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Review Article

Evaluating the Protective Effects of Influenza Vaccination in Pregnant Women and Their Infants: An Umbrella Review

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Abstract

Background: Maternal influenza immunization is a primary strategy for protecting mothers and infants under six months, though its comprehensive efficacy and safety profiles undergo continuous evaluation. However, the reliability of current evidence is moderated by varying degrees of primary study overlap across existing reviews.

Methods: Five electronic databases—PubMed, Embase, Web of Science, ProQuest, and Scopus—were systematically searched up to August 2024**.** Study eligibility and quality were assessed using the ROBIS tool. To ensure the integrity of the findings and address potential primary study overlap, the Corrected Covered Area (CCA) formula was applied.

Results: Eleven systematic reviews and meta-analyses were evaluated. Maternal influenza vaccination may reduce the risk of laboratory-confirmed influenza (LCI) in both mothers and infants; however, no clear effect was observed on influenza-like illness (ILI). Vaccination is generally associated with a reduced risk of fetal mortality and no consistent evidence suggests a significant increase in congenital anomalies or spontaneous abortion. Maternal influenza vaccination may modestly reduce preterm birth risk, shows no clear effect on small for gestational age, and is associated with reduced low birth weight (LBW). The studies on influenza vaccination in pregnant women showed high overlap for LCI (0.66), infant LCI (0.50), and varying overlap for stillbirth (0.38), congenital anomalies (0.28), spontaneous abortion (0.23), premature birth (0.13), SGA (0.27), and LBW (0.14).

Conclusion: Influenza vaccination during pregnancy effectively reduces LCI in mothers and infants without increasing adverse neonatal outcomes, though its impact on ILI remains inconsistent. Due to high study overlap and variable quality, further large-scale research is required to confirm effects on preterm birth and congenital anomalies.

Keywords: Influenza; Vaccine; Infant; Safety; Efficacy

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Introduction

Pregnant women are at an increased risk of severe influenza-related complications, including pneumonia and acute respiratory distress syndrome, due to physiological and immunological changes during pregnancy (1). Furthermore, as infants under six months are ineligible for direct vaccination, they remain highly susceptible to severe morbidity and mortality (2). Consequently, maternal immunization serves as a critical intervention for passive antibody transfer via the placenta (3). Aligning with these findings, the WHO advocates for universal influenza vaccination throughout all stages of pregnancy to ensure dual protection for the mother and neonate (4).

Clinical trial evidence suggests that influenza vaccination during pregnancy may reduce the incidence of laboratory-confirmed influenza (LCI) among both pregnant women and infants under six months of age (1, 5, 6). Moreover, multiple systematic reviews have examined the safety of maternal influenza vaccination and have consistently reported no conclusive evidence of an increased risk of adverse outcomes in either pregnant women or their infants (7, 8).

Despite the growing body of supportive evidence, vaccination coverage among pregnant women remains suboptimal worldwide, particularly in low- and middle-income countries (LMICs). One systematic review identified key barriers to vaccine uptake, including insufficient awareness of vaccine safety and effectiveness, concerns about potential risks, and limited or inconsistent recommendations from healthcare providers (9).

Although existing systematic reviews have yielded valuable insights regarding the safety and efficacy of maternal influenza vaccination, the proliferation of reviews, heterogeneity in their scopes, and potential overlap of primary studies pose challenges for healthcare professionals and policymakers in obtaining a clear, consolidated synthesis of the evidence. While the increasing number of systematic reviews in a given field can sometimes result in inconsistent findings and complicate decision-making, it is therefore essential to critically appraise the reliability and quality of these reviews (10).

This umbrella review aimed to evaluate the effectiveness and safety of influenza vaccination during pregnancy, focusing on maternal and infant outcomes including LCI, Influenza-like illness (ILI), congenital anomalies, preterm birth, and infant mortality.

Methods

An initial exploration of the literature revealed multiple systematic reviews on influenza vaccination during pregnancy. Consequently, we adopted an overview of reviews approach to synthesize pertinent data. The methods were designed in accordance with the guidelines outlined in the chapter on overviews of reviews in the Cochrane Handbook guidance (11).

