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Costs and effectiveness of influenza vaccination: a systematic review

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Abstract
Background. Seasonal influenza can cause a significant public health burden. Vaccination is proposed as the most effective measure to prevent influenza and related undesired outcomes.
Objective. To estimate the efficiency of influenza vaccination.
Methods. A literature review of economic evaluations of influenza vaccinations, published over the last 5 years, was performed using MEDLINE (through PubMed), Web of Science and Scopus.
Results. 935 papers were identified and 30 were selected, including studies performed in different population subgroups: general population, children, adults, elderly, pregnant women and high risk patients. Twenty-one studies were performed in Europe and in US. The majority of the studies were carried out on elderly patients and children. All except one were cost-effectiveness analyses and reported influenza vaccination as a cost-saving or cost-effective intervention.
Conclusions. Vaccination strategies are economically favourable in a range of countries and sub-groups of patients.

Key words
- influenza
- vaccine
- cost-effectiveness
- systematic literature review
- ICER

INTRODUCTION

Seasonal influenza is an acute viral infection that circulates worldwide and spreads easily from person to person. It can affect any age group and cause annual epidemics, representing a serious public health and economic problem of society, due to increased medical resource utilisation and loss of production [1].

Vaccination is proposed as the main effective strategy for preventing influenza and related complications. Annual influenza immunization is recommended in elderly subjects, children with ≥ 6 months of age or older, pregnant women and individuals with chronic conditions [2]; however, these recommendations are different by country [3].

Current available influenza vaccines licensed for use are Trivalent Inactivated Influenza Vaccine (TIV, IIV3), Quadrivalent Inactivated Influenza Vaccine (QIV, IIV4), Trivalent Live Attenuated Influenza Vaccines (LAIV3), Quadrivalent Live Attenuated Influenza Vaccines (LAIV4). Live Attenuated Influenza Vaccines (LAIV) are administered intranasally, while Inactivated Vaccines (IIV) are administered by intramuscular injection [4].

Despite the number of countries recognizing the importance of vaccines has grown in recent years, it is not clear whether the benefits of newer vaccines justify their added costs [5].

An increasing number of health-care systems, both public and private, are adopting results from economic evaluations, as cost-effectiveness analysis (CEA), to better understand the clinical and economic impact of health technologies, including vaccines, to support decisions on allocation of healthcare resources. The aim of this review is to estimate the efficiency of influenza vaccination.

METHODS

To collect and critically review the health economics evidence on influenza vaccination, a systematic literature review was performed. Considering as a starting point the review published by Peasah and colleagues in 2013 [6], and in order to focus on the most recent practice, original studies and analyses published over the last 5 years (from January 2012 until January 2017) were included [6].

The bibliographic search was performed in PubMed, Web of Science and Scopus, using "cost effectiveness" OR "cost utility" OR "cost benefit" OR "cost consequence" AND "influenza vaccination" as keywords research terms. To maximise retrieval of all pertinent papers, we applied medical subject headings (MeSH terms), or keyword searches when appropriate.

Papers were examined by two members of the team

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(AL, SR) in a three-steps process. First, the abstract was considered; second, potentially relevant articles were reviewed in full text; third, articles that met the inclusion criteria were analysed. Disagreement between the two reviewers was resolved by consensus of a third party (PAC).

Original articles that estimated cost-effectiveness, cost-utility or cost-benefit of influenza vaccination, for the entire population or specific subgroups (e.g. children, elderly), were included. Furthermore, the other inclusion criteria used to select the articles were: articles that summarize findings in English; articles not related to pandemic influenza; original studies and analyses published between January 2012 and January 2017. After scanning all titles and abstracts, full text for all potentially relevant studies were retrieved. Papers focused only on cost, without including treatment effectiveness (e.g. cost of illness studies) were excluded. Further, studies that evaluated the cost-effectiveness of communication campaign on influenza vaccination were excluded. Data from eligible studies were extracted and a spreadsheet was used for data entry. The extracted data were aim, design, perspective, subjects' characteristics, description of comparators, data sources, results including costs, outcome, authors' conclusions and Incremental Cost-Effectiveness Ratios (ICERs), defined as the ratio between the net total costs and the net effects. The influenza vaccination strategies assessed in the included studies were classified based on their cost-effectiveness ratios (e.g. cost per influenza-related deaths averted, cost-benefit ratios, cost/influenza cases averted) and on the cost-effectiveness threshold that each study considered. Those influenza vaccination strategies reported as less costly and more effective than the comparators were classified as cost-saving.

RESULTS

The literature search found 253 references in PubMed, 462 in Scopus and 220 in Web of Knowledge; however, after removal of duplicates (n = 11 studies), all abstract were screened, and 888 studies were excluded because they did not meet the inclusion criteria. Thirty-six articles were retrieved for full review, and six of them were excluded for different reasons, as reported in *Figure 1*. Consequently, 30 papers were included in our systematic review: 29 studies were CEA and 1 study was a cost-benefit analysis (CBA) [7]. Details of the studies are presented in the Supplementary Material, Table 1 available online.

Twelve out of 30 studies were performed in Europe [8-19], 9 in USA [5, 7, 20-26], 3 in Canada [18, 27, 28], 3 in China [29-31], 1 in Turkey [32], 1 in Thailand [33], 1 in Australia [34] and 1 in Israel [35].

