA	37	86.0
	Monetary	12	27.9		CBA	1	2.3
	Mixed (two or three of them)	16	37.2		CUA	1	2.3
					Mixed (CEA + Others)	4	9.4
	Others	4	9.3		**Total**	**43**	**100**
	Total	**43**	**100**				
Type of study design	Modeling	13	30.2	Type of intervention	Prevention interventions	43	100
	Modeling and	21	48.8		Diagnostic procedures	-	-

	Cohort study						
	Randomized clinical trial	5	11.6		Curative procedures	-	-
	Retrospective data analysis	4	9.4		Services deliveries	-	-
	Total	**43**	**100**		**Total**	**43**	**100**
Type of perspective	Healthcare system	10	23.3	**Type of cost included**	Direct medical costs	16	37.2
	Societal	14	32.6		Mix (Direct medical + Direct non-medical costs)	3	7.0
	Payer	3	7.0		Mix (Direct medical + Indirect costs)	7	16.3
	Provider	3	7.0		Mix (3 of them)	4	9.3
	Mixed	8	18.6		Not specific	13	30.2
	N/a	5	11.6		**Total**	**43**	**100**
	Total	**43**	**100**				
Time horizon	<= 1 year	16	37.2	**Type of sensitive analysis**	One-way analysis	4	9.3
	1-5 years	12	27.9		Multi-way analysis	5	11.6
	>5-10 years	11	25.6		Univariate/ multivariate regression	5	11.6
	Over 10 years	1	2.3		Probabilistic analysis	5	11.6
	Not specific	3	7.0		Mixed	18	41.9
	Total	**43**	**100**		Not performed	6	14.0
					Total	**43**	**100**
Type of data used	Primary data	2	4.7	**Discount rate**	Applied to costs	22	51.2
	Secondary data	3	7.0		Not applied	14	32.6
	Mixed	38	88.3		Not mentioned	7	16.3
	Total	**43**	**100**		**Total**	**43**	**100**

QALYs: quality adjusted life-years; ICERs: incremental cost effectiveness ratios; CBA: cost-benefit analysis; CUA: cost-utility analysis; CEA: cost-effectiveness analysis

Table 1 also shows the connection of the total quantity of studies and their countries of original publications. The United States is the country has the greatest number of economic evaluation studies in the entire time horizon of this review (17 studies with 39.5%), followed by some European countries such as Italy, United Kingdom (3 studies with 7% and 4 studies with 9.3%, respectively).

The cost-effectiveness analysis (CEA) was brought into use more regularly during the time horizon of this review, (86% of the 37 articles), followed by the combination of CEA and others (9.4% of the 4 articles), and finally the cost-benefit analysis (CBA) and the cost-utility analysis (CUA) with 2.3% of each. The monetary was used independently in 12 studies (27.9%) and 5 studies (11.6%) only showed QALY (quality adjusted life-years) as a result analysis. The incremental cost effectiveness ratio (ICER) were conducted in total 6 studies (14%). However, the mixed outcome analysis was showed frequently in several studies (16 studies with 37.2%) such as QALY and ICER combined, or ICER and Monetary combined, or QALY and Monetary combined, or all of them combined.

The study design for this systematic review was showed in four types. Modeling and Cohort study (48.8%) is the study design with the highest percentage. The rate of modeling, randomized clinical trial, and retrospective data analysis are 30.2 percent, 11.6 percent, and 9.3 percent, respectively in the study design. All articles were mentioned in prevention intervention.

The perspective of economic evaluation was mentioned in 38 (88.4%) articles, and other articles (11.6%) were not explicit. Costs were calculated from the societal perspective in 14 (32.6%) publications, the healthcare system perspective in 10 (23.3%) publications, the payer perspective and the provider perspective in 3 (7%) publications for each, and mixed perspective in eight (18.6%) publications.

Within less than one year of time horizon, 16 (37.2%) papers were published. Meanwhile, a majority of studies had their time horizon ranging from 1 to even above 10 years (from 1 to 5 years: 27.9%, between 5 and 10 years: 25.6%, above 10 years: 2.3%). In consideration of the

studies with time horizon shorter than a year, the discount rate was applied only to costs in 22 articles (51.2%), whereas it was not applied to costs or results in 14 articles. None of discount rate in 7 articles was explicitly described.