Eligibility criteria

Studies eligible for analysis followed the PICO framework, focusing on pregnant women receiving influenza vaccines (monovalent, trivalent, or quadrivalent) compared with unvaccinated pregnant women. Outcomes measured included the efficacy of the vaccine in reducing ILI, infant mortality, spontaneous abortion, congenital anomalies, premature birth (PTB), Small for Gestational Age (SGA), and Low Birth Weight (LBW), using hazard ratios (HRs), odds ratios (ORs), and relative risks (RRs). Included studies were systematic reviews and meta-analyses evaluating the efficacy, effectiveness, and safety of influenza vaccines in pregnant women and infants up to six months old. Brief conference presentations and studies without full-text availability were excluded.

Search strategy

The study protocol received was reviewed and approved from the Ethics Committee of the Kerman University of Medical Sciences (IR.KMU.REC.1399.303). Databases Embase, PubMed, Web of Science, Scopus, and ProQuest were searched using the following keywords until

August 2024: (Influenza OR FLU) AND immunization OR immunotherap* OR vaccin* OR immuni* OR effectiveness OR efficacy OR adverse OR inocul* AND pregnancy OR fetal OR infant, newborn OR fetus OR pregnan* OR maternal OR neonat* AND systematic review. The source list of all identified articles and reports was reviewed. A manual search was also conducted to review the unpublished missing studies. Language and time restrictions were not applied. The search strategy was reviewed and confirmed by an experienced librarian.

Data screening

Articles retrieved through reference management software were managed, and duplicate entries were eliminated. The titles and abstracts of the articles were then reviewed, and any irrelevant articles were excluded. The full text of the remaining articles was reviewed, and the reasons for their exclusion were documented. All article selection steps were conducted independently by two independent reviewers. Any disagreements were discussed and resolved by a third party.

Data Extraction

The checklist was designed by analyzing other overview of reviews and pilot data extraction was conducted. After making sure that the present checklist could help extract the desired results, two researchers collected the results using the checklist. Extracted titles include authors' names, year of publication, the purpose of systematic review, searched databases, last search date, inclusion and exclusion criteria, number of studies entered in the systematic review, and whether a meta-analysis was performed or not. Based on the findings, an independent table was drawn for each clinical outcome. Then, the author's name, year of publication, type of vaccine used, the definition of the desired outcome, and outcome data were extracted. The impact of vaccination was shown as the intensity of RRs, ORs, and HRs effects in the tables. All data extraction steps were performed by two researchers independently.

Risk of bias

The risk of bias was assessed using the ROBIS tool (12). ROBIS is used to assess the risk of bias in systematic reviews (rather than in preliminary studies). The assessment was conducted in three phases by two independent reviewers.

Data synthesis and analysis

The results were interpreted using a narrative synthesis approach and tabulation. We assessed RRs, Ors, HRs effects, and their confidence intervals. We reviewed the effect size, Confidence Interval (CI), and I^2 of studies. I^2 was used to quantify statistical heterogeneity among studies. Values above 50% and 75% indicate substantial and considerable heterogeneity, respectively.

In addition, citation matrices were generated, and Corrected Covered Areas (CCAs) were calculated to determine the overlap in studies across the meta-analysis. The formula for calculating it was as follows: $(N - r)/ (rc - r)$ where N= sum of the number 1(number of included publications), R=number of rows, and C=number of the reviewer (CCA = 0–5: slight overlap, 6–10: moderate overlap, 11–15: high overlap, > 15: very high overlap) (13).

All data management procedures were conducted using Microsoft Excel 2019.

Results

Characteristics of the included studies

Out of 276 initially obtained articles, 17 remained after eliminating duplicates and reviewing the titles and abstracts. During the full-text review, six articles were excluded: three for not meeting the inclusion criteria (14-16) two for not performing a meta-analysis (17, 18), and one for employing different methodologies (19) (Fig. 1). Finally, 11 articles were (7, 8, 20-28) included in the risk-of-bias assessment and final analysis of the study.

The citation map illustrates a moderate sharing of primary studies among the included reviews (Fig. 2). Specifically, ten out of the primary (1, 5, 6, 29-63) these studies were shared across four or five systematic reviews (Fig. 2).

