Title	Interventions to increase the uptake of seasonal influenza vaccination among pregnant women: A systematic review
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Citation	Vaccine, 2016, v. 34, n. 1, p. 20-32
Issued Date	2016
URL	http://hdl.handle.net/10722/228236
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Interventions to increase the uptake of seasonal influenza vaccination among pregnant women: A systematic review

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Word count (abstract): 279

Word count (main text): 4,385

Running head: Influenza vaccination and pregnancy

Highlights

- This is the first review to identify and evaluate interventions aimed at increasing maternal influenza vacine uptake.
- There is little high-quality evidence from randomized controlled trials to guide public health recommendations on improving maternal influenza vaccination rates.
- Based on the existing evidence, clinicians should provide influenza education pamphlets to pregnant women accompanied by a verbalized statement on the benefits of maternal vaccination to newborns.
- High-quality RCTs are needed to further evaluate interventions to successfully improve maternal influenza vaccination rates.

ABSTRACT

Background: Pregnant women and their infants under 6 months of age infected with influenza have a high risk of serious morbidity and mortality. Influenza vaccine during pregnancy offers 3-for-1 benefits to pregnant women, fetuses and newborn infants. Current vaccination uptake rates during pregnancy, however, are often lower than other high-risk groups and the general population.

Methods: We systematically reviewed evidence on the effectiveness of interventions to improve influenza vaccination coverage in pregnant women. Risk differences (RDs) were calculated from the included studies.

Results: Eleven studies were included in the review, of which four were randomized controlled trials (RCTs). Three cohort studies assessed provider-focused interventions while four RCTs and one cohort study evaluated pregnant women-focused interventions. Two cohort studies and a prospective intervention study assessed the effectiveness of bundled interventions. No study solely assessed the effectiveness of interventions to enhance access to influenza vaccination. One moderate quality RCT showed that an influenza pamphlet, with or without a verbalized benefit statement, improved the vaccination rate (RD = 0.26; RD = 0.39). The other reviewed RCTs showed discordant results, with RDs ranging from -0.15 to 0.03. Although all observational studies significantly improved vaccination rates (RDs ranged from 0.03 to 0.44), the quality of the evidence varied.

Conclusions: There is a lack of effective interventions to increase the influenza vaccination rate in pregnant women. Based on the existing research, we recommend

that clinicians provide influenza pamphlets to pregnant women with a verbalized statement about the benefits of influenza vaccine to newborns. Further high-quality RCTs are needed to develop successful maternal influenza vaccination programs. Increased clarity in reporting the content of interventions would help to improve the comparability and generalizability of the published studies.

1. Background

Morbidity and mortality due to influenza infection is disproportionately higher in pregnant women and infants under six months old than in the general population (1-5). Pregnant women infected with influenza are much more likely to experience serious illness, and the infection may have an adverse impact on fetal growth and development (6,7). In addition, when compared with other age groups, infants under 6 months of age infected with influenza have higher rates of severe influenza-related complications, resulting in excess hospitalizations (8-14), prolonged stays in the intensive care unit (10), and higher mortality rates (15).

Inactivated influenza vaccine is safe at any stage of pregnancy (16-20) and it provides substantial protection to pregnant women, unborn fetuses (21) and infants up to 6 months old (17). Early infant protection is important since the current influenza vaccine is not licensed for this age group because of its low immunogenicity in newborns (22). In view of this triple protection provided by influenza vaccine, the World Health Organization (WHO) now recommends that pregnant women have the highest priority for vaccination in national seasonal influenza vaccination programs (2). However, seasonal influenza vaccination rates among pregnant women have not increased substantially (23-25) and are often much lower than national targets, other high-risk groups, and the general population (26-28). In an era of increasing threats from both seasonal and pandemic influenza, effective interventions that can enhance vaccination uptake among pregnant women need to be identified.

Researchers have reviewed strategies to improve influenza vaccination in the general population (29,30), healthcare workers (31), those over 60 years of age (32-34), and

children (35,36). A recent review summarized the factors associated with vaccine uptake in pregnant women (37). Although some recent studies have evaluated the effectiveness of various interventions in improving maternal influenza immunization rates, to our knowledge no systematic review of these interventions has been conducted. Thus, we systematically reviewed the literature to identify and evaluate interventions used to improve immunization uptake among pregnant women. This review will present the best available evidence that can be used by public health policy makers and obstetric health care providers to develop effective vaccination programs that can increase influenza vaccine uptake in this high-risk group.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (38).

2.1. Search strategy

We systematically searched electronic databases including PubMed, MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2014, issue 8), containing the Cochrane Acute Respiratory Infections Group's Specialized Register. Since annual influenza vaccination was first recommended in any trimester in the US in May 2004 (39), we included articles published from May 2004 to August 2014. The following search terms were used in all fields regardless of publication date and language:

#1: vaccin*(truncation) OR immuni*

#2: influenza* OR flu

#3: preg* OR matern*

To identify further studies of interest, we also performed a manual search of the reference lists of relevant publications.

2.2. Eligibility criteria

We included all original research articles that reported on interventions to increase influenza vaccine uptake during pregnancy. Studies comparing the immunization rate with either a historical control group during different observation seasons or a concurrent control group during the same observation season were considered. The study outcome measure assessed was the influenza vaccination rate, confirmed by either medical records or self-reported data. Study protocols and conference abstracts were excluded.

2.3. Study selection

Two reviewers (VW and KL) independently screened all study titles identified by the initial search and subsequently reviewed the abstracts of potentially relevant studies. If the studies described interventions to enhance maternal influenza vaccine uptake, the reviewers performed a full review. The reference lists of included studies were reviewed for additional studies that might have been missed in the initial search. The relevance and eligibility of each study was determined through consensus discussions between the two reviewers.

2.4. Data analysis

Standardized study effects were reported as the ratio of the odds to be vaccinated in the intervention group compared with the standard care group and risk differences (RD) and 95% confidence intervals (CI) were calculated (40). Recalculated RDs prior to adjustment for confounders and 95% CIs were reported along with the results reported in the studies. And if available, a list of all confounders adjusted for in the data analysis and the differences in the vaccination rate after adjustment were described.