The major source of information came from mixed (88.3%) primary data and secondary data in items relevant to the chosen resource, costs, and health outcomes. Only two studies (4.7%) used the information with primary origin, and in other three publications (7.0%) solely applied secondary information.

Both direct and indirect costs could be involved in economic analysis, such as in this review, 30 studies applied direct medical costs, which indicated illness management, from prevention to complication treatment. Furthermore, direct medical costs was enumerated in a number of about 30 studies , of which three studies took direct non-medical costs and seven others - indirect medical cost into account. In addition, the combinations of three type of cost analysis were accounted for 9.3%. It is clear that direct medical costs related to vaccine, its administration, adverse events management, hospitalizations, general practitioner consultations, drugs administrated to treat influenza related illness and intensive care. Considering of 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.

Sensitivity analysis was performed in 86% of the publications (14% for no performance). The combined sensitivity analysis was used in 18 (41.9%) papers, there were probabilistic analysis and one-way analysis/ multi-way analysis combined, and/ or addition of Univariate/ multivariate regression. However 14% of reviewed publications were not performed any sensitivity analysis.

Table 2: Articles evaluated in this review (n=43)

Of the 43 studies included, 14 (33%) were conducted in Europe (United Kingdom, France, Italy, The Netherlands, Germany)[18-30] and 29 (67%) in extra-European countries, mainly in the United States (17 of the 40% articles) [2,31-46]. In particular, most of these studies displayed the cost-effectiveness of Influenza vaccination in preventing Influenza.

According to all studies conducted in Europe, the incremental cost-effectiveness Ratio (ICER) had its range spreader from 5,000 to 33,000 euros per quality-adjusted life-year (QALY) [18-30].

On the other hand, James Piercy et al. [23] estimated the cost per death avoided is 123,985 euros and the cost per life year gained (LYG) is 14,821 euros. According to Gasparini et al. [27], influenza vaccination had the feature of cost-benefit (cost-benefit ratio of 8.22) and produced a net saving of 110.20 euros per vaccinated person.

Finding by the studies carried out in the America revealed the range from 20 to 100,000 dollars per QUALY saved between the cost-effectiveness of the vaccination program comparing to no vaccination program[2, 18, 32-35]. Some American economic evaluation studies with societal perspective revealed the fact that net cost savings resulted from influenza vaccination [37,38,43-45]. Such as the study performed in 2004, in which Kristin Nichol et al. [38] concluded that 71 dollars in net cost savings, was the value for each senior receiving vaccination and prevented 9 deaths per 1000 persons vaccinated. This was the equivalent value of 810 dollars per life-year gained in net cost savings. Moreover, Dana B. Mukamel et al. [41] mentioned incremental cost-utility ratios (ICUR) as a study outcome; estimates of ICUR spread within a range from 4,215 dollars to 12,617 dollars per QALY, regarding the underlying suppositions focusing the model.

A common tendency shared among three Asian countries (Hong Kong, Japan and Taiwan) along with Australia and New Zealand showed estimates about health economic for influenza vaccine, in which the cost-effectiveness of the vaccination program was performed through ICER per QALY, LYG; benefit cost ratios; cost savings per vaccination or per person vaccinated [3,47-55]. Nevertheless, only the study of Vital Mogasale et al. [48] in Australia had shown the incremental cost-effectiveness ratio of costs per disability adjusted life years (DALY).

About 65.1% of the studies investigated did not identify the funding source. Meanwhile, studies explicitly mentioning the funding source, which was sponsored by either the government in 30.2% of cases, by private non – profit organization in 7% of cases, by healthcare industry in 23.3% of cases, or by mixed in 7% of cases.

DISCUSSIONS

Influenza is known as seasonal and pandemic happening, both of which are associated with severe health and economic consequences. Seasonal influenza is a major reason that leads to morbidity and mortality worldwide, as well as significant health and health economics issues. So the number of publications reporting economic evaluation studies has increased remarkably in recent years. Epidemics of influenza occurred annually during the late twentieth Century [56], which clearly causes excessive rate of mortality, morbidity and hospitalization in many countries. This explains the reason why the current years have witnessed a rise in the number of economic evaluation studies about influenza vaccine among elderly people.

It is clear that the CEA, CBA and CUA studies tower above the economic evaluation analysis. The evaluations with high value of cost-effectiveness are likely to indicate that it is the best choice of different analysis type to reflect the forthright impacts of vaccination (case prevented or LYG). Meanwhile, vaccination has already been seen as a complicated healthcare technology due to numerous elements and uncertain sources to consider, for example,

efficacy/ effectiveness of the vaccine, vaccine serotypes, number of doses, vaccine adherence, vaccine coverage, immunological protection duration, herd immunity , ability to generate immunity and infection epidemiology.