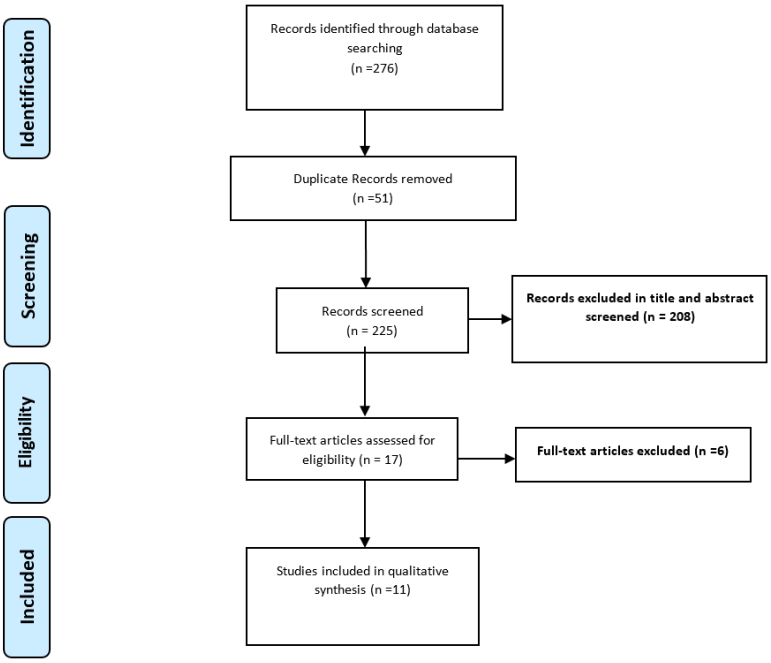


Fig. 1: The process of selecting studies based on PRISMA instructions

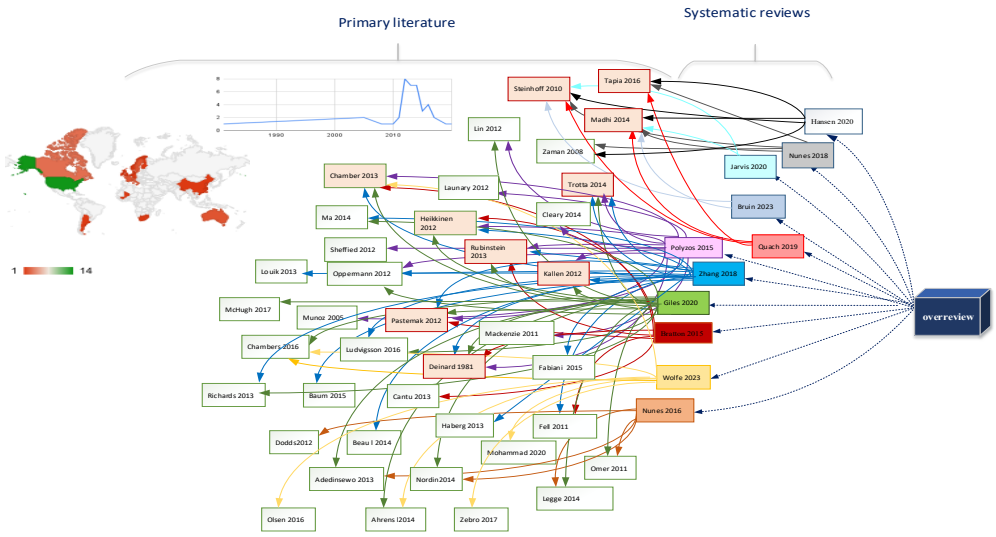


Fig. 2: Diagram depicting the citation network among systematic reviews and their corresponding primary studies

Risk of bias

Assessment of risk of bias using ROBIS indicated that 80% of articles had a low risk of bias, while 20% had a high risk (Fig. 3). One study had a high risk in the synthesized part (22), whereas the remaining studies were at low risk.