To enhance the generalizability of our review results, we used the intervention classification guidelines from the Task Force on Community Preventive Services (41). They identified three types of interventions to enhance uptake of universally recommended vaccinations: (1) interventions to overcome provider and system barriers (i.e., physician-focused interventions), (2) interventions to increase demand for vaccination (i.e., pregnant woman-focused interventions), and (3) interventions to enhance vaccine access.

Given the broad heterogeneity in study design and types of interventions, we did not conduct a quantitative pooled analysis.

2.5. Evidence quality assessment

Two reviewers (VW and KL) independently evaluated the methodological quality of the included studies. The Cochrane Collaboration method, a well-validated and reliable domain-based evaluation tool, was used for the risk of bias assessment of randomized controlled trials (42). The risk of bias was assessed in six domains:

sequence generation, allocation concealment, blinding, handling of incomplete outcome data, selective outcome reporting, and "other" potential threats to validity. A 'risk of bias summary' showing the quality assessment of all included studies was generated using RevMan (43). For each outcome, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria were also used to assess the risk of bias (42). The GRADE criteria were adopted in addition to the Cochrane Collaboration tool because these criteria, take into account the consistency, directness, and precision of the results in addition to the risk of bias. The quality rating of randomized trials begins as high. The quality of evidence of each study is then downgraded to moderate, low or very low after considering the severity of the risk of bias, consistency, directness, and precision of the results.

Since both the "risk of bias" tool and GRADE criteria were not developed with observational studies in mind, these studies were assessed separately using the Newcastle-Ottawa Scale (42). Studies were appraised across three categories: (1) selection of cohorts (4 criteria), (2) comparability of cohorts (1 question), and (3) ascertainment of the exposure of interest for cohort studies (3 questions). All criteria receive a maximum score of "one star" except for comparability of study groups where an additional star may be allocated for the control of confounding factors. The Coding Manual and Assessment Scale of Newcastle-Ottawa scale are described in the Supplementary File.

3. Results

155 3.1. Search results

156 The initial search yielded 2,941 published articles, from which 1,376 duplicate papers
157 were removed (see Figure 1). After examining the titles and abstracts, irrelevant
158 articles such as interventions with non-pregnant populations, studies with no
159 intervention components, commentaries, and guidelines and recommendations, were
160 removed. Finally, twenty-five of the remaining 1,565 articles were retrieved based on
161 their title and abstract content. After full review, we excluded 14 papers because they
162 included an ineligible population (n=5) or outcome (n=4), did not have a standard
163 care group for comparison (n=4), or were a review article (n=1), (44-57) (see
164 Supplementary File). No additional articles were identified from the reference lists of
165 the relevant publications and 11 studies that met the selection criteria were reviewed.

166 3.2. Study characteristics

167 *3.2.1. Study design*

168 The 11 included studies, which involved 16 intervention components, were all
169 published between 2007 and 2014 (Table 1). Nine studies were conducted in the
170 United States (US) (58-61,63,65-68), one in Canada (64) and one in Australia (62).

171 *3.2.2. Participants*

172 The sample sizes varied from 126 to 21,292 participants, with a mean of 2,531.
173 Pregnant women were recruited from antenatal outpatient clinics, primary care
174 outpatient clinics, tertiary hospitals and multispecialty medical organization. In all but
175 one historical control study (64) a priori sample size calculations were performed.

Apart from two studies that recruited postnatal participants (62,68), all studies included only pregnant women who had antenatal medical appointments (58-61,63-67). The characteristics of participants varied across the studies. They ranged from 14 to 50 years old and were Hispanic, Caucasian, African-American, Asian or multiracial; four studies did not provide this information (63,64,66,67).

3.2.3. Types of interventions

All included studies involved at least one of the three previously identified intervention components with most studies (n=8) using only one component (58-61,63-66). Three studies used provider-based interventions only (63,65,66), five studies used pregnant woman-focused interventions only (58-61,64), and three studies used a combination of the three types of intervention components (62,67,68) (Table 2).

3.2.4. Use of standard care group

Standard care varied and included routine automated telephone appointment reminders (58), text messages about general preventive health in pregnancy (60), a standard vaccine information sheet (61) and routine antenatal care (58,59,61-68).

3.2.5. Outcome measures

Six studies ascertained the vaccination status through medical records from hospital databases (58,60,63,65-67), four studies used self-reported data (61,62,64,68), and one study used a combination of self-reported data and medical records (59).

196 3.3. Critical appraisal

197 *3.3.1. Risk of bias (internal validity)*

198 *3.3.1.1. Randomized controlled trials*

199 The evidence quality of one RCT was "high" (60), two were "moderate" (58,59) and
200 one was "low" (61) (see Table 3). Random sequence generation was done in three of
201 the four RCTs (58-60) and the other RCT did not report this information (61).
202 Allocation concealment was judged as adequate in only one study (60) while others
203 did not report this clearly (58,59,61). No RCTs blinded the participants due to the
204 nature of the intervention, and only two RCTs blinded the outcome assessors to the
205 treatment allocation (59,60). In three studies, the proportion of missing outcomes
206 likely resulted in negligible bias of the effect estimates (58-60). In one RCT targeting
207 minority women, however, less than one-half of the participants completed follow-up
208 (61). Study protocols were only available for two (59,60) of the four RCTs (58-61).
209 Both of these studies included all of the pre-specified primary outcomes (i.e., the
210 vaccination rate among pregnant women). Volunteer bias may have been a risk in two
211 included RCTs since only a subset of eligible participants had been recruited (59,61).
212 One study reported a dropout rate of 54% at the 30-day postpartum follow-up (61).
213 However, other than educational attainment there were no significant differences in
214 the baseline characteristics of participants retained in the study and those lost to
215 follow-up. A priori sample size calculation was performed in all RCTs. Meharry et al.
216 (59), Moniz et al. (60) and Stockwell et al. (58) Three studies had a sufficient number
217 of participants in both arms to achieve 80% power (58-60), while one study did not
218 meet the required sample size (61). It should also be noted that although adequately

powered, two studies had a small number of participants, with less than 50 per group in one study (59) and around 100 per group in another (60). The risk of bias of all RCTs is summarized in Figure 2.