In general a great number of facets rely completely on specific biology issues, and hence, they are uncontrollable. As a consequence, it is considerably complex to include the life quality, and only 2.3% of the studies mentions of cost utility. Moreover, the small value in the number of CUA is related to a variety of countries, for example, United States [41].

The importance of influenza vaccination programs among the senior population has been recognized with a large number of clinical and field studies. In this review the influenza vaccination for senior people is discovered to be cost saving in general. Data shows its effectiveness through the cost per year of life gained and saved (ICER). Overall results of the studies in Hong Kong and Australia unveiled that the influenza vaccination program for senior people is only cost effective in case of severe pandemics, during which the vaccine efficacy is high, and the vaccine cost is low [47,50]. Consequently, the outcome of most of studies was very sensitive to the overall vaccine effectiveness and vaccine cost.

In total 79% of the studies, economic evaluation is performed with a model, consists of Modeling and cohort study with the most popular (48.8%), and Modeling model applied in 30.2% of the cases, due to their good quality, which are highly demanded with requirements of excessively dynamic perspective.

In consideration of economic evaluation methods, the general quality is considered to be comparatively high possibly due to it being the result of studies executed in sites with well-founded health economics. A majority of these settings has the national methodological guidelines for conducting economic evaluations. Thus, its ability to affect researchers' option of methods applied. In order to enhance the correlation of further evaluation, internationally accepted methodological guidelines is to be presented. However, despite an overtly available guide for standardization of economic evaluations of immunization program from WHO, it is only appropriate with vaccination, while antiviral drugs and non-pharmaceutical interventions are excluded.

It is possible to expand the length of the time horizon to over than one year, though with longer study time the immunity needs to be confirmed of its availability of conference via a particular vaccine, reaching in some cases life expectancy.

Only seven studies (16.3%) were found with the inclusion of the direct medical costs and indirect costs combined, which were also validated with the fact that a majority of the elderly is no longer doing paid jobs. It is debatable that hospitalization, time investment receiving the vaccination and other periods for healthcare contacts should be mentioned in pharmacoeconomic evaluation, even for the elderly, who are likely to work numerous types of unsalaried jobs, for example, housekeeping or grandchild sitting, deserving monetary valuation such as using the replacement cost approach. In several countries, it is common for direct medical costs, direct non-medical costs and even indirect costs to be mentioned and considered due to their recognized significance and author- recommended application in economic evaluation studies.

Sensitivity analysis is a positive element which is extremely represented (86%), yet relies on evaluated work, and a probabilistic analysis is required to be conducted. In this issue, the ideal optimum has yet to be achieved as every international guidelines directs the feature of being a marker of precise economic evaluation. On a global scale, immunity persistence, vaccine cost, vaccine efficacy, vaccine coverage, and the side effects are the most trending and sensitive variables. Similarly, any studies should indicate their source of funding in order to avoid unnecessary conflicts of interest.

CONCLUSION

In consideration of the accessible pharmacoeconomic evidence from several particular Western countries and the United States, It appears that influenza vaccination for seniors play the role of an interference with favorable cost effectiveness and cost saving potentials. Particularly, influenza vaccination for elderly people is considered to be economical in general. Moreover, the studies reviewed suggest that under certain conditions, such as in severe pandemics, vaccinating against seasonal influenza among elderly people is not generally only cost saving, but also cost-effectively attractive with the higher vaccine efficacy and the lower cost of vaccination. This is one of some limitations of this review.

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Table 2: Articles evaluated in this review (n=43)