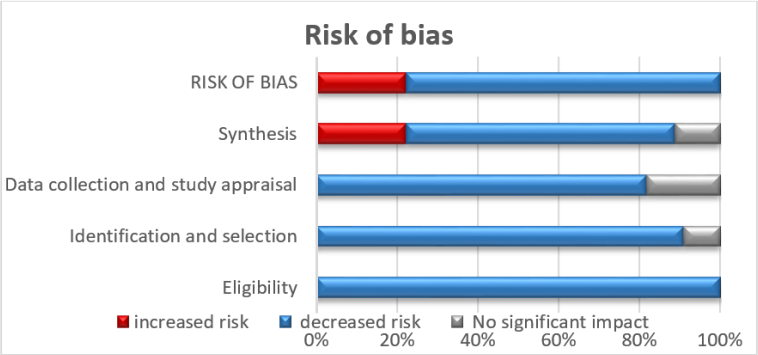


Fig. 3: Assessment of risk of bias with the ROBIS checklist

Efficacy/effectiveness of influenza vaccine in the prevention of ILI and LCI cases in pregnancy and infants

Significant reductions in maternal LCI risk were reported (RR= 0.47, 95%, CI 0.31-0.71, I^2=48%) (8) and (RR=0.66, 95% CI 0.52-0.85, I^2=0) (24). Additionally, no significant association with ILI risk was observed (RR = 0.94, 95% CI 0.85-1.03, I^2=3.6%) (8). The included reviews consistently demonstrated a reduction in infant LCI risk associated with maternal vaccination. For instance, a significant reduction was found in randomized controlled trials (RR=0.64, 95% CI 0.52-0.78, I^2=0) (22). Other studies also yielded significant reductions with ORs and RRs of 0.66, with low heterogeneity (7, 24). The two studies that investigated the relationship between influenza vaccination in pregnant women and LCI have a high overlap, with a CCA value of 0.66.

In terms of infant outcomes, the overall overlap was 0.50. Specifically, the overlap between Nunes et al. study and (22) others (7, 24) was 0.50, while the overlap between Jarvis et al. (7) and Bruin's et al. (24) study was 1. A review of study overlaps, both generally and pairwise, indicated a high overlap in existing studies (Table 1). Despite this, findings across the three reviews remained consistent, demonstrating a reduction in infant LCI cases following maternal vaccination.

The impact of maternal influenza vaccination on fetal death, congenital anomalies, and spontaneous abortion

Studies indicated a reduced risk of fetal mortality (RR=0.73, 95% CI 0.55-0.96) (26) but with higher heterogeneity (I^2=68%). adjusted hazard ratios (aHR) of 0.80 (95% CI 0.69-0.92) with low heterogeneity (I^2=7.7%) (20) was also reported. Some studies demonstrated no significant effect with no heterogeneity (OR=0.84, 95% CI 0.65-1.08, I^2=0) (27), (RR=1.09, 95% CI 0.90-1.31, I^2=0) (28).

The reviewed studies generally indicated no significant increase in the risk of congenital malformations associated with maternal vaccination. For instance, one study reported a RR of (1.07 (95% CI 0.82-1.28, I^2=6%) (20), which suggested no strong evidence for increased risk. Other studies presented an OR of 1.03 (95% CI 0.99-1.07, I^2=0) (27), and OR of 0.96 (95% CI 0.86-1.07, I^2=36) (25) further supporting the lack of significant association.

The studies reviewed generally indicated no significant increase in the risk of spontaneous abortion associated with maternal vaccination. For instance, one study reported a relative risk RR of 1.04 (95% CI 0.72-1.5, I^2=0) (20), suggesting no strong evidence for increased risk. Another study presented an OR of 0.27 (95% CI 0.14-0.52, I^2=61%) (28), which indicated a significant risk reduction. Additionally, a separate study showed an adjusted odds ratio (aOR) of 0.80 (95% CI 0.60-1.10, I^2=86%) (23), while this suggested a potential reduction in risk, though the high I^2 value indicated substantial heterogeneity.

The overlap for studies on neonatal stillbirth, congenital anomalies, and spontaneous abortion was 0.38, 0.28, and 0.23, respectively. A detailed comparison of these studies was presented in Table 1. Within the domain of congenital anomalies, the overlap among the three studies was substantial, and their findings were consistent (20, 25, 27). These studies indicated no association between influenza vaccination during pregnancy and congenital anomalies (Fig. 4).