3.3.1.2. Observational studies

The quality assessment of the seven observational studies is described in Table 4. For all studies, exposure was ascertained from existing interventions implemented to improve influenza vaccination rate among pregnant women; outcome assessment was based on either a medical records or vaccination billing record an in-person interview by the research staff. The response rates of questionnaires in two studies were low (64,68). Only one study compared the confounders between the different participant groups (65). The overall quality scores for the observational studies ranged from 3 to 7 out of a maximum of 9.

Significant changes in the vaccination rate of study participants in some observational studies may have been affected by changes in national vaccination recommendations for pregnant women over the years of those studies (64-67). Although the Advisory Committee on Immunization Practices (ACIP) in the US officially recommended maternal influenza vaccine in 1997, the recommendation was originally for vaccine administration in the second and third trimester only. In 2004, this recommendation was modified to include vaccination in any trimester (39) and Canada (69) and Australia (70) issued similar recommendations in 2007 and 2008, respectively. In four studies, the standard care groups included pregnant women that were recruited prior to 2004 in the US and prior to 2007 in Canada and the intervention groups included

participants recruited after the change in the vaccination recommendations (64-67). Thus, in these studies, the groups observed over time may not be comparable.

3.4 Effect of various interventions in increasing influenza vaccine uptake

3.4.1. Provider-focused interventions

Provider-focused interventions are those that aim to reduce missed opportunities for influenza vaccination among pregnant women. Common strategies include notifying providers about the influenza vaccination status of pregnant women, setting up standing orders authorizing nursing staff to administer the vaccine without a medical consultation, giving provider feedback by reporting the clinic's or department's influenza vaccination rate, and providing education to improve the knowledge and attitudes of healthcare staff toward influenza vaccination in pregnancy. All studies assessing the effect of provider-focused interventions on vaccination rates were cohort studies.

Two studies involved delivering either electronic reminders (63) or manually attaching notifications to antenatal records (65). Both studies compared provider reminders and recall systems alone with historical controls and reported a significant increase in the influenza vaccination rate. The RD generated from Klatt et al. (63) was 0.19 (95% CI 0.14 to 0.25) while that from Sherman et al. (65) was 0.37 (95% CI 0.32 to 0.41). Mouzoon et al. (66) evaluated the combined effect of implementing standing orders, giving provider feedback, and provider education on vaccination rates over six influenza seasons from 2003–04 to 2008–09. The RD increased with each successive influenza season ranging from 0.19 (95% CI 0.17 to 0.20) to 0.44 (95% CI 0.42 to 0.46).

3.4.2. Pregnant woman-focused interventions

Interventions to increase demand for influenza vaccination aim to enhance the self-initiation and motivation of pregnant women to seek out influenza vaccine. Education and promotion materials targeting pregnant women can be disseminated by mass media campaigns, via the Internet, through posters and leaflets, through lectures and workshops, and by personalized reminder and recall systems. Five (45%) studies (58-61,64) assessed the effect of pregnant woman-focused interventions alone while two studies also included other intervention components (62,68). Four of the five studies assessing the sole effect of pregnant woman-focused interventions were RCTs (58-61), and the other was a historical control study (64).

Stockwell et al. (58) assessed the combined effect of providing reminders and education via mobile phone text messages to increase seasonal influenza vaccination uptake among urban, low-income pregnant women. Although, the complete case analysis showed an insignificant increase [RD = 0.03, 95% CI -0.03 to 0.08] in the vaccination rate, after adjustment for gestational age and the number of clinic visits, participants in the intervention group were 30% more likely to be vaccinated [AOR = 1.30, 95% CI 1.003 to 1.69] and to be vaccinated early in the 3rd trimester [AOR = 1.88, 95% CI 1.12 to 3.15].

Education has been shown to be effective in changing various health behaviors in pregnant women (71-73). Four studies assessed the effectiveness of influenza vaccination education. Frew et al. (61) found that neither gain- nor loss-framed messages increased the likelihood of vaccination in minority women [RD = -0.14, 95% CI -0.33 to 0.06 and RD = -0.15, 95% CI -0.33 to 0.05, respectively]. Moniz et

al. (60) found that 12 weekly electronic text messages about the importance of influenza vaccination during pregnancy did not significantly increase influenza vaccine uptake [RD = 0.02, 95% CI -0.11 to 0.14]. Conversely, Meharry et al. (59) found a significant increase in vaccination uptake with an education pamphlet alone [RD = 0.26, 95% CI 0.07 to 0.45] and when combined with a verbalized benefit statement [RD = 0.39, 95% CI 0.21 to 0.57]. In the observational studies, Yudin et al. (64) also found that an education pamphlet significantly increased seasonal influenza vaccine uptake [RD = 0.38, 95% CI 0.25 to 0.50].

3.4.3. Interventions to enhance access to influenza vaccination

Interventions to enhance access to the influenza vaccine aim to reduce barriers that pregnant women may encounter, such as the cost and availability of the vaccine. Interventions in this category include providing influenza vaccine for free or at a reduced cost to all pregnant women, extending vaccination services to more locations and/or with longer hours, and ensuring adequate stock of the vaccine. We found no studies that implemented interventions solely focused on enhancing access to the vaccine. Three of the reviewed studies included strategies to enhance vaccine access along with other components, such as pregnant woman-focused or provider-focused strategies (62,67,68). Two were cohort studies (62,67) and one was a prospective intervention study (68). These studies are discussed in the next section on bundled interventions.

3.4.4. Bundled interventions

McCarthy et al. (62) found that implementing an education campaign that involved putting provider reminders in the antenatal progress notes, providing influenza vaccination education to health care providers, developing an information brochure on influenza immunization for pregnant clients, and increasing vaccine stocks significantly increased the influenza vaccination rate among pregnant women [RD = 0.10, 95% CI 0.01 to 0.19]. Similarly, Panda et al. (68) found that implementing a vaccine promotion intervention that included education and reminders to both providers and pregnant women and the provision of vaccine at antenatal clinics significantly increased influenza vaccine uptake [RD = 0.12, 95% CI 0.07 to 0.17]. Ogburn et al. (67) evaluated two combined interventions over two consecutive influenza seasons. In 2003-04, they provided education to providers and extended locations for vaccination service and in 2004-05, standing vaccination orders were added. The increase in vaccination after the 2003-04 influenza season was minimal [RD = 0.03, 95% CI 0.00 to 0.05] but after standing orders were implemented, the vaccination rate increased substantially [RD = 0.36, 95% CI 0.30 to 0.43].