S.No.	Study (year)	Country	Objectives	Outcomes	Results	Disclosed funding resource
1	G. Meier et al.[18] (2015)	UK	To update a former assessment about the cost-effectiveness of quadrivalent influenza vaccination (QIV) comparing to trivalent influenza vaccination (TIV)	QALYICER	The estimated ICER was £14,645 per QALY. A comparison about cost-effectiveness between QIV and TIV in 68% of simulations with a willingness-to-pay threshold of <£20,000/QALY and 87% with a willingness-to-pay threshold of <£30,000/QALY.	X
2	Minchul Kim et al.[2] (2015)	US	To examine the impact of the public health, of budget , and cost-utility of HD versus IIV3 and IIV4 for immunization of US seniors 65 years of age and older.	ICER	The estimated ICER was $23.54 (95% confidence interval $14.21–$39.37) per additionally vaccinated Medicare elderly in a probabilistic analysis	
3	Ayman Chit et al.[31] (2015)	US	To examine the public health impact, budget impact, and cost-utility of HD versus IIV3 and IIV4 for immunization of US seniors 65 years of age and older.	QALYICER	The Incremental Cost Effectiveness Ratio (ICER) for this comparison is $5299/QALY. 71% of the probabilistic sensitivity analysis (PSA) simulations were <$100,000/QALY.	
4	Joyce HS You et al.[3] (2014)	Hong Kong	To estimate the difference in costs and QALYs gained by Quadrivalent influenza vaccine, when compared to Trivalent influenza vaccine, in elderly population over the period of 2001–2010.	QALYICER Monetary	Highest cost savings and QALYs gained by QIV occurred in 2007 with 92.9% for age groups 65–79 years (USD266,473 and 22.8 QALYs) and ≥80 years (USD483,461 and 27.3 QALYs.	
5	Anthony T Newall et al.[47] (2014)	Australia	To assess the cost effectiveness of the current Australian influenza vaccination program for the elderly (65 years and over)	QALYICER	The base-case results of the analysis discovered the likeliness to be cost-effective (under A$50,000 per quality-adjusted life year gained) of the existing elderly vaccination program in case of percentage of vaccine efficacy above 30%	X
6	Constantins I Michaelidis et al.[32] (2014)	US	To evaluate the cost-effectiveness of four hypothetical vaccination programs designed to eliminate disparities in elderly vaccination rates and differing in the number of interventions.	QALYICER	The preference of the considerably high intensity vaccination program ($24,479/QALY) was at willingness-to-pay-thresholds of $50,000 and $100,000/QALY and prevented 37,178 influenza cases, 342 influenza deaths, 1,158 invasive pneumococcal disease (IPD) cases and 174 IPD deaths over the birth cohort's lifetime	
7	Laure-Anne Van Bellinghen et al.[19] (2014)	UK	To assess the potential cost-effectiveness of quadrivalent influenza vaccine comparing to trivalent influenza vaccine in the UK.	QALYICER	The estimated base case incremental cost-effectiveness ratio (ICER) was £5,299/quality-adjusted life-year (QALY)	X
8	ChyongchiouJeng Lin et al.[33] (2013)	US	To examine the cost-effectiveness of Standing order Programs to improve both pneumococcal and influenza vaccination rates in outpatient settings for individuals 65 years and older.	QALY	SOPs cost $14,171 per QALY gained compared with no program from a third-party payer perspective.	X
9	Constantinos I. Michaelidis et	US	To assess the cost-effectiveness of a hypothetical national influenza vaccination	QALYICER	$48,617 per QALY saved was the gap between the cost-effectiveness of the vaccination program comparing to that of no vaccination program	X