Regarding neonatal stillbirth, the pairwise comparisons, excluding one study (28), demonstrated a high degree of overlap (20, 26, 27). Two studies reported a slight reduction in neonatal deaths (20, 26), whereas the remaining two studies found no significant association. In the context of spontaneous abortion, pairwise comparisons showed a high degree of overlap, with except for one study (23), also demonstrated a high degree of overlap. One study reported a significant reduction in spontaneous abortion rates (27), while the other two studies did not observe any significant association.

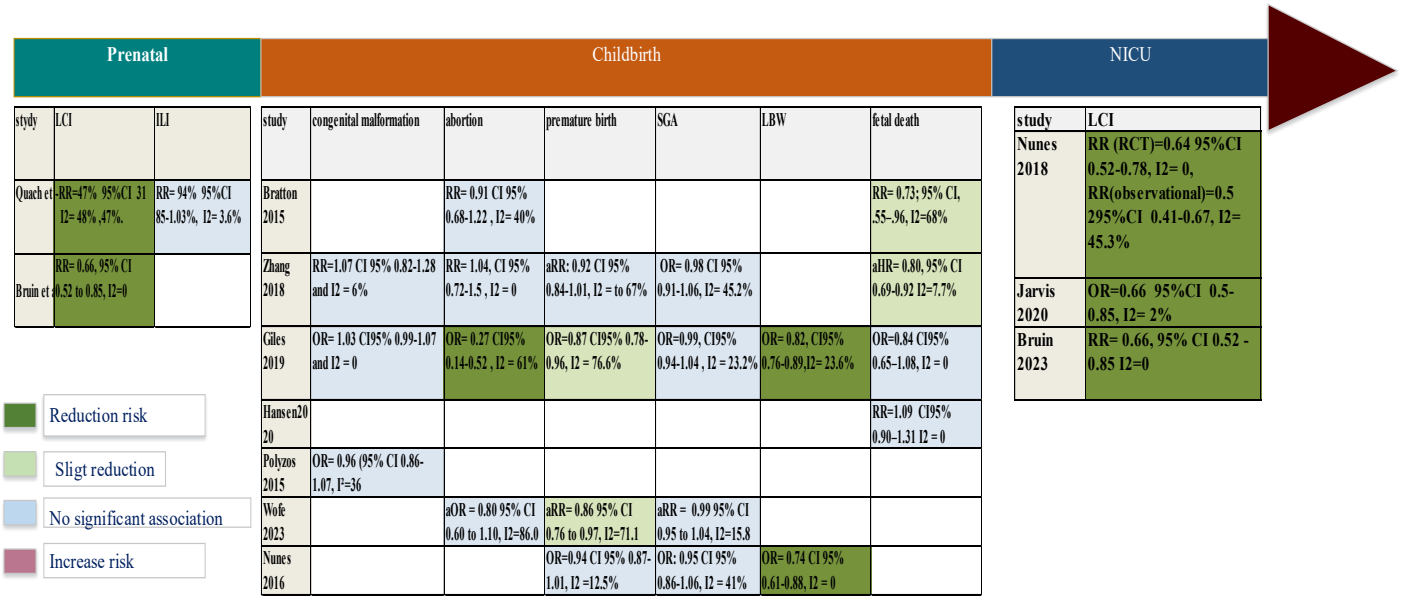
Effects of Maternal Influenza Vaccination on Preterm Birth, SGA, and Low Birth Weight

Studies showed mixed results regarding the impact of maternal vaccination on preterm birth (PTB). Some research indicated a slight but significant reduction in PTB cases following vaccination, with an RR of 0.86 (95% CI 0.76 to 0.97, I^2=71.1) (23) and another OR of 0.87 (95% CI 0.78-0.96, I^2 = 76.6%) (27). However, other studies found no significant association between vaccination and PTB, with an adjusted RR of 0.92 (95% CI 0.84-1.01, I^2 = 67%) (21). Regarding small for gestational age (SGA), four systematic reviews examined this relationship and found no significant association between maternal vaccination and SGA in their meta-analysis results (20, 21, 23, 27). Additionally, meta-analyses revealed a reduction in low birth weight following maternal vaccination, with an OR of 0.82 (95% CI 0.76-0.89, I^2 = 23.6%) (27) and another OR of 0.74 (95% CI 0.61-0.88, I^2 =0%) (21).