4. Discussion

4.1. Summary of evidence

Our analysis reveals that there are only 11 studies assessing the effectiveness of interventions that promote influenza vaccination in pregnant women. Only one moderate quality RCT showed that providing an education pamphlet, with or without a verbalized benefit statement, improved the influenza vaccination rate among

pregnant women. Three other RCTs did not significantly improve vaccination rates in the intervention groups. All of the observational studies did show significant increases in influenza vaccination rates, but the quality of evidence varied.

Researchers in five studies reported a statistically significant difference in the vaccination rate of more than 0.20 (59,64-67), three studies showed a statistically significant difference of 0.10 to 0.19 (62,63,68), and three RCTs had no significant effect of the interventions (58,60,61). In general, higher quality studies showed a decrease in statistical significance and effect size. The overall quality and amount of evidence for the effectiveness of strategies to increase influenza vaccination uptake among pregnant women varied and the risks of bias in the observational studies is substantial. RCTs typically provide the best evidence for the efficacy of interventions. Unfortunately, the interventions in three of the four RCTs included in this review failed to increase the vaccination rate, even though two were adequately powered (58-60).

The quality of evidence was low among observational studies. Three cohort studies that showed a positive effect of provider-focused interventions (63,65,66) had relatively high quality scores. In particular, interventions involving provider reminders and/or recall only were associated with an increase in maternal vaccination uptake (63,65). Although the evidence should be interpreted with caution given the risk of bias, studies promoting vaccination in other target groups support this finding (71-73). In addition, an extensive systematic review found that provider reminders and recall systems are effective in increasing childhood vaccinations, influenza vaccinations among children and adults, and adult hepatitis B, pneumococcus, and tetanus vaccine uptake (30). Provider attitudes and practices matter because studies

show that HCPs have a substantial influence on decisions about influenza vaccination by pregnant women (28,37,74,75). However, at present there is insufficient high-quality evidence from more rigorous study designs to draw firm conclusions about the effects of provider-focused interventions.

The quality of evidence in studies assessing the effect of pregnant woman-focused interventions varied from very low to high with inconsistent results among the reviewed RCTs (58-61). A cohort study with a low-quality score also supports the effectiveness of pregnant woman-focused interventions. Although interventions such as text messages were well received by pregnant women, they failed to increase the actual vaccination rate (60). Using text messages to provide education and reminders has been shown effective in promoting human papillomavirus vaccination among children (76), hepatitis vaccination among travelers (77) and influenza vaccination in children (78). However, further studies are required to determine their effect on pregnant women. Moniz et al. (60) suggested that the content of the message might influence its effectiveness. Individualized messages using direct quotes from HCPs who unequivocally state the importance of maternal influenza vaccination and address vaccine barriers can be further investigated (60). Given the inconsistency of study findings and the low quality of evidence, we were unable to assess the specific effects of providing influenza-related education and/or advice to pregnant women. Therefore, more high-quality RCTs are necessary to assess the impact of interventions that directly target pregnant women.

The studies in this review primarily focused on interventions targeting either providers or pregnant women. Interventions aimed at increasing access to influenza vaccination, such as on-site influenza vaccines for free or at a reduced cost, were not

found. With respect to increasing access to the vaccine, the reviewed studies included only three intervention components as part of bundled interventions: increasing vaccine stocks (62), increasing the number of locations to get the vaccine (67,68), and implementing standing orders for vaccination (67). Although the provision of free influenza vaccine has been an effective strategy to improve vaccination coverage in other high-risk groups and the general population (79-81), no study has assessed its effectiveness in pregnant women, who have different knowledge of and attitudes toward vaccination (37).

Three studies, all with low to medium quality scores, evaluated the effectiveness of bundled interventions (62,67,68). All comprehensive bundled interventions demonstrated statistically significant increases in vaccination rates in pregnancy. However, unlike findings from studies in other populations (31,34), the magnitude of increase from bundled interventions was not higher than that from single component interventions.

Higher quality and more methodologically rigorous studies were less likely to show significant improvements in influenza vaccine uptake when compared with studies of lower quality. While most of the reviewed studies were conducted over a single influenza season, Mouzoon et al. (66) demonstrated that sustained efforts over time could lead to increasingly higher vaccination uptake rates. Thus, the sustained impact of influenza vaccine promotion interventions should be explored in future studies.

The effectiveness of influenza vaccination programs depends on their content. However a clear description of the content of many interventions, such as the wording used in pamphlets and the timing of the intervention, was not included in most study

401 reports. Increased clarity in reporting what specific provider and pregnant woman-
402 focused interventions were assessed and when they were implemented would help
403 both researchers and practitioners to understand whether the effectiveness of a given
404 strategy differs according to the specific content of the intervention. The reviewed
405 studies provide some evidence that targeted interventions can improve influenza
406 vaccine uptake among pregnant women across a wide range of settings, gestational
407 ages, and socio-demographic backgrounds. The review findings are relevant to
408 different end users, including HCPs and public health administrators, to guide the
409 formulation of maternal vaccination programs. However, given the heterogeneity of
410 the included studies, the broad range of intervention strategies and the limitations of
411 the resulting evidence, there is insufficient evidence to give definitive
412 recommendations for practice.

