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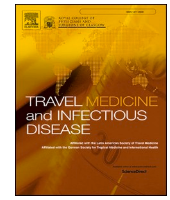

Cost-effectiveness analysis of seasonal influenza vaccination during pregnancy: A systematic review

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A B S T R A C T

Background: Seasonal influenza vaccination is clinically important and reduces hospitalization costs for pregnant women. However, is it also a cost-effective intervention?
Method: We conducted a systematic search of Medline (via PUBMED), EMBASE, SCOPUS, and Web of Science databases. We included any economic evaluation studies that reported Incremental Cost-Effectiveness Ratios for vaccinating pregnant women against influenza.
Result: Out of 927 potentially eligible articles, only 14 full texts met our inclusion criteria. In almost all studies, vaccinating pregnant women was a cost-effective and cost-saving strategy. In one study, it was not cost-effective when the researchers used costs and probabilities related to other groups (healthy adults) due to the lack of data for pregnant women. The main factors influencing the cost-effectiveness of the studies were vaccine efficacy and vaccination cost.
Conclusion: Influenza vaccination of pregnant women is a cost-effective intervention. More studies on the cost-effectiveness of this intervention in underdeveloped countries are needed.
Keywords: pregnancy, cost-effectiveness, cost-utility, cost-benefit, influenza vaccine, women, economic evaluation.

1. Introduction

Pregnant women are more susceptible to severe influenza and related hospitalization than non-pregnant women, especially in their third trimester of pregnancy [1]. Influenza also imposes a significant economic burden on society due to health care costs and lost productivity associated with maternal health [2,3].

Moreover, infants younger than 6 months have an immature immune system and cannot receive influenza vaccination because of their poor antibody response [4]. However, maternal vaccination during pregnancy can protect their infants in the first months of life. Therefore, vaccinating pregnant women is one of the best ways to reduce the morbidity and mortality of influenza in this population and their offspring [5].

All clinical trials [6–9] on the efficacy of the influenza vaccine in preventing laboratory-confirmed influenza (LCI), influenza-like illness (ILI), and hospitalization in pregnant women were conducted in low-income and middle-income countries. This was because of the easier recruitment of participants, their higher compliance, and the lower operational costs of the studies in these countries [10]. In each of the four studies, the influenza vaccine was effective in preventing LCI in pregnant women. Therefore, these countries are interested in conducting economic analysis studies with their own data to determine whether vaccinating pregnant women is a cost-effective intervention.

Therefore, the answer to whether vaccinating pregnant women is a cost-effective intervention can help health decision-makers in developing countries to adopt or reject universal influenza vaccination for this population. We conducted a systematic review of studies on the cost-effectiveness of the influenza vaccine in pregnant women to provide an overview and identify key issues that may inform future research and national guidelines.

2. Methods

2.1. Search strategy

The search strategy was designed to find both published and unpublished studies up to January 2018, and then updated until September 2022. The searched electronic databases for published studies were PUBMED, EMBASE, SCOPUS, Web of Science, and NHS Economic

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Evaluation Database. The search for unpublished studies was performed in Proquest Dissertations and Theses and Cochrane Central Register of Clinical Trials. Hand searching was carried out for all studies meeting the reference criteria. Combinations of the search terms were used to search for the relevant records: “influenza vaccin*”, “influenza immuni*”, “cost-benefit analysis”, “cost-utility analysis”, “cost-effectiveness analysis”, “economic evaluation” and, “pregnan*”.

All titles and abstracts were screened for the study Population (pregnant women), Intervention (inactivated influenza vaccination), and Comparator (pregnant women not vaccinated against influenza, placebo, or other interventions). Studies were eligible if they reported:

1) The full economic evaluation (cost-effectiveness or cost-utility) of seasonal influenza vaccine in pregnant women that have reported the Incremental Cost-Effectiveness Ratio (ICER).
2) The results are reported as cost per quality-adjusted life-year (QALY), cost per the disability-adjusted life year (*DALY*), and cost per life-year gained (LYG).
3) There is no language restrictions considered for inclusion in this review.

Duplicate studies were removed and those that did not meet the criteria based on the title and abstract were excluded. The full-text papers were then read and the same criteria were applied. The screening was performed independently by three authors and any disagreement was resolved by discussion. The reference lists of all identified reports and articles were also searched for additional studies. The PRISMA statement was followed for reporting the study. The study protocol was registered in PROSPERO (CRD42018090287).