The payer-only perspective was adopted in 11 studies [8-10, 13, 17-19, 24, 31, 34, 35], while the societal-only perspective was adopted in 7 studies [5, 20, 22, 26, 28,

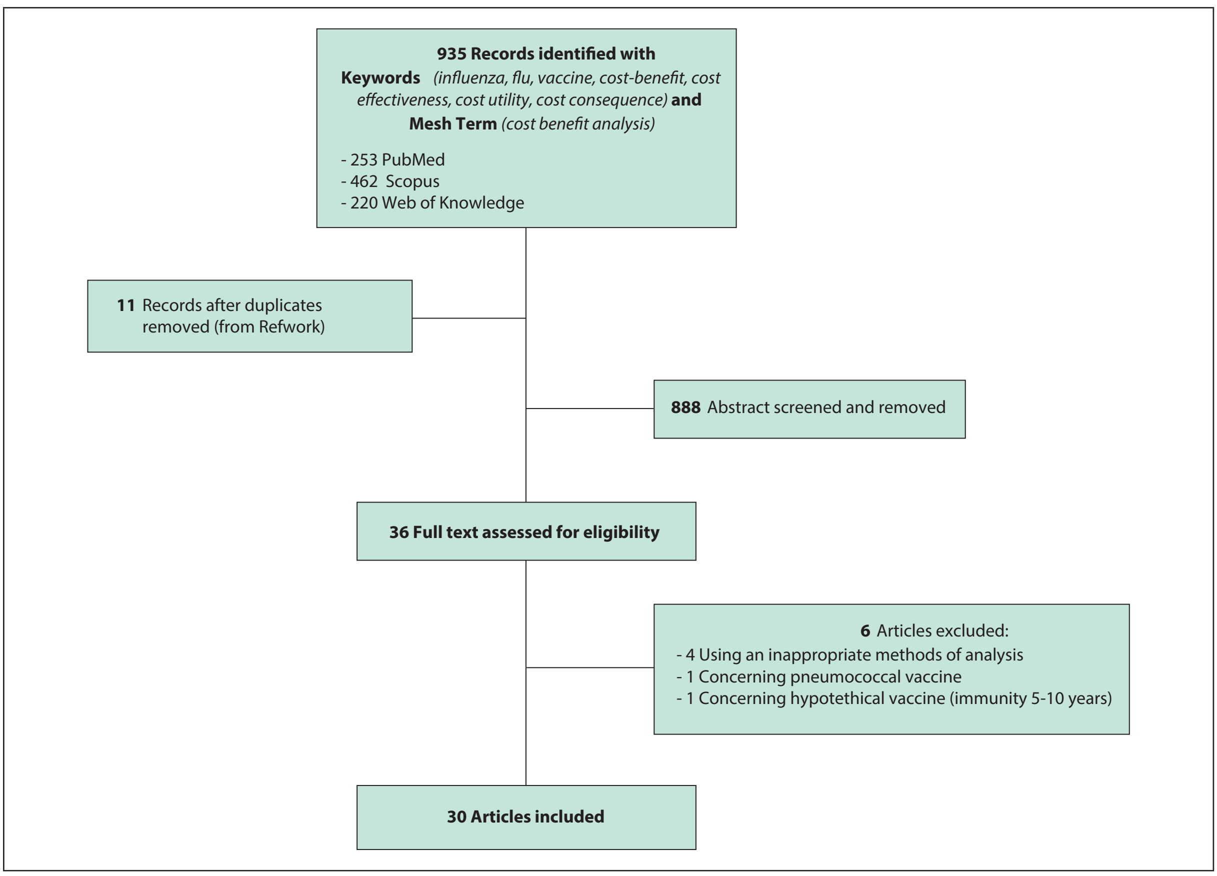

Figure 1
Flow-chart.

Table 1
Vaccination strategies compared in the selected studies by Region and patients' group

	All population	Children	Adult	Elderly	Pregnant	High-Risk
Europe (12)	No vaccination/ Increasing TIV uptake [8]	No vaccination/ Current situation/ Increasing TIV uptake/Increasing LAIV uptake [17]	No vaccination/ Increasing TIV uptake[a] [8]	TIV/QIV [9, 11]	No vaccination/ Increasing TIV uptake [8]	TIV/QIV [9, 15]
	TIV/QIV [14, 18]	No vaccination/ Vaccination program extension [19]		No vaccination/ Alternative influenza vaccination policies [10]		No vaccination/ Alternative influenza vaccination policies [10]
	No vaccination/ TIV/QIV/ LAIV4 % [16]	TIV/TIV+LAIV [12]		Current situation/New situation (vaccination coverage rate) [13]		
USA (9)	TIV/QIV [22]	LAIV/IIV [25, 26]		No Vaccination/TIV/ QIV/TIV HD [21] TIV SD/TIV HD [23] No vaccination/TIV/ QIV/TIV HD [5] No vaccination/TIV (ED) [24]	No vaccination/ Vaccination [7, 20]	
Canada (3)	TIV/QIV [18, 27][b]	Vaccination/No vaccination [28]				
China (3)	TIV /QIV [30]			ID vaccine/IM vaccine [31] TIV/QIV [29]		
Turkey (1)						Current situation/ Projected situation (vaccination coverage rate) [32]
Israel (1)						No vaccination/ Vaccination [35]
Thailand (1)		No vaccination/ LAIV/TIV [33]				
Australia (1)				No vaccination/ Vaccination [34]		
No of studies (31)	7	7	1	11	3	5

TIV: Trivalent Inactivated Influenza Vaccine, QIV: Quadrivalent Inactivated Influenza Vaccine, LAIV: Live Attenuated Influenza Vaccine, LAIV4: Quadrivalent Live Attenuated Vaccine, IIV: Inactivated Vaccine, HD: High-dose, SD: Standard-dose, IM: Intra-Muscular, ID: Intra-Dermal, ED: Emergency Department. [a]Analysis was performed on healthcare workers. [b]Thommes *et al.* performed the analysis in Canada and UK.