413 4.2. Strengths and limitations

414 Although the majority of studies reported significant increases in influenza vaccine
415 uptake in pregnant women after the interventions, we did identify some limitations in
416 the reviewed studies. First, the majority of included studies were non-randomized
417 interventions. Most were adequately powered but susceptible to bias and thus provide
418 only indirect evidence of effectiveness. One of the included RCTs did not achieve an
419 adequate number of participants needed to achieve 80% power. As previously noted,
420 changes in national vaccination policies for pregnant women cast doubt on the
421 similarity of the standard care and intervention groups in some observational studies,
422 a criterion that is not included in the Newcastle-Ottawa scale. Moreover, it was not
423 possible to perform a meta-analysis because of the heterogeneity of the interventions
424 and study methods. Also, most of the reviewed studies were done in the US, and the

findings may not be generalizable to other populations. Although our review attempted to standardize intervention into distinct components to increase their comparability (i.e., provider-focused, pregnant-women focused, or bundled), some studies included more than one component, which complicated comparisons between interventions. Furthermore, there were different implementation strategies for similar intervention components in different settings. For example, provider- and/or pregnant woman-focused reminders may use different wording in different studies. Lastly, publication bias may also be a concern in our review. Studies not demonstrating an increase in vaccination uptake may be less likely to be published. We assessed the publication bias graphically using a Begg's funnel plot (82). However, since there were only 11 included studies, the power of the test for funnel plot asymmetry was too low to distinguish chance from real asymmetry. Nevertheless, we systematically searched the WHO clinical trial portal (www.who.int/trialsearch), which contains the registration data from trial registries around the world, with the same search terms we used for this review. In addition to our included studies, we found only one registered pilot study to assess the effectiveness of text message reminders on maternal influenza vaccination uptake (#ACTRN12613000553774). No other registered studies were found.

5. Conclusions

Influenza vaccine in pregnancy is effective against influenza infection and lowers the risk of influenza-related complications and mortality in both pregnant women and their newborns. This review highlights the need for well-designed trials of various

single-component or bundled interventions that can be incorporated into a comprehensive antenatal vaccination programs. In the meantime, the best available evidence suggests that to increase vaccination rates, HCPs should inform all pregnant women about the benefits of vaccination, provide positive vaccination recommendations, use some type of reminder system to target unvaccinated pregnant women, and make influenza vaccine easily accessible. Given the well-documented benefits of influenza vaccine for pregnant women, establishing cost-effective interventions to increase vaccine uptake should be a public health priority.

References

1. World Health Organization. WHO Public Health Research Agenda For Influenza. Geneva, Switzerland: WHO, 2010.
2. World Health Organization (WHO). Vaccines against influenza WHO position paper - November 2012. Weekly Epidemiological Record. 2012;87(47):461-476.
3. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. American Journal of Epidemiology. 1998;148(11):1094-1102.
4. Mullooly JP, Barker WH, Nolan TF, Jr. Risk of acute respiratory disease among pregnant women during influenza A epidemics. Public Health Reports. 1986;101(2):205-211.
5. Callaghan WM, Chu SY, Jamieson DJ. Deaths from seasonal influenza among pregnant women in the United States, 1998-2005. Obstetrics and Gynecology. 2010;115(5):919-923.
6. Cox S, Posner SF, McPheeters M, Jamieson DJ, Kourtis AP, Meikle S. Hospitalizations with respiratory illness among pregnant women during influenza season. Obstetrics and Gynecology. 2006;107(6):1315-1322.
7. Mendez-Figueroa H, Raker C, Anderson BL. Neonatal characteristics and outcomes of pregnancies complicated by influenza infection during the 2009 pandemic. American Journal of Obstetrics and Gynecology. 2011;204(6, Supplement):S58-S63.
8. Bender JM, Ampofo K, Gesteland P, Sheng X, Korgenski K, Raines B, et al. Influenza virus infection in infants less than three months of age. Pediatric Infectious Disease Journal. 2010;29(1):6-9.
9. Coffin SE, Zaoutis TE, Rosenquist AB, Heydon K, Herrera G, Bridges CB, et al. Incidence, complications, and risk factors for prolonged stay in children hospitalized with community-acquired influenza. Pediatrics. 2007;119(4):740-748.
10. Ampofo K, Gesteland PH, Bender J, Mills M, Daly J, Samore M, et al. Epidemiology, complications, and cost of hospitalization in children with laboratory-confirmed influenza infection. Pediatrics. 2006;118(6):2409-2417.
11. Izurieta HS, Thompson WW, Kramarz P, Shay DK, Davis RL, DeStefano F, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. New England Journal of Medicine. 2000;342(4):232-239.
12. Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Jr., Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. New England Journal of Medicine. 2000;342(4):225-231.
13. Griffin MR, Walker FJ, Iwane MK, Weinberg GA, Staat MA, Erdman DD. Epidemiology of respiratory infections in young children: insights from the new vaccine surveillance network. Pediatric Infectious Disease Journal. 2004;23(11 Suppl):S188-192.
14. Nelson EA, Ip M, Tam JS, Mounts AW, Chau SL, Law SK, et al. Burden of influenza infection in hospitalised children below 6 months of age and above in Hong Kong from 2005 to 2011. Vaccine. 2014; 32(49):6692-6698.
15. Bhat N, Wright JG, Broder KR, Murray EL, Greenberg ME, Glover MJ, et al. Influenza-associated deaths among children in the United States, 2003-2004. New England Journal of Medicine. 2005;353(24):2559-2567.
16. Munoz FM. Safety of influenza vaccines in pregnant women. American Journal of Obstetrics and Gynecology. 2012;207(3, Supplement):S33-S37.

17. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. New England Journal of Medicine. 2008;359(15):1555-1564.
18. France EK, Smith-Ray R, McClure D, Hambidge S, Xu S, Yamasaki K, et al. Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants. Archives of Pediatrics and Adolescent Medicine. 2006;160(12):1277-1283.
19. Chambers CD, Johnson D, Xu R, Luo Y, Louik C, Mitchell AA, et al. Risks and safety of pandemic h1n1 influenza vaccine in pregnancy: birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants. Vaccine. 2013;31(44):5026-5032.
20. Louik C, Ahrens K, Kerr S, Pyo J, Chambers C, Jones KL, et al. Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: exposure prevalence, preterm delivery, and specific birth defects. Vaccine. 2013;31(44):5033-5040.
21. Adedinsewo DA, Noory L, Bednarczyk RA, Steinhoff MC, Davis R, Ogbuanu C, et al. Impact of maternal characteristics on the effect of maternal influenza vaccination on fetal outcomes. Vaccine. 2013;31(49):5827-5833.
22. Groothuis JR, Levin MJ, Rabalais GP, Meiklejohn G, Lauer BA. Immunization of high-risk infants younger than 18 months of age with split-product influenza vaccine. Pediatrics. 1991;87(6):823-828.
23. Meharry PM, Colson ER, Grizas AP, Stiller R, Vazquez M. Reasons why women accept or reject the trivalent inactivated influenza vaccine (TIV) during pregnancy. Maternal & Child Health Journal. 2013;17(1):156-164.
24. Henninger M, Naleway A, Crane B, Donahue J, Irving S. Predictors of seasonal influenza vaccination during pregnancy. Obstetrics and Gynecology. 2013;121(4):741-749.
25. Tarrant M, Wu KM, Yuen CY, Cheung KL, Chan VH. Determinants of 2009 A/H1N1 influenza vaccination among pregnant women in Hong Kong. Maternal and Child Health Journal. 2013;17(1):23-32.
26. Centers for Disease Control and Prevention (CDC). Influenza vaccination coverage among pregnant women--United States, 2012-13 influenza season. Morbidity & Mortality Weekly Report. 2013;62(38):787-792.
27. Privileggio L, Falchi A, Grisoni ML, Souty C, Turbelin C, Fonteneau L, et al. Rates of immunization against pandemic and seasonal influenza in persons at high risk of severe influenza illness: a cross-sectional study among patients of the French Sentinelles general practitioners. BMC Public Health. 2013;13:246.
28. Yuen CYS, Fong DYT, Lee ILY, Sing C, Siu ES-M, Tarrant M. Prevalence and predictors of maternal seasonal influenza vaccination in Hong Kong. Vaccine. 2013;31(45):5281-5288.
29. Lau D, Hu J, Majumdar SR, Storie DA, Rees SE, Johnson JA. Interventions to improve influenza and pneumococcal vaccination rates among community-dwelling adults: a systematic review and meta-analysis. The Annals of Family Medicine. 2012;10(6):538-546.
30. Jacobson Vann JC, Szilagyi P. Patient reminder and patient recall systems to improve immunization rates. Cochrane Database Systematic Review. 2005(3):Cd003941.
31. Hollmeyer H, Hayden F, Mounts A, Buchholz U. Review: interventions to increase influenza vaccination among healthcare workers in hospitals. Influenza Other Respi Viruses. 2013;7(4):604-621.

32. Thomas RE, Russell M, Lorenzetti D. Interventions to increase influenza vaccination rates of those 60 years and older in the community. Cochrane Database Syst Rev. 2010(9):Cd005188.
33. Thomas RE, Russell ML, Lorenzetti DL. Systematic review of interventions to increase influenza vaccination rates of those 60 years and older. Vaccine. 2010;28(7):1684-1701.
34. Ndiaye SM, Hopkins DP, Shefer AM, Hinman AR, Briss PA, Rodewald L, et al. Interventions to improve influenza, pneumococcal polysaccharide, and hepatitis B vaccination coverage among high-risk adults: a systematic review. American Journal of Preventive Medicine. 2005;28(5 Suppl):248-279.
35. Cawley J, Hull HF, Rousculp MD. Strategies for implementing school-located influenza vaccination of children: a systematic literature review. Journal of School Health. 2010;80(4):167-175.
36. Jones Cooper SN, Walton-Moss B. Using reminder/recall systems to improve influenza immunization rates in children with asthma. Journal of Pediatric Health Care. 2013;27(5):327-333.
37. Yuen CY, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women - A systematic review. Vaccine. 2014;32(36):4602-4613.
38. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine. 2009;151(4):264-269, W264.
39. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB, Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report Recommendation Report. 2004; 53(RR-6):1–4
40. Deeks JJ, Higgins JP, Altman DG, on behalf of the Cochrane Statistical Methods Group. Analysing data and undertaking meta-analyses. In: Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. West Sussex, England: John Wiley & Sons Ltd; 2008.
41. Briss PA, Rodewald LE, Hinman AR, Shefer AM, Strikas RA, Bernier RR, et al. Reviews of evidence regarding interventions to improve vaccination coverage in children, adolescents, and adults. The Task Force on Community Preventive Services. American Journal of Preventive Medicine. 2000;18(1 Suppl):97-140.
42. Higgins JPT, Sally G (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011] 2011. Available from: http://handbook.cochrane.org/.
43. Review Manager (RevMan) .Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2008.
44. Keith LA, Sherrod RA. Improving Influenza Immunization Rates Through a Specialized Clinic Review. Journal of Community Health Nursing. 2012;29(3):133-142.
45. Dexter LJ, Teare MD, Dexter M, Siriwardena AN, Read RC. Strategies to increase influenza vaccination rates: Outcomes of a nationwide cross-sectional survey of UK general practice. BMJ Open. 2012;2(3):e000851.
46. Skedgel C, Langley JM, MacDonald NE, Scott J, McNeil S. An incremental economic evaluation of targeted and universal influenza vaccination in pregnant women. Canadian Journal of Public Health Revue Canadienne de Sante Publique. 2011;102(6):445-450.