2.2. Assessment of methodological quality, data extraction and data synthesis

Two reviewers independently assessed the methodological quality of the included papers using the standardized critical appraisal instruments from the Joanna Briggs Institute’s Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) [11]. We also examined the affiliation of each author to check for potential bias in the cost-effectiveness studies. We resolved any disagreement between the reviewers by discussion [12].

Two reviewers independently extracted the study characteristics using a data extraction tool developed by the researchers. The extracted information included: study design, perspective, time horizon, health outcome, vaccine type, vaccine efficacy/effectiveness, vaccine dose, ICER, threshold, sensitivity analysis, comparators, and costs. If the main text did not provide enough information, we reviewed the supplementary attachments. The reviewers were blinded to the authors’ names. We contacted the authors to request missing or additional data. We used the local threshold reported in the studies to interpret the ICER results. If the studies did not report the local threshold, we used the WHO’s Commission on Macroeconomics and Health pervasive threshold [13]. We interpreted the ICER results as follows:

- ❖ **Dominated**: more costly and less effective than another strategy
- ❖ **Weakly dominated**: less effective and a higher cost-effectiveness ratio than another strategy
- ❖ **Dominate**: less costly and more effective than another strategy
- ❖ **Cost-saving**: better effective and less cost than another strategy
- ❖ Cost neutral: ICER = 0
- ❖ **Very cost-effective**: 0 < ICER< \$25,000 per QALY or LYG and ICER < 1GDP per capita
- ❖ **Cost-effective**: \$25,000 < ICER ≤\$50,000 per QALY or LYG and 1GDP per capita < ICER< 3GDP per capita
- ❖ **Not cost-effective**: ICER > \$100,000 per QALY or LYG and ICER >3 GDP per capita

3. Results

3.1. Results of the search

The literature search identified 927 potentially eligible articles. The titles and abstracts of the articles were screened and 18 articles were read in full. Four studies were excluded based on the full text [14–17]. Fourteen studies were included in this review (Fig. 1). Due to the nature and high heterogeneity of the studies, a meta-analysis of the findings was not possible. Therefore, the results were synthesized and summarized narratively.

3.2. Characteristics of the included studies

Table 1 shows the cost-effectiveness studies included in this review. All the studies assessed the seasonal influenza vaccine. The studies were conducted in Africa (n = 4) [18–21], Japan (n = 1) [22], Laos (n = 1) [23], USA (n = 6) [4,24–28] and Europe (n = 2) [29,30]. Most of the studies used cost-utility analysis.

3.3. Critical appraisal

All 14 studies met at least 10 out of the 11 JBI-QARI criteria and were included in the data synthesis. Two-thirds of the studies were from the USA and Europe and evaluated the cost-effectiveness of influenza vaccination in pregnant women. The studies were funded by various sources, such as government agencies [26,29], private foundation [18], self-funded [19,20,22], British Pharmaceutical Company [4], the policy research program in the Department of Health, England [30], Capital Health Research [25], the Ministry of Health, Labour and Welfare, Japan [22] and Laos [23], WHO Department of Immunization, Vaccines and Biologicals [21]. Some studies did not report their funding sources [24,27,28]. All studies clearly stated their objectives and defined their control and intervention groups. All studies also performed sensitivity analyses to assess the robustness of their results.

3.4. Cost-effectiveness model

Most of the studies [18–23,25–30] used the Decision Tree model to evaluate the cost-effectiveness of influenza vaccination in pregnant women. One study used a dynamic model [4] and another study used both the Decision Tree and the Markov model [24]. The dynamic model accounted for the changing risk of influenza over time and gestational age, unlike the other models [4].

3.5. Perspective and time horizon

The studies used different perspectives to calculate the costs of influenza vaccination in pregnant women. These perspectives included societal [4,18,20,22–24,27,28], third-party payer [19,25,29,30], both views [26] and public health care provider [21]. The perspectives affected the types of costs (direct, indirect, and intangible) that were considered in the analysis. All studies reported their results as cost per quality-adjusted life-year gained (QALYs), except for three studies. Two studies estimated cost per disability-adjusted life year (DALY) lost [18,23] and one study estimated South African Rand per maternal influenza-associated hospitalization averted [19].

Most of them used a one-year time horizon in their study.