29, 33] and both perspectives were used in 12 studies [7, 11, 12, 14-16, 21, 23, 25, 27, 30, 32].

Damm *et al*. was the only study that performed the analysis using a narrow and a broad third-party payer perspective: the former perspective included reimbursed direct health care costs only, while the latter accounted for all reimbursed direct costs and specific transfer payments [12].

All CEA papers reported the results in terms of ICER's, presented as cost per Quality Adjusted Life Year (QALY) or LY (Life Year) gained, except 3 analyses that reported ICER expressed in cost per Disability Adjusted Life Year (DALY) [33], cost per cases of influenza averted [28] and cost per life saved [24].

Population

Within the 30 studies, 7 assessed the vaccine program in the whole population [8, 14, 16, 18, 22, 27, 30], 7 among children (0-18 years) [12, 17, 19, 25, 26, 28, 33], 11 among elderly [5, 9-11, 13, 21, 23, 24, 29, 31, 34], 3 among pregnant women [7, 8, 20], 1 among adult healthcare workers [8] and 5 among high risk populations [9, 10, 15, 32, 35] *(Table 1)*. Generally, subjects were considered at high risk if they have a higher probability to be infected by influenza virus than the general population, or if they have a higher risk of developing influenza-related complications. Within the high risk subpopulations included in the studies, we found subjects affected by chronic respiratory disease; chronic heart disease; chronic renal disease; chronic liver disease; chronic neurological conditions; diabetes mellitus; or immunosuppressed [9, 10, 15, 32, 35]. Further, Garcia *et al*. [11] assumed a different risk classification, including patients with different clinical risk in only one group and patients aged 65 or older, in a second group. The first group included the population who was at risk of serious complications from influenza due to other conditions and chronic diseases, such as chronic lung disease, metabolic disease, morbid obesity, haemoglobin disorders and anaemia, asplenia, severe neuromuscular diseases, cochlear implanted, cognitive dysfunction, people living in institutions, pregnant women and children from 6 months to 18 years, receiving long-term treatment with acetylsalicylic acid [11].

Vaccination strategies

All included studies considered vaccines already on the market (but not necessarily in the country where the analysis was performed). TIV, QIV, LAIV were included in most of them [9, 11, 12, 14-19, 22, 25, 26, 30, 33]; different vaccination strategies (consisting in extending or modifying the vaccination program) were also evaluated [8, 10, 13, 19, 32] *(Table 1)*. Influenza vaccination was compared with no vaccination in 14 of the selected studies [5, 7, 8, 10, 16, 17, 19-21, 24, 28, 33-35]; while in the other studies different vaccination doses (e.g. high-dose (HD) *vs* standard-dose (SD)) [5, 21, 23], and/or different types of vaccine (e.g. IIV *vs* LAIV) [25, 26] were compared. Finally, Leung *et al*. compared Intra-Muscular vaccine (IM) *vs* Intra-Dermal (ID) vaccine to the ones who refused the previously offered IM vaccine [31] *(Table 1)*.

Costs

Following the perspective of the analysis, 13 studies investigated only direct cost (all costs directly related to the disease, e.g. hospitalizations, visits, pharmaceutical therapy) [5, 8-10, 13, 17-19, 24, 26, 31, 34, 35], while the other 17 [7, 11, 12, 14-16, 20-23, 25, 27-30, 32, 33] included both direct and indirect costs (costs for production loss and work absences from the employees', patients' and caregivers' perspectives).

In the general population, vaccination was found to be more costly than no vaccination. The cost of influenza vaccination with TIV and QIV in the general population was found to be similar [14, 18]. However, the incremental costs obtained with TIV or QIV was influenced by the analysis perspective (see Supplementary Material, Table 2 available online).

In children, the costs for vaccinated patients were usually higher than for unvaccinated [19, 33]. For example, in Canada, costs per patient varied widely from $32.66 in patients without influenza immunization programs to $69.07, in patients with immunization [28]. Only Pitman *et al*. in England and Wales estimated that the direct costs of no vaccination program were higher than the costs of influenza vaccination program, in children aged 2-18 years [17] (see Supplementary Material, Table 2 available online).

In elderly patients, the cost associated with vaccination and no vaccination scenarios were comparable among studies [5, 13, 24]. However, the results from the model of Baguelin *et al*. [10] showed that in England and Wales the vaccination program (consisting in the extensions to the elderly and high risk patients) was four times more expensive than no vaccination in elderly and high risk group (see Supplementary Material, Table 2 available online). The majority of the costs of the vaccination program were associated with the cost of vaccine. However, the incremental cost of the vaccination program was partially counterbalanced by costs averted from additional cases of influenza and prevented hospitalizations.