	al.[34] (2011)		program made to eradicate particular discrepancies of influenza vaccination in the population of African-American and Hispanic elderly.			
10	S. Iannazzo et al.[20] (2011)	Italy	The aim of this study is the assessment of the financial budget impact of a seasonal vaccination program based on the use of the MF59 adjuvant vaccine as compared with the traditional vaccine or the absence of vaccination in Italian elderly population.	Monetary	The standard vaccination program produced a moderate direct cost increase of about 50 million Euro (+4.6%), whereas the adjuvant vaccine provided an estimated saving of about 74 million Euro (-6.8%), both compared to the non vaccination.	X
11	Vital Mogasale et al.[48] (2011)	Australia	Influenza cost-effectiveness studies use models for influenza clinical evolution based on a spectrum of assumptions, of which the significance and implication in policy decision was discovered	ICERDALY	The scenario and sensitivity analysis has shown the incremental cost-effectiveness ratio of the proposed compared to current policy varies from $112,000 to $6,000 per DALY	
12	Kenneth J. Smith et al.[35] (2010)	US	To estimate the cost-effectiveness of dual influenza and pneumococcal vaccination in 50 year-olds.	QALY	With 100% vaccine uptake, dual vaccination cost $37,700/QALY gained compared to a CDC recommendation strategy; with observed vaccine uptake, dual vaccination cost $5,300/QALY	X
13	J H S You et al.[49] (2009)	Hong Kong	To compare cost and QALYs gained by influenza vaccination with or without pneumococcal vaccination in the elderly living in long-term care facilities	QALY Monetary BCR	Both vaccination strategies had high BCRs and net present value (NPVs) (6.39 and US$334 for influenza vaccination; 5.10 and US $332 for influenza plus pneumococcal vaccination.	
14	CM Schooling et al.[50] (2009)	Hong Kong	To evaluate the cost-effectiveness of influenza vaccination in Hong Kong for people aged 65 years and over living in the community.	Monetary	Vaccination would cut medical costs in the 75 years and over age-group if the vaccination cost per person was HK$40 or less. For the 65 to 74 years age-group, public health care would not be diminished with vaccination even if the vaccination cost per person were as low as HK$15.	X
15	S.M.A.A Evers et al.[21] (2007)	10 Western European countries	To display the cost- effectiveness Of the pneumococcal vaccination's prevention towards invasive pneumococcal illness in each country	QALY CERs	The cost-effectiveness ratios ranged from €9239 to €23,657 per quality-adjusted life-year.	X
16	Shu-Ling Hoshi et al.[51] (2007)	Japan	To investigate the following two questions: (1) is the current subsidy strategy efficient? (2) is there any alternative strategy which could be efficient?	YOLS ICER	Probabilistically estimated mean incremental cost–effectiveness ratio of current strategy is US$ 15,535 per YOLS (year of life saved), which can be concluded that current program is cost–effective.	X
17	Samuel Aballea et al.[22] (2007)	Brazil, France, Germany, Italy	To assist policymakers calculate whether or not should wide application of the policy should be executed consider whether such a policy should be adopted more widely, we conducted an economic evaluation of lowering the age limit for routine influenza vaccination to 50 years in Brazil, France, Germany, and Italy.	QALY	Costs per QALY gained were R$4,100, €13,200, €31,400 and €15,700 for Brazil, France, Germany, and Italy, respectively, from a TPP perspective	

18	Mitesh S. patel et al.[36] (2006)	US	To estimate the cost-effectiveness of a 10-year federal program to promote influenza vaccine, intended to increase vaccination rates among persons ≥65 years old.	ICER	The incremental cost-effectiveness of the program was $16,300 ($11,347–$25,174) per life-year saved in 2006 and increased to $199,906 ($138,613-$307,423) per life-year saved by 2015	
19	K. L Nichol et al.[37] (2006)	US	To explore the implications of these varying approaches by comparing two health economic analysis models of influenza vaccination of community-dwelling elderly persons.	Monetary	The alternate model found costs of $3.50/person vaccinated (5th–95th percentile $−11 to 5) and net costs of $91/year of life saved (5th–95th percentile $−309 to 126)	X
20	Li Cai et al.[52] (2006)	Japan	To examine vaccination strategies' benefits in health and economy of for both influenza and pneumonia specifically for the seniors in Japan.	ICER CER	CER of influenza-only vaccination was 516,332 Japanese yen per one year of life saved, while the combined vaccinations of influenza with pneumococcal was 459,874 Japanese yen for the same benefit. ICERs of the strategies versus was 426,698 Japanese yen per one year of life saved for 100,000 people.	
21	Sen-Te Wang et al.[53] (2005)	Taiwan	To calculate the possibility of whether the expanded vaccination program for all elderly persons was cost-effective.	ICER	Vaccination against influenza for the elderly persons can lead to a 29% (95% CI: 23–35%) major decrease of all-cause deaths. 20% (95% CI: 9–30%) major decrease in hospitalization, which was perceived for average-risk group but 4% (95% CI:−4–11%) minor decrease for high-risk group.	
22	Nancy A. Risebrough et al.[57] (2005)	Canada	To compare the cost-effectiveness of oseltamivirpostexposure prophylaxis during influenza A outbreaks with that of amantadine postexposure prophylaxis or no postexposure prophylaxis in long-term care facilities.	Monetary	Oseltamivir was a dominant strategy because it was associated with the fewest influenza-like illness cases, with cost savings of $1,249 per 100 patients in 2001 Canadian dollars compared with amantadine and $3,357 per 100 patients compared with no prophylaxis.	X
23	J. Plun-Favreau et al.[58] (2004)	Argentina	To evaluate the long-term cost effectiveness of influenza immunization program, in the elderly and at-risk adult populations covered by an Argentinean Managed Care Organization (MCO)	Cost per LYG	Vaccination leads to negative incremental cost-effectiveness ratios due to lower costs and higher effectiveness in the ''Vaccination'' alternative, the ''No vaccination'' alternative being thus dominated. The mean (S.D.) value of total costs avoided is of US$ 2,252,385 (747,775) or US$ 92 per patient.	X
24	James Piercy et al.[23] (2004)	France	To estimate the economic benefits of adjuvanted vaccination compared with non adjuvanted vaccines.	Cost per LYG Cost per death avoided	The cost per death avoided is 123,985 euros and the cost per life year gained is 14,821 euros. The cost per life year gained in the best and worst cases (influenza A/H3N2 and A/H1N1, respectively) are 13,759 euros and 117,496 euros.	X
25	K.L. Nichol et al.[38] (2004)	US	To estimate a cost effectiveness and cost benefit of influenza vaccination among elderly, and a comprehensive assessment of potential direct medical care cost savings	Monetary	Vaccination would result in net saving of $71 for each elderly person vaccinated; and resulted in the prevention of 9 deaths per 1000 persons vaccinated, which translated into net savings of $810 per life-year gained.	X
26	Stephen Allsup et al.[24] (2004)	UK	To determine the cost effectiveness of influenza vaccination for healthy people aged 65–74 years living in the UK.	QALY Monetary	(1) Incremental NHS cost per GP consultation avoided = £2000; (2) incremental NHS cost per hospital admission avoided = £61,000; (3) incremental NHS cost per death avoided = £1,900,000 and (4) incremental NHS cost per QALY gained = £304,000.	X
27	E. Hak et al.[39] (2004)	US	In the absence of trial results that are applicable to the target population, nested case-control studies might be an alternative to	Monetary	978 P&I hospitalizations and 1,339 deaths were observed. The adjusted estimates of relative estimates (VE, AUC) and their corresponding 95% confidence intervals were virtually the same using both study designs,	X