3.6. Thresholds

The studies used different thresholds to assess the cost-effectiveness of influenza vaccination in pregnant women. Seven studies used the WHO-recommended threshold of one or three times the GDP per capita [18–23,27]. Five studies used local thresholds based on willingness to pay or other criteria [24–26,29,30]. One study used a threshold of less

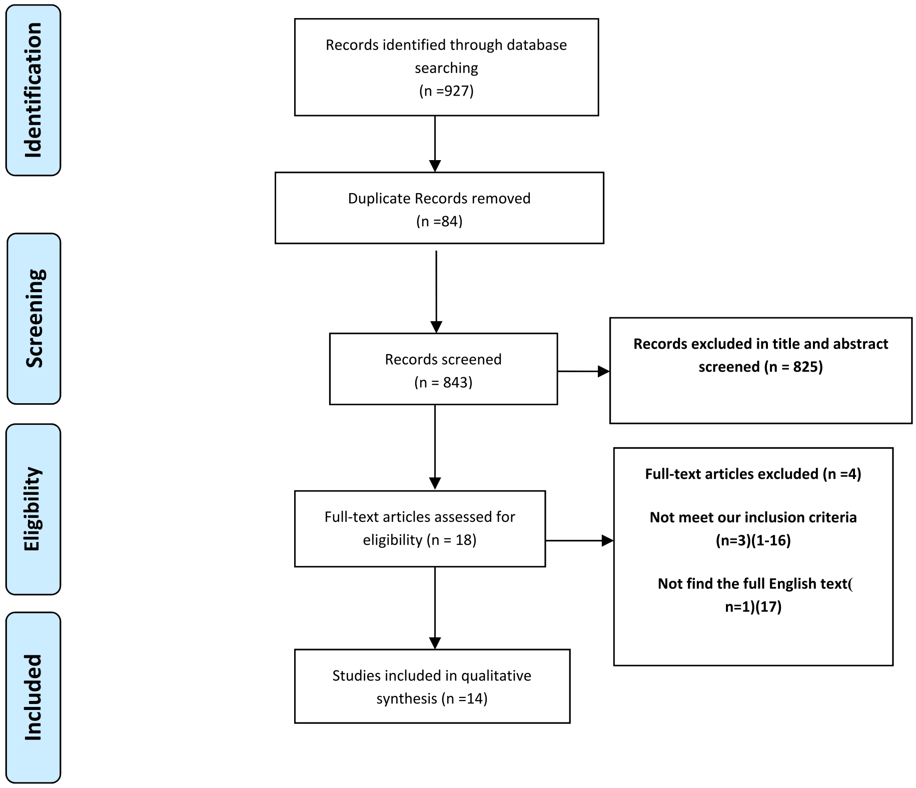

Fig. 1. PRISMA flow diagram.

than $100,000 per QALY [28]. Another study compared the ICERs of more than two strategies based on different vaccination times [4].

3.7. Participants and comparison group, vaccine type, vaccine efficacy/effectiveness and dose used

The studies compared the influenza vaccine in pregnant women with different alternatives. All participants in the intervention group received the influenza vaccine, while those in the comparator group received either no vaccine [4,19–29], placebo [30], or the meningococcal conjugate vaccine [18]. Six studies [18–21,27,29] have used the trivalent vaccine. One study [25] only mentioned that it was inactive without mentioning its type. Others used both a seasonal vaccine and a pandemic vaccine [26], a quadrivalent inactivated influenza vaccine [22], H1N1, H3N2 or B type [28], and three studies [4,24,30] did not mention the type of vaccine.

Studies have considered different vaccine efficacy/effectiveness of laboratory-confirmed influenza/hospitalization for their analysis, for example 73% [25,26], 50% [22], 50.4% [18–20], 47–85% [24], 80% [30], 63.9% [28], 57% [23] and, 59% [29] for pregnant women and 63% [25,26], 61% [22], 48.8% [18–20], 52% [23] and, 56.8% [28] for infants. The vaccine efficacy for influenza-like illnesses is considered 40% for pregnant women [27].

Most of the studies used a one-dose approach for influenza vaccination in pregnant women [4,18,20–24,27–30]. Only one study considered both single-dose and double-dose approaches [26].

Three clinical trials did not report any serious complications from influenza vaccination in pregnant women [6–8]. Some studies did not include the adverse effects of influenza vaccination in their QALY and cost estimates [18,20,22,26,29,30], while others did.

3.8. Duration of influenza (hospitalization-outpatient of pregnant women)

The average number of hospitalization days due to influenza ranged from 3 to 13 days in different studies [4,22–24,26,30]. Time for outpatient care is 4 h [4,26] or half of the day [24]. For the rest of the studies, we did not find the duration of hospitalization or outpatient days.