The studies conducted on pregnant women suggested that influenza vaccination can be beneficial in terms of costs for society and payers [7, 20], compared with no vaccination.

Programs of vaccination against seasonal influenza for high risk subgroups were generally more costly than no vaccination, except in patients with a positive history for pneumonia, probably because they were more susceptible to become infected and to be hospitalized in the subsequent season than the general population [35]. QIV was found to be generally more costly than TIV [9, 15] *(* see Supplementary Material, Table 2 available online*)*.

Effectiveness

Vaccination programs were more effective than no-vaccination in all studies, preventing a substantial number of hospitalizations and deaths and obtaining lower total QALYs lost and LYs lost [5, 8, 10, 16, 17, 20-22, 24, 28, 33, 34].

Different types of vaccinations reported different efficacy within the populations. Several analyses have been conducted to compare LAIV *vs* TIV and various inactivated forms of vaccines. LAIV was more effective in preventing illness than IIV in children [25, 26]. Furthermore, LAIV efficacy in children was consistently found to be higher than TIV [17]. In Europe, the introduction of a universal childhood vaccination program using LAIV would result in fewer QALYs lost compared with TIV (273 483 *vs* 449 443) [12] (see Supplementary Material, Table 3 available online). In an assessment performed on children, Meeyai *et al*. [33] used the number of averted DALYs by specific vaccination policies as measure of the overall disease burden, reporting vaccination of children with TIV as more effective than LAIV (see Supplementary Material, Table 3 available online).

In elderly patients high-dose TIV has the potential to be favoured over other vaccines (TIV SD, QIV) [5, 21, 23]. QIV seemed to be effective as TIV, however several analyses indicated that QIV would deliver substantial health benefits in terms of reduced number of symptomatic influenza cases and deaths and consequent gains in QALYs and LYs [24, 29] (see Supplementary Material, Table 3 available online).

In adults at risk, QIV would be expected to improve health outcomes (QALYs and LYs) and to reduce influenza related events, compared with TIV [9]. In UK, QIV was estimated to avoid 1.4 million influenza cases, nearly 42 thousand hospitalizations and almost 20 thousand deaths and to gain more than 50 thousands QALYs and LYs, compared with TIV [15], when used in the at risk population (see Supplementary Material, Table 3 available online).

Cost-effectiveness

The most common cost-effectiveness measures reported in the included studies were cost per QALY and

LY *(Table 2)*. The Cost-Effectiveness results of influenza vaccination programs compared with no vaccination are reported in *Figure 2a* and *2b*, stratified by the perspectives adopted in the analysis. From the payer's perspective *(Figure 2a)*, two studies reported vaccination as cost-saving strategy (1 in children and 1 in patients at high risk); eight studies had an ICER below €20,000 (2 in general population, 1 in children, 3 in elderly, 1 in pregnant women and 1 in patients at risk). Two studies focussing, respectively, on adult patients and elderly reported an ICER between €20,000 and €50,000. Only one study in pregnant women reported an expected

Table 2

Incremental Cost-Effectiveness Ratios (ICERs) reported in the selected studies by Region and patients' group

	All population	Children	Adult	Elderly	Pregnant	High-Risk
Belgium (1)	ICER for increasing TIV: 14,378-24,768 €/QALY [8]		ICER for increasing TIV: 24,096 €/QALY [8]		ICER for increasing TIV: 6,616 €/QALY [8]	
UK/Wales (5)	ICERs for QIV: 7,656 £/QALY and 10,722 £/LY [18]	Current policy with or without TIV and LAIV *vs* No vaccination was cost saving [17]		ICERs for QIV: 5,299 £/QALY and 5,144 £/LY [9]		ICERs for QIV: 5,299 £/QALY and 5,144 £/LY [9]
		ICER for vaccination: 3,117-16,152 £/QALY [19]		ICER for alternative influenza vaccination policies was 7,475 £/QALY [10]		ICER for alternative influenza vaccination policies was 7,475 £/QALY [10]
Spain (1)				ICER for QIV: 8,748-11,188 €/QALY [11]		
Germany (3)	QIV was cost-saving from SP and cost effective from PP (ICER 14,461 €/QALY) [14]	TIV + LAIV was cost-saving from SP and cost effective from PP (ICER 1,228-2,265 €/QALY) [12]				ICERs for QIV: 13,497-14,645 £/QALY and 13,067-14,178 £/LY from SP and PP [15]
Finland (1)	QIV ± LAIV and TIV + LAIV *vs* No vaccination were cost- saving from SP. QIV/TIV ± LAIV were cost-effective from PP [16]					
Poland (1)				ICER for new situation: 26,118 PLN/QALY [13]		
USA (9)	ICER for QIV was 90,301 $/QALY [22]	LAIV was cost-saving [26]		HD TIV, TIV and QIV *vs* No vaccination were cost-effective (ICERs 8,833 $/QALY, 11,331 $/QALY and 15,001 $/QALY) [21]	Vaccination was cost-saving [20]	
		LAIV was cost-effective [25]		TIV HD was cost-saving [23]	Vaccination was cost-beneficial from SP. Vaccination would not generate net savings from PP [7]	
				ICER for TIV *vs* No vaccination: 3,693 $/QALY [5]		
				ICER for vaccination: 13,084-34,610 $ per life saved [24]		