			full-cohort analysis. We compared relative and absolute estimates of associations in an influenza vaccine study using both designs.		notably when the case-control ratio was high (1:4).	
28	Stephen Allsup et al.[25] (2003)	UK	To determine the cost-effectiveness of influenza vaccination in people aged 65–74 years in the absence of co-morbidity.	Monetary	Each general practitioner consultation avoided by vaccination was estimated from trial data to generate a net NHS cost of £174.	
29	Chong-Shan Wang et al.[54] (2002)	Taiwan	To evaluate its efficacy and cost effectiveness, we conducted a 2 month influenza vaccination campaign in southern Taiwan's A Lein township for all the elderly.	Monetary	Savings for each person vaccinated were at least three times the cost of vaccination.	X
30	R. Gasparini et al.[27](2002)	Italy	To evaluate the weekly incidence of the disease	CBR	The cost benefit ratio is 8.22, a net saving is 110.20 euros for each vaccinated subject.	X
31	P.A. Scuffham et al.[26] (2002)	England and Wale, France, Germany	To estimate the incremental costs and consequences of the vaccination programmes.	ICER	Vaccination strategies were the most cost-effective. Chemoprophylaxis strategies were highly expensive even under assumptions of optimal timing.	X
32	Kristin L. Nichol et al.[40] (2002)	US	To assess the health and economic benefits of routine influenza vaccination of healthy persons between 65 and 74 years of age.	Monetary	Over the six consecutive study seasons, 1990–1991 to 1995–1996, vaccination of healthy elderly person was associated with a 36% reduction in hospitalization for pneumonia or influenza (95% CI, 2–39%), an 18% reduction in hospitalization for all respiratory conditions (95% CI, −6 to 37%) and a 40% reduction in death (95% CI, 14–38%)	X
33	Marten J. Postma et al.[28] (2001)	The Netherlands	To assess the cost effectiveness (net costs per life year gained) of pneumococcal vaccination of elderly individuals aged 65 years and over in The Netherlands.	Monetary LYG	Stochastic and univariate sensitivity analysis net costs per life year gained were estimated to be between 6000 and 16000 euro. A scenario analysis on alternative age dependent vaccination strategies indicated even higher net costs per life year gained, up to EUR28 000 for vaccinating only those elderly aged 85 years and over.	
34	Dana B. mukamel et al.[41] (2001)	US	To evaluate the costs and the cost utility of immunization in nontraditional settings (community clinics set up to provide influenza and pneumococcal vaccinations) as a strategy to increase pneumococcal immunization rates.	QALY Monetary ICUR	Unlike immunizations in physician offices, immunizations in nontraditional settings are not cost saving. Estimates of incremental cost-utility ratios ranged from $4215 per QALY to $12,617 per QALY, depending on the underlying assumptions of the model.	X
35	Marcia Weaver et al.[42] (2001)	US	A cost-effectiveness analysis was conducted as part of a randomized, controlled trial of a community based outreach initiative to promote the pneumococcal and influenza vaccines for people aged 65 years or older.	QALY	The cost-effectiveness ratio of the combined outreach initiative as implemented was $35486 per QALY, whereas it was $53547 per QALY for the pneumococcal vaccine and $130908 per QALY for the influenza vaccine	X
36	A. Ament et al.[29] (2000)	5 Western European countries	To estimate the cost effectiveness of pneumococcal vaccination in preventing invasive pneumococcal disease	QALY ICER	The ICERs varied from ~11,000 to ~33,000 European currency units per QALY. For preventing pneumococcal pneumonia, vaccinating all elderly persons would be highly cost-effective to cost saving.	X
37	Kristin L. Nichol et al.[43] (1999)	US	To assess the health and economic benefits of influenza vaccination in both healthy and at-risk seniors aged 65 to 74 years.	Monetary	The economic analysis demonstrated that vaccination against influenza in the base case was associated with direct and total cost savings for both healthy and at-risk seniors aged 65 to 74 years.	X