3.9. Sensitivity analysis

Most studies performed both one-way and probabilistic sensitivity analyses [18–20,22,23,25,27,28,30]. Two key variables mentioned in all the studies were: 1) vaccine efficacy [20–22,25–27,30] the cost of the vaccination [18,21,22,24,28,30].

3.10. Cost-effectiveness results

The studies reported different results on the cost-effectiveness of influenza vaccination in pregnant women. Most studies found that vaccination was a cost-effective [4,18,20,22,23,26,29,30], or cost-saving [21,23–25,27]. However, one study found that vaccination was not cost-effective [19] when it used costs and probabilities from healthy adults instead of pregnant women. This was because of the lack of data for pregnant women and the higher hospitalization rates from influenza in this population. Some studies also acknowledged the uncertainty in their estimates due to this data limitation [22,27]. Most of the studies were from developed countries, except for four studies from underdeveloped countries [18–20,23]. Using costs and probabilities from high-income countries was a major limitation in the studies from developing countries [19]. None of the studies considered the effects of herd immunity on influenza transmission. However, some authors argued that pregnant women had a low chance of transmitting the disease because they were a small proportion of the population [24].

Some studies included infant outcomes (such as death, premature birth, or Guillain Barre Syndrome) in their cost-effectiveness analysis of influenza vaccination in pregnant women [18,19,23–26,28]. These outcomes had a significant impact on the results of the analysis. For example, one study found that vaccination was not cost-effective when

Table 1
Results of economic evaluation analysis on influenza vaccination in pregnancy—Summary.

Name, Year, location	Study design, Perspective	Population	Interventions/ comparators	Health parameters	Costs	Cost-effectiveness	Sensitivity analysis/ most sensitive parameter
Edoka et al., 2021 South Africa [21]	● Cost-effectiveness analysis (utility measured as QALYs) ● A decision tree model ● Societal perspective and public healthcare provider	323889 pregnant women	● Intervention: TIV ● Comparator: no vaccination	QALY loss *Influenza-associated mild:* 0.009 *Influenza-associated severe illness:* 0.031 *Influenza-associated mortality:* 8.79 *Vaccine-associated mild adverse event:* 0.009 *Vaccine-associated severe adverse event:* 0.090 Incremental QALY: 478 *Vaccine efficacy: 33% for pregnant women 17% for infant*	Public healthcare provider perspective Incremental Cost (2018 US$): 961,756 Societal perspective Incremental Cost: −99,666	Public Healthcare Provider Perspective ICER: 2010 Societal Perspective ICER: Dominant Threshold: GDP per capita US$ 3400 per QALY	● one-way sensitivity analyses PSA vaccine efficacy against influenza-associated mortality, vaccine delivery costs, vaccine efficacy against hospitalization and vaccine price
Ortega-sanchez et al., 2021 Laos [23]	● Cost-effectiveness analysis (life-year and DALY saved) ● A decision tree model ● Societal perspective	● pregnant women	● Intervention: seasonal influenza vaccination ● Comparator: no vaccination	Disability-adjusted life years scores in morbidity outcomes Inpatient: 0.022 Outpatient: 0.008 Ill but not seeking medical care: 0.005 A disability-adjusted life year: 1361 Effectiveness of vaccine: 57% for women 52% for infant Influenza attack rate: 0.7800 for pregnant women 0.0720 for neonatal	Total cost saved: 3,460,501	$ 5295 per life-year saved $ 782 per DALY saved Threshold: GDP per capita	● one-way sensitivity analyses PSA attack rate and vaccine effectiveness
haiken et al., 2021 US (28)	● Cost-effectiveness analysis (utility measured as QALYs) ● A decision tree model ● Societal perspective	● 4 million pregnant women	● Intervention: influenza vaccination H1N1, H3N2 or B type ● Comparator: no vaccination	● Utility of any death: 0 ● Utility of influenza: 0–0.5 ● Utility of perfect health: 0-1 ● Utility of infant death: 0.75–1 ● Utility of cerebral palsy: 0.5–1 ● Utility of stillbirth, maternal: 0.75–1 ● Effectiveness (QALYs) for vaccination: 226,852,076 ● Effectiveness (QALYs) for no vaccination: 226,770,380	● cost for vaccination: 63,320,272,456 ● cost for no vaccination: 67,007,265,909	● Vaccination was considered a dominant strategy savings of $3.7 billion ($63.3 billion vs. $67.0 billion) QALYs of 81,696 (226,852,076 vs 226,770,380) ● Threshold: ICER of less than or equal to $100,000/QALY to be cost-effective	● one-way sensitivity analyses PSA ● cost of the influenza vaccine and ratio of H1N1 to A or B type influenza
Shu-ling Hoshi et al. [22] 2020 Japan	● Cost-effectiveness analysis (utility measured as QALYs) ● A decision tree model ● Societal perspective	● AMVP targeted pregnant women aged 20–49 years old at or over 12 weeks gestation	● Intervention: influenza vaccination ● Comparator: NO-AMVP strategy	● Vaccine effectiveness (VE) Infants: 61% Pregnant/ postpartum women: 50%	● Costs per vaccination ¥3529 ● Costs for outpatient treatment/case Pregnant/post-partum woman: ¥15,000 Infant: ¥10,000 ● Costs for hospitalization Treatment/case Pregnant/post-partum woman:	● US$7 0,721 per QALY gained ● Threshold: 1–3 times of GDP (US $45,455)- (US $90,909)	● one-way sensitivity analyses and PSA ● VE protect infant from outpatient treatment and costs per shot