The overlap for studies on premature birth, SGA, and LBW were 0.13, 0.27, and 0.14, respectively. Table 1 shows varying degrees of pairwise overlap between studies, with some studies showing significant overlap while others showing none.

Table 1: Overlap Categorization for Pairs of Reviews Based on CCA Calculations for LCI cases in infants, neonatal stillbirth, congenital anomalies, spontaneous abortion, and Premature Birth, SGA.

Outcomes	LCI cases in infants		Congenital anomalies		Neonatal stillbirth			Spontaneous abortion			Premature Birth			SGA		
Studies	Bruin 2023	Jarvis 2020	Giles 2020	Zhang 2018	Wolfe 2023	Giles 2020	Zhang 2018	Hansen 2020	Giles 2020	Zhang 2018	Wolfe 2023	Giles 2020	Zhang 2018	Wolfe 2023	Giles 2020	Zhang 2018
Nunes 2018	0.50	0.50														
Jarvis 2020	1	0														
Polyzos 2015			0.26	0.33												
Zhang 2018			0.37		0	0.37		0	0.31							
Bratton 2015					0	0.33	0.4	0	0.28	0.31						
Giles 2020					0			0								
Nunes 2016											0	0.36	0	0	0.36	0
Zhang 2018											0	0.41		0	0.29	
Giles 2019											0			0		



stydy	LCI	ILI
Quach et	RR=47% 95%CI 31 I2= 48% ,47%.	RR= 94% 95%CI 85-1.03%, I2= 3.6%
Bruin et a	RR= 0.66, 95% CI 0.52 to 0.85, I2=0	

study	congenital malformation	abortion	premature birth	SGA	LBW	fetal death
Bratton 2015		RR= 0.91 CI 95% 0.68-1.22 , I2= 40%				RR= 0.73; 95% CI, .55-.96, I2=68%
Zhang 2018	RR=1.07 CI 95% 0.82-1.28 and I2 = 6%	RR= 1.04, CI 95% 0.72-1.5 , I2 = 0	aRR: 0.92 CI 95% 0.84-1.01, I2 = to 67%	OR= 0.98 CI 95% 0.91-1.06, I2= 45.2%		aHR= 0.80, 95% CI 0.69-0.92 I2=7.7%
Giles 2019	OR= 1.03 CI95% 0.99-1.07 and I2 = 0	OR= 0.27 CI95% 0.14-0.52 , I2 = 61%	OR=0.87 CI95% 0.78-0.96, I2 = 76.6%	OR=0.99, CI95% 0.94-1.04 , I2 = 23.2%	OR= 0.82, CI95% 0.76-0.89,I2= 23.6%	OR=0.84 CI95% 0.65-1.08, I2 = 0
Hansen2020						RR=1.09 CI95% 0.90-1.31 I2 = 0
Polyzos 2015	OR= 0.96 (95% CI 0.86-1.07, I²=36					
Wofe 2023		aOR = 0.80 95% CI 0.60 to 1.10, I2=86.0	aRR= 0.86 95% CI 0.76 to 0.97, I2=71.1	aRR = 0.99 95% CI 0.95 to 1.04, I2=15.8		
Nunes 2016			OR=0.94 CI 95% 0.87-1.01, I2 =12.5%	OR: 0.95 CI 95% 0.86-1.06, I2 = 41%	OR= 0.74 CI 95% 0.61-0.88, I2 = 0	

study	LCI
Nunes 2018	RR (RCT)=0.64 95%CI 0.52-0.78, I2= 0, RR(observational)=0.5 295%CI 0.41-0.67, I2= 45.3%
Jarvis 2020	OR=0.66 95%CI 0.5-0.85, I2= 2%
Bruin 2023	RR= 0.66, 95% CI 0.52 - 0.85 I2=0

Fig. 4: Summarizes the results of meta-analyses on the effectiveness of the influenza vaccine in preventing ILI and LCI, stillbirth, congenital anomalies, spontaneous abortion, preterm birth, small for gestational age (SGA), and low birth weight (LBW).