603 47. Riley M, Galang S, Green LA. The impact of clinical reminders on prenatal
604 care. Family Medicine. 2011;43(8):560-565.
605 48. Walter EB, Hellkamp AS, Goldberg KC, Montgomery D, Patterson B, Dolor
606 RJ. Improving influenza vaccine coverage among asthmatics: A practice-based
607 research network study. Journal of Clinical Outcomes Management. 2008;15(5):227-
608 234.
609 49. Tong A, Biringer A, Ofner-Agostini M, Upshur R, McGeer A. A cross-
610 sectional study of maternity care providers' and women's knowledge, attitudes, and
611 behaviours towards influenza vaccination during pregnancy. Journal of Obstetrics and
612 Gynaecology Canada. 2008;30(5):404-410.
613 50. Wallis DH, Chin JL, Sur DK, Lee MY. Increasing rates of influenza
614 vaccination during pregnancy: a multisite interventional study. The Journal of the
615 American Board of Family Medicine. 2006;19(4):345-349.
616 51. Nichol KL. Improving influenza vaccination rates among adults. Cleveland
617 Clinic Journal of Medicine. 2006;73(11):1009-1015.
618 52. Nichol KL. Improving influenza vaccination rates for high-risk inpatients.
619 American Journal of Medicine. 1991;91(6):584-588.
620 53. Zimmerman RK, Nowalk MP, Raymund M, Tabbarah M, Hall DG,
621 Wahrenberger JT, et al. Tailored Interventions to Increase Influenza Vaccination in
622 Neighborhood Health Centers Serving the Disadvantaged. American Journal of Public
623 Health. 2003;93(10):1699-1705.
624 54. Marsh HA, Malik F, Shapiro E, Omer SB, Frew PM. Message Framing
625 Strategies to Increase Influenza Immunization Uptake Among Pregnant African
626 American Women. Maternal and Child Health Journal. 2013;18(7):1639-1647.
627 55. Yeager DP, Toy EC, Baker B, 3rd. Influenza vaccination in pregnancy.
628 American Journal of Perinatology. 1999;16(6):283-286.
629 56. Yudin MH, Salaripour M, Sgro MD. Acceptability and feasibility of seasonal
630 influenza vaccine administration in an antenatal clinic setting. Journal of Obstetrics &
631 Gynaecology Canada. 2010;32(8):745-748.
632 57. Wiley KE, Massey PD, Cooper SC, Wood NJ, Ho J, Quinn HE, et al. Uptake
633 of influenza vaccine by pregnant women: a cross-sectional survey. The Medical
634 journal of Australia. 2013;198(7):373-375.
635 58. Stockwell MS, Westhoff C, Kharbanda EO, Vargas CY, Camargo S, Vawdrey
636 DK, et al. Influenza Vaccine Text Message Reminders for Urban, Low-Income
637 Pregnant Women: A Randomized Controlled Trial. American Journal of Public
638 Health. 2013;104 Suppl 1:e7-12.
639 59. Meharry PM, Cusson RM, Stiller R, Vazquez M. Maternal Influenza
640 Vaccination: Evaluation of a Patient-Centered Pamphlet Designed to Increase Uptake
641 in Pregnancy. Maternal and Child Health Journal. 2013;18(5):1205-1214.
642 60. Moniz MH, Hasley S, Meyn LA, Beigi RH. Improving influenza vaccination
643 rates in pregnancy through text messaging: a randomized controlled trial. Obstetrics
644 and Gynecology. 2013;121(4):734-740.
645 61. Frew PM, Saint-Victor DS, Owens LE, Omer SB. Socioecological and
646 message framing factors influencing maternal influenza immunization among
647 minority women. Vaccine. 2014;32(15):1736-1744.
648 62. McCarthy EA, Pollock WE, Nolan T, Hay S, McDonald S. Improving
649 influenza vaccination coverage in pregnancy in Melbourne 2010-2011. The Australian
650 & New Zealand Journal of Obstetrics & Gynaecology. 2012;52(4):334-341.

63. Klatt TE, Hopp E. Effect of a best-practice alert on the rate of influenza vaccination of pregnant women. Obstetrics and Gynecology. 2012;119(2 Pt 1):301-305.
64. Yudin MH, Salripour M, Sgro MD. Impact of patient education on knowledge of influenza and vaccine recommendations among pregnant women. Journal of Obstetrics and Gynaecology Canada. 2010;32(3):232-237.
65. Sherman MJ, Raker CA, Phipps MG. Improving influenza vaccination rates in pregnant women. The Journal of Reproductive Medicine. 2012;57(9-10):371-376.
66. Mouzoon ME, Munoz FM, Greisinger AJ, Brehm BJ, Wehmanen OA, Smith FA, et al. Improving influenza immunization in pregnant women and healthcare workers. The American Journal of Managed Care. 2010;16(3):209-216.
67. Ogburn T, Espey EL, Contreras V, Arroyo P. Impact of clinic interventions on the rate of influenza vaccination in pregnant women. Journal of Reproductive Medicine. 2007;52(9):753-756.
68. Panda B, Stiller R, Panda A. Influenza vaccination during pregnancy and factors for lacking compliance with current CDC guidelines. Journal of Maternal-Fetal & Neonatal Medicine. 2011;24(3):402-406.
69. Public Health Agency of Canada National Advisory Committee on Immunization (NACI) statement on seasonal influenza vaccination for 2013–2014. CCDR. 2013;39(ACS-4):1–39
70. Pre-pregnancy counselling and rou□ne antenatal assessment in the absence of pregnancy complica□ons. In: RANZCOG, editor. College Statement 2009
71. Humiston SG, Serwint JR, Szilagyi PG, Vincelli PA, Dhepyasuwan N, Rand CM, et al. Increasing adolescent immunization rates in primary care: strategies physicians use and would consider implementing. Clinical Pediatrics. 2013;52(8):710-720
72. Kharbanda EO, Stockwell MS, Fox HW, Andres R, Lara M, Rickert VI. Text message reminders to promote human papillomavirus vaccination. Vaccine. 2011;29(14):2537-2541
73. Kempe A, Barrow J, Stokley S, Saville A, Glazner JE, Suh C, et al. Effectiveness and cost of immunization recall at school-based health centers. Pediatrics. 2012;129(6):e1446-1452
74. Eppes C, Wu A, Cameron KA, Garcia P, Grobman W. Does obstetrician knowledge regarding influenza increase HINI vaccine acceptance among their pregnant patients? Vaccine. 2012;30(39):5782-5784.
75. Maher L, Dawson A, Wiley K, Hope K, Torvaldsen S, Lawrence G, et al. Influenza vaccination during pregnancy: a qualitative study of the knowledge, attitudes, beliefs, and practices of general practitioners in Central and South-Western Sydney. BMC Fam Pract. 2014;15:102.
76. Kharbanda EO, Vargas CY, Castano PM, Lara M, Andres R, Stockwell MS. Exploring pregnant women's views on influenza vaccination and educational text messages. Preventive Medicine. 2011;52(1):75-77.
77. Vilella A, Bayas JM, Diaz MT, Guinovart C, Diez C, Simo D, et al. The role of mobile phones in improving vaccination rates in travelers. Preventive Medicine. 2004;38(4):503-509.
78. Stockwell MS, Kharbanda EO, Martinez RA, Vargas CY, Vawdrey DK, Camargo S. Effect of a text messaging intervention on influenza vaccination in an urban, low-income pediatric and adolescent population: a randomized controlled trial. JAMA. 2012;307(16):1702-1708.