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Table 1 (*continued*)

Name, Year, location	Study design, Perspective	Population	Interventions/ comparators	Health parameters	Costs	Cost-effectiveness	Sensitivity analysis/ most sensitive parameter
					¥609,186 Infant: ¥286,339		
Biggers et al. [20] (2019) South African	● Cost-effectiveness analysis (utility measured as QALYs) ● A decision tree model ● Societal perspective	● 1.52 million pregnant women ● The number of pregnant women to include in the cohort was based on the monthly recorded number of live births in South Africa in 2016	● Intervention: influenza vaccination ● Comparator: no vaccination	● QALYs lost for hospitalization: 0.0088 (0.0065–0.0011) ● QALYs lost for outpatient influenza: 0.0035 (0.0019–0.0051) ● Effectiveness of vaccine: 0.504 (0.145–0.712)	● Influenza case cared for at home: 0.18 (0.15–0.21) (in 2016 USD) ● Influenza-associated outpatient visit: 8.11 (6.35–9.31) ● Influenza-associated hospitalization: 798.74 (652.35–945.12) ● Influenza-associated death: 341.74 (319.65–463.11)	● $9240 (6187–14445) per Quality Adjusted Life Year (QALY) Threshold: 2015 GDP per capita of South Africa US $5724	● one-way sensitivity analyses and PSA ● Vaccine Effectiveness (VE) and Attack Rate
Orenstein et al. [18] (2017) Bamako, Mali	● Cost-effectiveness analysis (utility measured as DALYs) ● Decision tree model ● Societal perspective	● All pregnant women during their third trimester in 6 community and referral health centers in Bamako	● Interventions: TIV vaccination ● Comparator: meningococcal conjugate vaccination	● DALYs lost for maternal death = 32.27 For infants death = 57.28 ● Vaccine efficacy: Mothers = 70.3% Infants = 60.7% ● Attack rate: Mothers = 0.010 Infants = 0.028 ● Risk of hospitalization: Pregnant women = 0.006 Infants = 0.013	● Influenza vaccine = $1 Influenza-attributed hospitalization: mothers = $157.51 Infants = $157.50 ● Influenza-attributed outpatient visits: Mothers = $4.84 Infants = $4.41 ● Programmatic cost per pregnant women vaccinated = $1.00	● $486 per DALY saved ● Threshold = 2013 GDP per capita in Mali US $715	● one-way sensitivity analyses, two-way sensitivity analysis and PSA ● Cost per pregnant women vaccination program and proportion LCI among infants
Xu et al. [24] 2016 USA	● Cost-effectiveness analysis (utility measured as QALYs) ● Simplified decision tree and Markov state- transition ● Societal perspective	● A hypothetical cohort of 5.2 million pregnant women and infant age <6 months ● Mean age = 25.8 years	● Intervention: TIV vaccination ● Comparator: no vaccination	● Health Utility Index: ● Outpatient visit for mothers = 0.69 for infants = 0.99 ● Hospitalization for mother = 0.5 for infants = 0.95 ● Vaccine efficacy: Mothers = 0.73 Infant = 0.63	● Vaccine cost = $12.34 ● Hospitalization: Mother = $14839 Infant = $15462 ● Outpatient visit: Mother = $488.57 Infants = $503.06 ● Transportation cost = $23.07	● cost saving (2010–2011) Cost saving (2012–2013) $ 250689 cost per QALY using 2011-12 data ● Threshold = Threshold = $100000 per QALY	● one-way sensitivity ● Time of vaccine availability and vaccine cost
Leong et al. [19] 2016 Africa	● Cost-effectiveness analysis (maternal influenza-associated hospitalization averted) ● Decision tree model ● Health service Payers perspective	● 100000 pregnant women	● Intervention: TIV vaccination ● Comparator: no vaccination	● Incremental effectiveness = −120	● Incremental cost = 121754000 south Africa rand	● South Africa rand 1197779 per maternal influenza-associated hospitalization averted ● Threshold = GDP per capita in South Africa 340800R	● one-way sensitivity analyses and PSA ● Incidence of LCI in mothers
Skeggel et al. [25] 2014 Canada	● Cost-effectiveness analysis (utility measured as QALYs) ● Decision tree model ● Health service Payers perspective	● 10000 pregnant women	● Intervention: TIV vaccination ● Comparator: no vaccination	● Vaccine efficacy = 0.64 ● Baseline utility weight = 0.95 ● Relative utility weight, influenza = 0.58 ● Relative utility weight, Guillain-barre syndrome = 0.25	● No vaccination = 344878$ ● Targeted strategy = 335392$ ● Universal vaccination = 426536$	● Relative to the targeted strategy, universal strategy was = $ 39942 per QALY ● Threshold = $100000 per QALY	● one-way sensitivity analyses and PSA VE and mode of delivery