Discussion

This study systematically reviewed 11 meta-analyses on the effectiveness and efficacy of the influenza vaccine in pregnant women and its impact on infants under 6 months. No evidence was found of an elevated risk of fetal death, congenital anomalies, spontaneous abortion, preterm birth, SGA, and LBW in babies whose mothers were vaccinated. The review of the overlap of studies showed a high CCA. However, when the studies were compared pairwise, some comparisons had zero overlap.

Vaccine Effectiveness in Mothers

Influenza vaccination was associated with a 44–53% reduction in (LCI) cases among pregnant women. This efficacy was established through a meta-analysis of clinical trials. In all these studies, the vaccine was effective in reducing LCI cases, except for one study where the RR was 0.7 (95% CI 0.45-1.11) due to changes in the time and duration of influenza and continuous antigenic changes in viruses in subtropical and tropical regions (6). In contrast, influenza vaccination did not result in a statistically significant reduction in ILI. This finding may reflect non-differential misclassification of influenza infections among patients presenting with ILI or other RI (8). Diagnostic challenges inherent to ILI and RI likely lead to under-detection or misclassification of true influenza cases, biasing vaccine effectiveness estimates toward the null. The findings of our study regarding the variable effectiveness of influenza vaccines against LCI versus ILI resonate with evidence from other populations, including older adults. For instance, a recent systematic review and network meta-analysis involving over 200,000 older adults demonstrated that while influenza vaccines effectively reduce LCI incidence, the precision of their effect on ILI and other respiratory outcomes remains uncertain, largely due to limited data and heterogeneity in study designs and populations (64). Similarly, our results emphasize that diagnostic challenges and misclassification in ILI cases complicate the assessment of vaccine effectiveness, a phenomenon also observed in older adults.

Vaccine Effectiveness in Infants

In 2014, a clinical trial study (37) showed that the influenza vaccine in pregnant women was 29% and 62% effective in reducing ILI and LCI cases in infants, respectively. Prospective studies, on the other hand, have reported significant reductions in LCI cases and reduced protection against ILI. The meta-analysis of observational studies revealed a 48% reduction in the risk of laboratory-confirmed influenza and a 72% reduction in hospitalization rates (22). Similarly, a meta-analysis of clinical trials showed a 38% reduction in the likelihood of infant LCI (22). Notably, these clinical trials were primarily conducted in resource-limited settings such as South Africa and Bangladesh (1, 6, 37) where influenza circulation can be persistent. This contrasts with observational studies from the United States and Europe, where influenza seasons are distinctly concentrated during autumn and winter. Consequently, the timing of vaccine administration remains a critical factor influencing its overall effectiveness (65).

The impact of maternal influenza vaccination on fetal death, congenital anomalies, and spontaneous abortion

Overall, the reviewed evidence did not indicate an increased risk of these outcomes following vaccination. Specifically, the meta-analysis by Bratton et al (26) identified a significant protective association between maternal influenza vaccination and stillbirth. This protective effect is likely mediated by the prevention of influenza-induced systemic inflammation and infection, which are known risk factors for adverse fetal outcomes. Other meta-analyses reported risk reductions of 20% (20) and 16% (27), respectively. However, residual confounding cannot be ruled out in these observational studies; therefore, the results should be interpreted with caution. Future large-scale clinical trials are needed to provide more definitive evidence regarding the impact of maternal influenza vaccination on stillbirth and spontaneous abortion.

Most systematic reviews examining the association between maternal influenza vaccination and congenital anomalies have reported no significant increase or decrease in risk when comparing vaccinated and unvaccinated populations. However, one meta-analysis (20), found a slight increase in the risk of congenital anomalies associated with H1N1 vaccination during pregnancy (OR = 1.14, 95% CI 1.01–1.29; $I^2 = 0$). In this study, cardiac anomalies were the most common type of congenital anomaly reported. Nevertheless, these results should be interpreted with caution because most included studies were observational and may be subject to various biases and errors. Furthermore, the overall meta-analytic estimate was heavily influenced by a single study (29), which accounted for approximately 71.8% of the total weight, thereby limiting the power and generalizability of the conclusions.