38	Maarten J. Postma et al.[59] (1999)	The Netherlands	To determine the costs associated with influenza and the cost effectiveness (net costs per life-year gained) of influenza vaccination in The Netherlands.	CER Monetary	The costs of influenza were estimated to be 31 million euros (EUR) for the influenza season 1995/96 in The Netherlands. For the extended programme in 1997-1998, i.e. all elderly people, the cost-effectiveness ratio was estimated at EUR1820 per life-year gained.	
39	R.M.P.M Baltussen et al.[30] (1997)	The Netherlands	To examine the cost-effectiveness of various strategies of pneumococcal vaccination for the elderly in The Netherlands.	QALY ICER	Vaccinating all individuals above the age of 55 years yields a CER of - ECU 3300 per life-year saved and vaccinating all individuals above the age of 65 years a CER of - ECU 1,500 per life-year saved.	X
40	W. Guy Scott et al.[55] (1996)	New Zealand	To evaluate the costs and benefits of influenza the population aged 65 years and over, from the perspectives of individuals and health insurers, government and society	Monetary	Direct medical costs of vaccination of $NZ1.42 million [$NZ17.78 per vaccination]; direct medical costs avoided of $NZ5.35 million ($NZ67.18 per vaccination); and net benefits of $NZ3.93 million ($NZ49.40 per vaccination).	
41	K.L Nichol et al.[44] (1994)	US	To assess the efficacy and cost effectiveness of influenza vaccine administered to older persons living in the community.	Monetary	Direct savings per year averaged $117 per person vaccinated (range, $21 to $235), with cumulative savings of nearly $5 million.	X
42	John P. Mullooly et al.[45] (1994)	US	To estimate the cost-effectiveness and net medical care costs of programs for annual influenza vaccinations for the elderly in a health maintenance organization	Monetary	The net savings to the HMO per vaccination was $6.11 for high-risk elderly persons and $1.10 for all elderly persons. The HMO incurred a net cost of $4.82 per vaccination for non-high-risk elderly persons.	X
43	John D. Grabenstein et al.[46] (1992)	US	To provide a full account of the marginal costs of implementing a pharmacy-based vaccine-advocacy program.	QALY Monetary	If Medicare reimbursed pharmacists for advising 100,000 patients at risk to accept influenza vaccine through vaccine-advocacy messages, for an apparent expenditure of $110,000, the increased rate of influenza vaccinations would avert 139 hospitalizations and 63 deaths, and actually yield Medicare a net savings of $280,588.	

CEA: cost-effectiveness analysis; CBA: cost-benefit analysis; CUA: cost-utility analysis; QALY: quality adjusted life years; LYG: life years gained; DALY: disability adjusted life years; ICER: incremental cost-effectiveness ratios; CBR: cost benefit ratios; ICUR: incremental cost-utility ratios; US: United States; UK: United Kingdom; HMO: Health maintenance organization.

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