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Table 1 (*continued*)

Name, Year, location	Study design, Perspective	Population	Interventions/ comparators	Health parameters	Costs	Cost-effectiveness	Sensitivity analysis/ most sensitive parameter
Blommaert et al. [29] 2014 Belgium	● Cost-effectiveness analysis (utility measured as QALYs) ● Decision tree model ● Health care payer perspective	● 121363 pregnant women	● Intervention: TIV vaccination ● Comparator: no vaccination	● Attack rate = .084 ● Incremental QALYs = 58	● Incremental direct Costs = £ 385978	● £6616 per QALY ● Threshold = a willingness to pay for a quality-adjusted life-year (QALY) of £ 35,000	● PSA ● VE and clinical protection against influenza transferred from mother to child
Myers et al. [4] 2011 USA	● Cost-effectiveness analysis (utility measured as QALYs) ● Dynamic model ● Societal perspective	● 2.6 million pregnant women in the USA	● Intervention: TIV vaccination ● Comparator: no vaccination	● Vaccine efficacy = 0.73 ● Utilities for influenza_ attributable outpatient visit = 0.65 ● Utilities for influenza_ attributable hospitalization = 0.5	● Influenza vaccine = 17.48$ ● Adverse effect of vaccine: Minor = 0.81$ ● influenza_ attributable outpatient visits mother = 218$ infant = 218$ ● influenza_ attributable hospitalization: mother = 6665$ infant = 3336$ ● influenza related death: mother = 19996$ infant = 11209$ ● cost of no vaccine = 84801058$	● ICER for vaccine (no reduction in infant disease) = $ 110093 per QALY ● ICER for vaccine (reduction in infant disease) = $ 70089 per QALY ● Threshold = Comparison of ICERs of different strategies	● single- and multivariate sensitivity analyses ● timing of vaccine delivery
Jit et al. [30] 2010 England	● Cost-effectiveness analysis (utility measured as QALYs) ● Decision tree model ● Health care payer perspective	● 570000 pregnant women 15–44 years	● Intervention: seasonal influenza vaccination ● Comparator: placebo	● Vaccine efficacy = 80% ● Attack rate = 5.9% ● QALYs lost due to influenza episode = 0.010 ● Quality of life detriment during hospital episode = 0.35 ● Quality of life detriment during intensive care = 0.48	● Hospitalization = £1446 ● Intensive care = £983 ● GP consultation = £52 ● GP prescription = £1.62 ● Dose of vaccine = £6.04 ● Administration cost = £10.33	● £23000 per QALY (95% CI £13000-£200000) If infants are partially protected by their mother ● Threshold = £ 20000–30000 per quality-adjusted life year.	● one-way sensitivity analyses and PSA ● Influenza QALY loss, VE and vaccine cost
Beigi et al. [26] 2009 USA	● Cost-effectiveness analysis (utility measured as QALYs) ● Decision tree model ● Third party payer And societal perspective	● All pregnant women in the USA Median age = 27.1 years	● Intervention: seasonal influenza vaccination ● Comparator: supportive care	● Vaccine efficacy: Mother = 0.73 Infant = 0.63 ● QALY attributed for the 7 days of infection = 0.5 ● QALY = 065 for influenza without hospitalization ● QALY = 0.95 FOR the vaccine side effect	● Cost for hospitalization: Mother = $3526 ± 302.10 Infant = $2323.84 ± 262.38 Influenza vaccine = $15.00 ● Third party payer = $37366 ● societal perspective = $58076.25	● ICER = ≤ $ 6787.77 per QALY ● Threshold = less than $50,000 per quality-adjusted life year.	● PSA ● Prevalence of influenza, Maternal mortality from influenza and vaccine efficacy
Roberts et al. [27] 2006 USA	● Cost-effectiveness analysis (utility measured as QALYs) ● Decision tree model ● Societal perspective	● A hypothetical cohort of all pregnant women 18–44 years in the USA	● Interventions: single and 2 doses of seasonal influenza vaccination ● Comparators: no vaccination	● Probability of Hospitalization = 0.005 Medical visit influenza like illness (ILI) = 0.554 ● Vaccine efficacy = 0.7 ● Health-related quality of life, ILI = 0.61 ● Incremental effectiveness = −0.00256HRQL	● hospitalization: $5128 ● vaccine = $10.00 ● Incremental cost = $25.22 All costs were adjusted to 2004 U.S. dollars.	● Dominated ● Threshold = less than $50,000 per quality-adjusted life year.	● a multivariate sensitivity and PSA ● incidence of ILI, probability of vaccination and VE