Continues

Table 2
Continued

	All population	Children	Adult	Elderly	Pregnant	High-Risk
Canada (3)	ICER for QIV: 7,961 $/QALY-11,211 $/LY [18] ICER for QIV: 62,792-94,248 $/QALY [27]	ICER for vaccination *vs* No vaccination 164.12 $ (per case of influenza adverted) [28]				
China (3)	ICER for QIV was 12,558-22,603 $/QALY [30]			ICER for IM vaccination: 14,528 $/ QALY [31] QIV was cost-saving [29]		
Turkey (1)						ICER for projected situation: 64-1,158 TRY/QALY from SP and PP [32]
Israel (1)						Vaccination was cost-saving [35]
Thailand (1)		ICER for TIV *vs* No vaccination: 4,445 $/DALY: ICER for LAIV *vs* No vaccination: 1,841-5,748 $/DALY [33]				
Australia (1)				ICER for vaccination *vs* No vaccination was 27.968 A$/QALY (with vaccine efficacy of 40 %) [34]		

TIV: Trivalent Inactivated Influenza Vaccine, QIV: Quadrivalent Inactivated Influenza Vaccine, LAIV: Live Attenuated Influenza Vaccine, IIV: Inactivated Vaccine, HD: High-dose, IM: Intra-Muscular, LYs: Life Years, QALYs: Quality Adjusted Life Years, DALYs: Disability Adjusted Life Years; SP: Societal Perspective; PP: Payer Perspective.

negative net societal benefit when vaccinated mothers were compared with unvaccinated mothers. From the societal perspective, one study in the general population found that vaccination was cost-saving compared to no vaccination and one study in pregnant women, showed that vaccination generated net cost saving. Five studies reported an ICER between €20,000 and €50,000: such studies were carried out in children (n = 2), in elderly (n = 2) and in pregnant women (n = 1) *(Figure 2b)*.

The definition of cost-effectiveness was based on different cost-effectiveness threshold values, according to different studies jurisdictions between Countries. The threshold used in studies performed in Europe ranged from €20,000 to €50,000 per QALY or LY gained, £20,000-30,000 per QALY or LY gained or three times GDP per capita of the country. Studies performed in US, in China, in Turkey and in Canada adopted the threshold values of $50,000, $100,000 or three times GDP per capita to define the influenza vaccination as cost-effective.

More than half of the selected studies did not include no vaccination as a comparator: on the contrary, they focused on CEA of different vaccination strategies, among different populations, countries and perspectives. Within these studies, TIV was the most commonly evaluated vaccination strategy, and it was generally compared to LAIV and QIV *(Table 2)*. Three studies reported TIV as less effective and more costly that the alternative vaccination options [12, 14, 23]. One study in children reported LAIV as a cost-saving option compared to TIV, from the society perspective in Germany [12]. Two studies reported QIV as a cost-saving option, compared to TIV, for the Chinese and the German society, and in elderly and whole population, respectively [14, 29]. Nine studies reported QIV as cost-effective option (but not cost-saving) compared to TIV, from societal and healthcare system perspective in the whole population, elderly and high-risk patients [9, 11, 12, 14, 15, 18, 22, 27, 30]. In children, LAIV was cost-effective from the payers' perspective if compared to TIV, and also from the societal perspective if compared to IIV [12, 25]. All cost-effectiveness ratios, comparing different vaccines and vaccination strategies, are reported in *Table 2*.

DISCUSSION

In the current era of budget constraints, it is necessary to make decisions on how to best allocate the limited available resources, and to establish priorities. Influenza vaccination is recognized for its potential