This disproportionate weighting indicates that the overall meta-analytic estimate was predominantly driven by the findings of this single study, thereby increasing susceptibility to any inherent methodological limitations or biases present within it. Such a reliance on one study can compromise the validity and robustness of the pooled results, as potential confounding factors or systematic errors in that study may disproportionately influence the combined outcome. Consequently, the certainty and generalizability of the evidence derived from the meta-analysis were limited, precluding definitive conclusions regarding the association between maternal H1N1 vaccination and congenital anomalies. To enhance the evidentiary strength, further high-quality, large-scale prospective studies with rigorous methodological designs and diverse populations are warranted to more accurately elucidate the safety profile of H1N1 vaccination during pregnancy.

Effects of Maternal Influenza Vaccination on Preterm Birth, SGA, and Low Birth Weight

Except for two studies (21, 27), the other studies did not show any decrease or increase in preterm birth and low birth weight due to influenza vaccination of the pregnant mother. Two meta-analysis studies reported a reduction in preterm births (27) and a reduction in low birth weight (21). Clinical trial studies have reported different outcomes due to different definitions of the intervention and

control groups, which could affect the results of meta-analyses in this field. For example, clinical trial studies from Bangladesh (37) and Nepal (6) demonstrated that receiving an influenza vaccination during pregnancy positively influenced LBW. In two clinical trial studies (1, 5) from Africa, no correlation was observed between these two variables.

Methodological Considerations

In this study, we assessed the overlap of primary studies for each subject both generally and in pairs. Our general review revealed a high degree of overlap across all studies, particularly in studies on LCI, which exhibited a 50% overlap. Despite this high overlap, the results were largely consistent. For example, regarding the relationship between maternal vaccination and congenital malformations, all meta-analyses consistently found no association. In the context of abortion, one study demonstrated a significant reduction in correlation (27), while others showed no correlation. Upon examining the overlap of studies in pairs, we observed that some studies exhibited no overlapping correlation (23, 27), while others demonstrated high overlap. The observed variation can be attributed to the differing inclusion criteria; for example, the study included all inactivated vaccines (27), whereas other focused exclusively on the H1N1 vaccine (20).

Limitations and Future Directions

This review provides a thorough and current summary of the evidence concerning the efficacy and safety of influenza vaccination in pregnant women and their infants. It uses a rigorous search strategy, quality assessment criteria, and synthesis of multiple outcomes related to influenza vaccination during pregnancy. However, this overview also has several limitations that need to be considered. One important limitation is that the reliability of the findings depends on the quality and validity of the primary studies and systematic reviews included, which vary widely across the evidence base. Notably, the included systematic reviews encompass both observational studies and clinical trials, yet these designs differ in their methodological strengths and vulnerabilities—particularly in terms of causal inference and susceptibility to bias. Another limitation is the heterogeneity among the included systematic reviews with respect to their methods, inclusion criteria, measured outcomes, and quality assessments, which may affect the comparability and consistency of results. A further limitation is the high CCA, indicating that many primary studies are duplicated across the systematic reviews, potentially introducing bias and overestimating the intervention's effect, as some studies may exert disproportionate influence. Therefore, healthcare professionals, decision-makers, and stakeholders should interpret and apply the findings of this overview with caution, considering both the type and quality of the underlying evidence.

Conclusion

Influenza vaccination in pregnant women is effective in reducing lower respiratory tract infections (LCI), thereby potentially lowering healthcare costs for both the health system and pregnant women. Importantly, no increase in serious adverse events has been reported.

To enhance the accuracy of future studies, it is essential to standardize the diagnostic criteria and classification of respiratory infections. This standardization will facilitate a more precise assessment of the true effectiveness of influenza vaccines. Furthermore, it is crucial to encourage and support additional research to address existing gaps, particularly focusing on diverse geographical regions and varying influenza seasons. This approach will ensure robust evidence for all outcomes and help refine vaccination strategies.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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