AMVP: antepartum maternal vaccination program.
TIV: Trivalent inactivated influenza vaccine.
HRQL: Health-Related Quality of Life.
DALY: Disability Adjusted Life Years.
QALY: Quality Adjusted Life Years.
PSA: Probabilistic sensitivity analysis.
LCI: laboratory confirmed influenza.
ILI: influenza like illness.

only maternal outcomes were considered, but it became close to cost-effective when neonatal outcomes were added [20]. Orenstein et al. [18] showed that changes in the influenza attack rate in infants had a greater effect on the cost-effectiveness than changes in this rate in pregnant women. Myers et al. [4] compared three different strategies: no vaccination, vaccination with no reduction in infant disease, and vaccination with reduction in infant disease. They found that vaccination was more cost-effective when it reduced infant disease ($110,093 per QALY vs. $70,089 per QALY).

Only one study [19] out of seven studies [4,19,23–25,27,28] found that universal vaccination of pregnant women was not cost-effective. The other study found that vaccination in the second and third trimesters or only in the third trimester was cost-effective. The authors of the study [19] explained that universal vaccination did not protect infants who were born before the peak of influenza season. These infants had mothers who received their vaccine in the first trimester of pregnancy, which did not affect their immunity to influenza [4].

The cost-effectiveness of influenza vaccination in pregnant women depends on the incidence rates of influenza in different seasons and regions [24]. A study using a dynamic model [4] found that vaccination was cost-effective compared to no vaccination from September to October, but not in the later months. Vaccination was also a dominant intervention in January when the influenza activity was high. Moreover, some studies showed that the timing of influenza vaccination had a greater impact on reducing the risk of influenza in infants than in pregnant women [4,20]. For example, in an African national vaccination campaign, pregnant women had a 60–70% risk reduction and infants had a 25–40% risk reduction from influenza [20].

4. Discussion

This systematic review evaluated the cost-effectiveness of seasonal influenza vaccination during pregnancy. Out of the 14 studies reviewed, 13 studies confirmed that vaccinating pregnant women was a cost-effective intervention. Given the increased risk of hospitalization and death from the co-circulation of influenza virus and SARS-CoV-2 in vulnerable groups, including pregnant women [31] vaccination of pregnant women should be prioritized as a cost-effective intervention.

The studies varied in their settings and contexts, which affected the cost-effectiveness of influenza vaccination in pregnant women. Most of the studies were from high-income countries with better health care access and lower costs. Only four studies were from Africa, a low-income region with different challenges and needs. Two of these studies found that vaccinating pregnant women was cost-effective [18,21]. One study found that vaccination was cost-effective only for the priority group of HIV-positive women [20]. Another study found that vaccination was not cost-effective for any group [19].