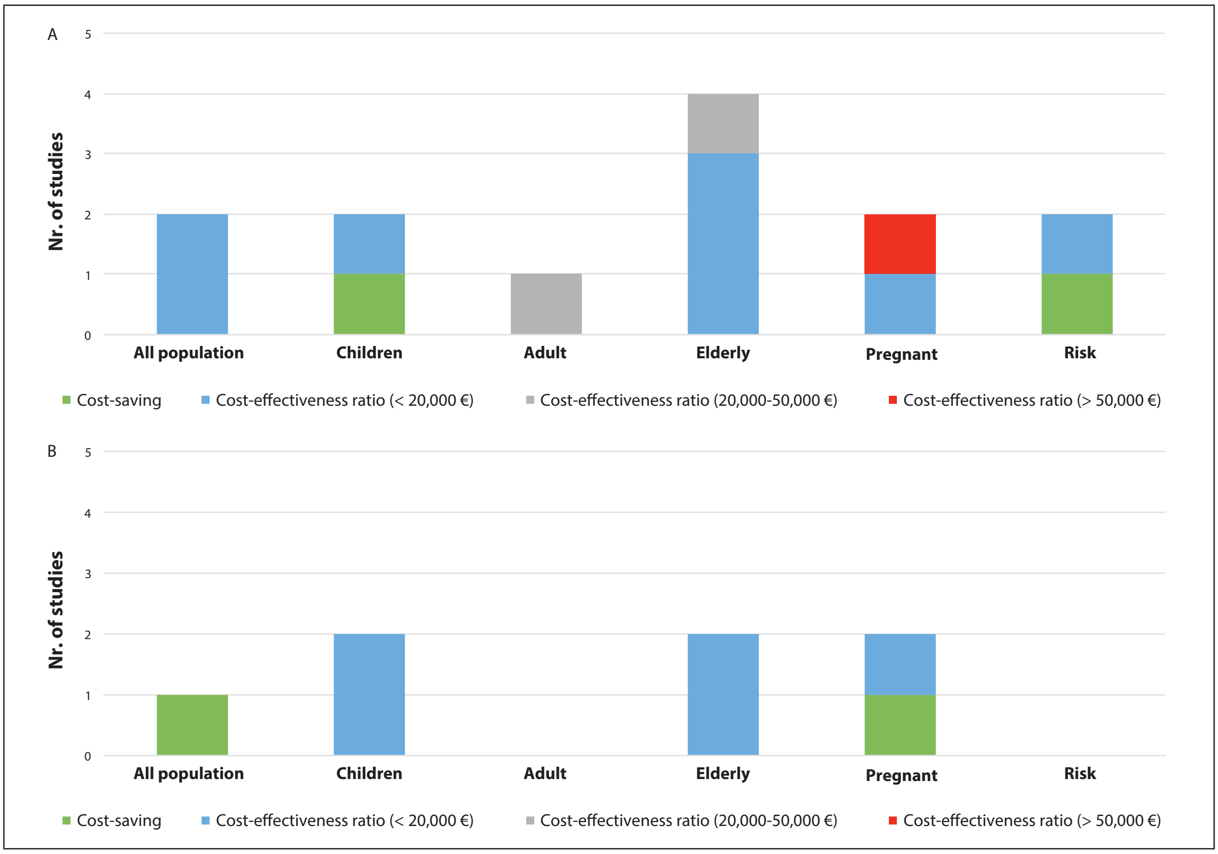

Figure 2
Stratification studies performed by patients' group and perspective vs No vaccination (A. Payer and B. Society).

benefits in terms of preventing cases of influenza and reducing complications, however the implementation of vaccination programs may require a noticeable economic investment.

We found that the majority of influenza cost-effectiveness analyses were performed in high-income countries and reported influenza vaccination as cost-saving in children and cost-effective in the elderly, in line with Paesah *et al*. [6]. All analyses found that influenza vaccination is always more effective than no vaccination; it is cost-saving in children and in high risk patients (from the payer perspective) and in pregnant women and in the general population (from the societal perspective) [16, 17, 20, 35]. Vaccinating children is likely to be cost-saving in the short and long term time horizon because of an indirect effect that protects entire communities, given that the children are considered major propagators of influenza [26, 28]. On the other hand, vaccinating elderly is also associated with a reduction in hospitalizations [15, 36]. Further, we found that maternal vaccination during pregnancy was an economically favorable approach to prevent influenza also in young infants. In US, vaccination during pregnancy was cost-effective and cost-beneficial from payer and societal perspective, compared to no vaccination [7, 20]. Furthermore, seasonal influenza vaccination in pregnant women was cost-effective from the societal perspective also in Europe [8]. Among new strategies to improve the efficacy of influenza vaccines, many studies compared trivalent vaccines with more recent quadrivalent products. Cost-effectiveness of QIV was reported in different subgroups and countries [9, 11, 14, 15, 18, 22, 27, 29, 30], showing that QIV could be a cost-effective option compared to TIV in the elderly and at high risk individuals [5, 9].

Our review showed different cost-effectiveness estimates of influenza vaccination programs, depending on the country where the analysis was carried out. These differences could depend on influenza activity, methods applied, population type and vaccine uptake; but also on differences in income and healthcare systems. For example, Xu *et al*. 2016, using a decision-analytic model, evaluated the cost-effectiveness of vaccinating pregnant women, from a societal perspective, in the US [20]. They built three different scenarios (simulating three recent influenza seasons) and concluded that, compared to a no vaccination strategy, vaccinating pregnant women against influenza was cost-saving in moderate or severe influenza seasons, but not in mild influenza seasons [20]. Thommes *et al*. assessed the cost effectiveness of a nationwide switch from TIV to QIV, in Canada and the UK, from payer's perspective, developing an age-stratified dynamic transmission model [18]. Despite the switch from TIV to QIV being reported as highly cost-effective in both countries, the authors found a significantly greater relative impact from the switch in Canada compared to the UK. The difference is mainly due to lower vaccine uptake in UK, as compared to Canada [18]. Joyce You *et al*. evaluated the cost-effectiveness of QIV versus TIV, in the Hong Kong population showing significantly different results in different age groups and with different analyses perspective. QIV was cost-effective in all age groups except 15-64 years, from the societal perspective. From the healthcare provider's perspective, QIV was cost-effective in young children (6 months-9 years) and elderly (≥ 80 years), but not cost-effective in other age groups (10-79 years) [30]. When vaccines with different method of administration were considered, the cost-effectiveness results were highly dependent on vaccine effectiveness and population type. Some recent studies estimated that the cost-effectiveness results of LAIV in children aged 2-8 years were highly sensitive to effectiveness variation [25, 26]. At last, concerning the methods used, the cost-effectiveness of vaccination was assessed using a wide range of models, including decision tree models, dynamic models, Markov models, etc., and some models did not include impact of herd immunity generated by vaccine coverage. Therefore, some studies could have underestimated the benefits of influenza vaccination programs.

A major limitation of our review is that we carried out a mainly descriptive review, with little evaluation of the qualities of the included studies. Nevertheless, in accordance to the aim of our study, we performed a systematic search of the literature, to reflect on current available data on cost-effectiveness of influenza vaccination, and to briefly summarize them with a particular focus on target groups and sub-populations.

CONCLUSIONS

Most of the studies found that influenza vaccination is cost-saving in children and generally cost-effective, particularly in the elderly and in pregnant women. Performing appropriate economic evaluations based on good clinical and economic data and rigorous methodology is of primary importance in order to make adequate decisions on the allocation of available resources for vaccination programs

Conflict of interest statement

No conflict of interest was reported by authors.

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REFERENCES

1. Health IDo. The Green Book. 2012. Available from. www.wp.dh.gov.uk/immunisation/files/2012/07/Green-Book-Chapter-19-v4_71.pdf.
2. WHO. Influenza (Seasonal). Available from: www.who.int/mediacentre/factsheets/fs211/en/2016.
3. WHO. Methods for assessing influenza vaccination coverage in target groups. Available from: www.euro.who.int/__data/assets/pdf_file/0004/317344/Methods-assessing-influenza-vaccination-coverage-target-groups.pdf?ua=12016.
4. Centers for Disease Control and Prevention NCfIaRDN. United States, 2016-2017 influenza season. 2017. Available from: www.cdc.gov/flu/protect/vaccine/vaccines.htm.
5. Raviotta JM, Smith KJ, DePasse J, Brown ST, Shim E, Nowalk MP, et al. Cost-effectiveness and public health effect of influenza vaccine strategies for US elderly adults. J Am Geriatr Soc. 2016;64(10):2126-31. DOI: 10.1111/jgs.14323
6. Peasah SK, Azziz-Baumgartner E, Breese J, Meltzer MI, Widdowson MA. Influenza cost and cost-effectiveness studies globally – a review. Vaccine. 2013;31(46):5339-48. DOI: 10.1016/j.vaccine.2013.09.013
7. Ding Y, Zangwill KM, Hay JW, Allred NJ, Yeh SH. Cost-benefit analysis of in-hospital influenza vaccination of postpartum women. Obstet Gynecol. 2012;119(2 Pt 1):306-14. DOI: 10.1097/AOG.0b013e318242af27
8. Blommaert A, Bilcke J, Vandendijck Y, Hanquet G, Hens N, Beutels P. Cost-effectiveness of seasonal influenza vaccination in pregnant women, health care workers and persons with underlying illnesses in Belgium. Vaccine. 2014;32(46):6075-83. DOI: 10.1016/j.vaccine.2014.08.085.
9. Van Bellinghen LA, Meier G, Van Vlaenderen I. The potential cost-effectiveness of quadrivalent versus trivalent influenza vaccine in elderly people and clinical risk groups in the UK: a lifetime multi-cohort model. PLoS One. 2014;9(6):e98437. DOI: 10.1371/journal.pone.0098437
10. Baguelin M, Camacho A, Flasche S, Edmunds WJ. Extending the elderly- and risk-group programme of vaccination against seasonal influenza in England and Wales: a cost-effectiveness study. BMC Med. 2015;13:236. https://doi.org/10.1186/s12916-015-0452-y
11. García A, Ortiz de Lejarazu R, Reina J, Callejo D, Cuervo J, Morano Larragueta R. Cost-effectiveness analysis of quadrivalent influenza vaccine in Spain. Hum Vaccin Immunother. 2016;12(9):2269-77. DOI: 10.1080/21645515.2016.1182275
12. Damm O, Eichner M, Rose MA, Knuf M, Wutzler P, Liese JG, et al. Public health impact and cost-effectiveness of intranasal live attenuated influenza vaccination of children in Germany. Eur J Health Econ. 2015;16(5):471-88. DOI: 10.1007/s10198-014-0586-4
13. Brydak L, Roiz J, Faivre P, Reygrobellet C. Implementing an influenza vaccination programme for adults aged ≥ 65 years in Poland: a cost-effectiveness analysis. Clin Drug Investig. 2012;32(2):73-85. DOI: 10.2165/11594030-000000000-00000
14. Dolk C, Eichner M, Welte R, Anastassopoulou A, Van Bellinghen LA, Poulsen Nautrup B, et al. Cost-utility of quadrivalent versus trivalent influenza vaccine in Germany, Using an individual-based dynamic transmission model. Pharmacoeconomics. 2016;34(12):1299-308. DOI: 10.1007/s40273-016-0443-7
15. Meier G, Gregg M, Poulsen Nautrup B. Cost-effectiveness analysis of quadrivalent influenza vaccination in at-risk adults and the elderly: an updated analysis in the UK. J Med Econ. 2015;18(9):746-61. DOI: 10.3111/13696998.2015.1044456
16. Nagy L, Heikkinen T, Sackeyfio A, Pitman R. The clinical impact and cost effectiveness of quadrivalent versus trivalent influenza vaccination in Finland. Pharmacoeco-