The study from South Africa [19] that found that influenza vaccination in pregnant women was not cost-effective had some limitations. The main limitation was the lack of data on the impact of the vaccine on the key outcomes of the study, such as hospitalization rates. The study used data from other groups (healthy adults) instead of pregnant women, which may not reflect the true burden of influenza in this population. The study also used cost information from high-income countries, which may not be applicable to the low-income setting of South Africa. These factors may have affected the results of the cost-effectiveness analysis.

The four studies from Africa [18–21] identified different parameters that had the greatest impact on the ICER of influenza vaccination in pregnant women. These parameters were: vaccine effectiveness and disease incidence among HIV-infected women [20], the estimated burden of influenza [21], cost of maternal vaccination and proportion of confirmed influenza in infants [18], and the incidence of hospitalization among vaccinated and unvaccinated women, both HIV-infected and non-HIV-infected [19].

Another finding was that the cost-effectiveness of the vaccination was affected by the timing of the injection. The vaccine should be administered before the virus spreads in the community, as this affects the main factor in the calculation of cost-effectiveness. There was a significant difference between the results of studies that assumed a constant risk of influenza throughout the year and across different gestational stages. Earlier vaccinations have a large impact on reducing the morbidity of mothers and their infants [4], as CDC recommends getting vaccinated by the end of October in the Northern Hemisphere [29]. Therefore, September and October are the optimal months for vaccination in the second and third trimesters [30].

In Myers et al. [4] and Xu et al. [24] investigated the cost-saving of seasonal-influenza vaccination during pregnancy under different scenarios of influenza incidence. They found that the vaccination was not cost-effective when the influenza incidence was low, but it was cost-effective when the incidence was moderate or high. Compared to supportive care only, vaccination would save about $50 and 0.00512 quality-adjusted life years per individual for preventing influenza-like illness (ILI) in the pre-pandemic period [27]. Moreover, vaccination was highly cost-effective for preventing both ILI and laboratory-confirmed influenza (LCI) in pandemic and post-pandemic periods [26].

Tree studies of targeted programs [19,20,25] compared influenza immunization of pregnant women with co-morbidities or HIV infection to no vaccination strategy. They found that vaccinating HIV-infected pregnant women was more cost-effective in reducing maternal influenza-associated hospitalization when the hospitalization rate was low. A study from North Africa [20] considered two scenarios: the first one prioritized HIV-infected pregnant women (70% of them were vaccinated) and the second one vaccinated both HIV-infected and uninfected women. The study concluded that vaccination in the first scenario was cost-effective and in the second scenario was borderline cost-effective. The co-morbidities targeted program was cost-saving if it was delivered by public health clinics and routine family practitioner visits.

This study has several limitations. One of them is the inability to conduct a meta-analysis of cost-effectiveness studies, which requires a high degree of methodological and clinical homogeneity among the studies that was lacking in this review. Another challenge is the variability of flu data across different seasons or years, as the flu prevalence and severity depend on various factors, such as the virus type and strain, the population immunity, the vaccination timing and coverage, and the environmental conditions. These factors can vary from year to year and from region to region, making it difficult to compare and generalize the results. Moreover, influenza vaccination rates are low in underdeveloped countries, where influenza poses a high risk of morbidity and mortality for pregnant women and their infants. Several barriers, such as lack of awareness, access, affordability, or acceptability of the vaccine among pregnant women and health care providers, may contribute to the low vaccination rates. This study shows that influenza vaccination in pregnancy is a cost-effective intervention that can prevent influenza-related complications and deaths in both mothers and infants. Therefore, this type of data could help increase the use and uptake of the vaccine in underdeveloped countries by providing evidence-based information and recommendations to policy makers, health care providers, and pregnant women.

5. Conclusion

Influenza vaccination of pregnant women is a cost-effective intervention, but more studies are needed to evaluate its impact in underdeveloped countries. The results of cost-effectiveness studies can provide valuable information to decision makers who are considering universal vaccination or insurance coverage for the influenza vaccine for pregnant women in their countries. However, they should conduct these studies using their own country's data, which would be more reliable and take into account the factors that affect the cost-effectiveness of the influenza vaccine.

CRediT authorship contribution statement

Zakieh Ostad-Ahmadi: Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Methodology, Visualization, Project administration. **Sara Boccalini:** Investigation, Methodology, Writing – review & editing. **Amin Daemi:** Methodology, Writing – review & editing. **Alireza Mahboub-Ahari:** Conceptualization.

Declaration of competing interest

Statement the authors declare that they have no conflict of interest.

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