nomics. 2016;34(9):939-51. DOI: 10.1007/s40273-016-0430-z
17. Pitman RJ, Nagy LD, Sculpher MJ. Cost-effectiveness of childhood influenza vaccination in England and Wales: Results from a dynamic transmission model. Vaccine. 2013;31(6):927-42. DOI: 10.1016/j.vaccine.2012.12.010
18. Thommes EW, Ismaila A, Chit A, Meier G, Bauch CT. Cost-effectiveness evaluation of quadrivalent influenza vaccines for seasonal influenza prevention: a dynamic modeling study of Canada and the United Kingdom. BMC Infect Dis. 2015;15:465. DOI: 10.1186/s12879-015-1193-4
19. Thorrington D, Jit M, Eames K. Targeted vaccination in healthy school children - Can primary school vaccination alone control influenza? Vaccine. 2015;33(41):5415-24. DOI: 10.1016/j.vaccine.2015.08.031
20. Xu J, Zhou F, Reed C, Chaves SS, Messonnier M, Kim IK. Cost-effectiveness of seasonal inactivated influenza vaccination among pregnant women. Vaccine. 2016;34(27):3149-55. DOI: 10.1016/j.vaccine.2016.04.057
21. Chit A, Roiz J, Briquet B, Greenberg DP. Expected cost effectiveness of high-dose trivalent influenza vaccine in US seniors. Vaccine. 2015;33(5):734-41. DOI: 10.1016/j.vaccine.2014.10.079
22. Clements KM, Meier G, McGarry LJ, Pruttivarasin N, Misurski DA. Cost-effectiveness analysis of universal influenza vaccination with quadrivalent inactivated vaccine in the United States. Hum Vaccin Immunother. 2014;10(5):1171-80. DOI: 10.4161/hv.28221
23. Chit A, Becker DL, DiazGranados CA, Maschio M, Yau E, Drummond M. Cost-effectiveness of high-dose versus standard-dose inactivated influenza vaccine in adults aged 65 years and older: an economic evaluation of data from a randomised controlled trial. Lancet Infect Dis. 2015;15(12):1459-66. DOI: 10.1016/S1473-3099(15)00249-2
24. Patterson BW, Khare RK, Courtney DM, Lee TA, Kyriacou DN. Cost-effectiveness of influenza vaccination of older adults in the ED setting. Am J Emerg Med. 2012;30(7):1072-9. DOI: 10.1016/j.ajem.2011.07.007
25. Shim, E Brown ST, DePasse J, Nowalk MP, Raviotta JM, Smith KJ, Zimmerman RK. Cost effectiveness of influenza vaccine for US children: Live attenuated and inactivated influenza vaccine. Am J Prev Med [Internet]. 2016;51(3):309-17. DOI: 10.1016/j.amepre.2016.02.027
26. Smith KJ, Raviotta JM, DePasse JV, Brown ST, Shim E, Patricia Nowalk M, et al. Cost effectiveness of influenza vaccine choices in children aged 2-8 years in the US. Am J Prev Med. 2016;50(5):600-8. DOI: 10.1016/j.amepre.2015.12.010
27. Chit A, Roiz J, Aballea S. An Assessment of the Expected Cost-Effectiveness of Quadrivalent Influenza Vaccines in Ontario, Canada Using a Static Model. PLoS One. 2015;10(7):e0133606. DOI: 10.1371/journal.pone.0133606
28. Gregg M, Blackhouse G, Loeb M, Goeree R. Economic evaluation of an influenza immunization strategy of healthy children. Int J Technol Assess Health Care. 2014;30(4):394-9. DOI: 10.1017/S0266462314000397
29. You JH, Ming WK, Chan PK. Cost-effectiveness analysis of quadrivalent influenza vaccine versus trivalent influenza vaccine for elderly in Hong Kong. BMC Infect Dis. 2014;14:618. DOI: 10.1186/s12879-014-0618-9
30. You JH, Ming WK, Chan PK. Cost-effectiveness of quadrivalent influenza vaccine in Hong Kong - A decision analysis. Hum Vaccin Immunother. 2015;11(3):564-71. DOI: 10.1080/21645515.2015.1011016
31. Leung MK, You JH. Cost-effectiveness of an influenza vaccination program offering intramuscular and intradermal vaccines versus intramuscular vaccine alone for elderly. Vaccine. 2016;34(22):2469-76. DOI: 10.1016/j.vaccine.2016.04.008
32. Akın L, Macabéo B, Caliskan Z, Altinel S, Satman I. Cost-effectiveness of Increasing influenza vaccination coverage in adults with type 2 diabetes in Turkey. PLoS One. 2016;11(6):e0157657. DOI: 10.1371/journal.pone.0157657
33. Meeyai A, Praditsitthikorn N, Kotirum S, Kulpeng W, Putthasri W, Cooper BS, et al. Seasonal influenza vaccination for children in Thailand: a cost-effectiveness analysis. PLoS Med. 2015;12(5):e1001829. DOI: 10.1371/journal.pmed.1001829
34. Newall AT, Dehollain JP. The cost-effectiveness of influenza vaccination in elderly Australians: an exploratory analysis of the vaccine efficacy required. Vaccine. 2014;32(12):1323-5. DOI: 10.1016/j.vaccine.2014.01.017
35. Yamin D, Balicer RD, Galvani AP. Cost-effectiveness of influenza vaccination in prior pneumonia patients in Israel. Vaccine. 2014;32(33):4198-205. DOI: 10.1016/j.vaccine.2014.05.015
36. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. N Engl J Med. 2003;348(14):1322-32. DOI: 10.1056/NEJMoa025028