79. Song JY, Park CW, Jeong HW, Cheong HJ, Kim WJ, Kim SR. Effect of a hospital campaign for influenza vaccination of healthcare workers. Infection Control and Hospital Epidemiology. 2006;27(6):612-617.
80. Nexoe J, Kragstrup J, Ronne T. Impact of postal invitations and user fee on influenza vaccination rates among the elderly. A randomized controlled trial in general practice. Scandinavian Journal of Primary Health Care. 1997;15(2):109-112.
81. Satterthwaite P. A randomised intervention study to examine the effect on immunisation coverage of making influenza vaccine available at no cost. New Zealand Medical Journal. 1997;110(1038):58-60.
82. Begg CB, Berlin JA. Publication bias and dissemination of clinical research. Journal of the National Cancer Institute. 1989; 81: 107-115.

Table1

Table 1
Characteristics of included studies

Author	Study design, period and methods	Participants, setting and sample size	Reported vaccine coverage rates	Computed RD (95% CI)	Authors reported results	Confounders adjusted for	Difference in vaccination rate after adjustment
A. Provider-focused intervention							
Klatt (63)	Historical control study Standard care: 2007–2008 influenza season; intervention: 2008-2009 influenza season Standard care: routine antenatal care; intervention: routine antenatal care and a provider electronic reminder	Pregnant women in an antenatal outpatient clinic USA N = 1280; standard care (2007) n = 638; intervention (2008) n = 645	Intervention: 393/ 645 (60.9%) Standard care: 267/ 639 (41.8%)	0.19 [0.14, 0.25]	After implementing the intervention, the 2008–2009 influenza vaccination rate was significantly higher than that in 2007–2008 ($p < .001$, 95% CI for difference in proportions 0.14 to 0.25).	None.	Not provided.

Table 1
Characteristics of included studies

Author	Study design, period and methods	Participants, setting and sample size	Reported vaccine coverage rates	Computed RD (95% CI)	Authors reported results	Confounders adjusted for	Difference in vaccination rate after adjustment
Mouzoon (66)	Retrospective cohort study Standard care: vaccination rates in 1998–2002; intervention: vaccination rates during influenza seasons 2003-2004 to 2008-2009 Standard care: routine antenatal care; intervention: routine antenatal care and provider-focused interventions including provider education, standing orders, and provider feedback	Pregnant women in a multispecialty medical organization USA N = 21292; standard care (1998-2003) n = 8813 intervention 1 (2003-04) n = 2231; intervention 2 (2004-05) n = 2035; intervention 3 (2005-06) n = 2040; intervention 4 (2006-07) n = 2111; intervention 5 (2007-08) n = 2039; intervention 6 (2008-09) n = 2023	Interventions: 2003-04 427/ 2023 (21.1%) 2004-05 579/ 1893 (30.6%) 2005-06 633/ 1945 (32.5%) 2006-07 603/ 1488 (40.5%) 2007-08 949/ 2039 (46.5%) 2008-09* 760/ 2032 (37.4%) Standard care: 1998-2002 222/ 8813 (2.5%)	2003-04 0.19 [0.17, 0.20] 2004-05 0.28 [0.26, 0.30] 2005-06 0.30 [0.28, 0.30] 2006-07 0.38 [0.35, 0.41] 2007-08 0.44 [0.42, 0.46] 2008-09* 0.35 [0.33, 0.37]	Influenza vaccination coverage rates among pregnant women increased from 2.5% at baseline to 21.1% in 2003-2004, 30.6% in 2004-2005, 32.5% in 2005-2006, 40.5% in 2006-2007, and 46.5% in 2007-2008 and decreased to 37.4% in 2008- 2009. The lower rate in 2008-2009 was attributed to clinic closure because of Hurricane Ike. Immunization occurred throughout pregnancy but was more likely to occur in second or third trimester.	None.	Not provided

Table 1
Characteristics of included studies

Author	Study design, period and methods	Participants, setting and sample size	Reported vaccine coverage rates	Computed RD (95% CI)	Authors reported results	Confounders adjusted for	Difference in vaccination rate after adjustment
Sherman (65)	Retrospective cohort study Standard care: 2003; intervention: 2005 Standard care: routine antenatal care; intervention: routine antenatal care and a provider-focused reminder	Pregnant women in a primary care outpatient clinic USA N = 1367; standard care (2003) n = 504; intervention (2005) n = 863	Intervention: 445/ 863 (51.6%) Standard care: 74/ 504 (14.7%)	0.37 [0.32, 0.41]	An absolute increase of 37% in vaccination rate before and after implementing intervention (RR = 3.51, $p < 0.0001$)	None; study reports no significant difference in age, ethnicity, language, insurance status, education attainment, or presence of chronic illness between groups.	Not provided.
B. Pregnant woman-focused interventions							

Table 1
Characteristics of included studies

Author	Study design, period and methods	Participants, setting and sample size	Reported vaccine coverage rates	Computed RD (95% CI)	Authors reported results	Confounders adjusted for	Difference in vaccination rate after adjustment
Frew[1] (61)	RCT Recruitment: Sep 2011 - May 2012; intervention: follow-up: Oct 2011 - May 2013 Standard care: standard vaccine information sheet; intervention 1: gain-framed messages targeting pregnant women to articulate maternal vaccination benefits; intervention 2: loss-framed messages targeting pregnant women to illustrate negative consequences of foregoing vaccination	Pregnant women in various venues (not specified) USA N = 126; standard care n = 39; intervention1 n = 45; intervention 2 n = 42	Intervention 1 11/45 [3] (24.4%) Intervention 2 10/42 [3] (23.8%) Standard care: 15/39 [3] (38.5%)	Intervention 1 -0.14 [-0.33, 0.06] Intervention 2 -0.15 [-0.35, 0.05]	Both gain- (OR = 0.5176; 95% CI = 0.203, 1.322) and loss-framed messages (OR = 0.5000; 95% CI 0.192 to 1.304) had insignificant associations with increased likelihood of immunization during pregnancy.	None; study reports no significant differences in age, educational attainment, ethnicity, employment status, income, or marital status at baseline among groups.	Not provided.

Table 1
Characteristics of included studies

Author	Study design, period and methods	Participants, setting and sample size	Reported vaccine coverage rates	Computed RD (95% CI)	Authors reported results	Confounders adjusted for	Difference in vaccination rate after adjustment
Meharry[2] (59)	RCT Recruitment: 22 Sep 2011 – 2 Feb 2012; follow-up: Apr 2012 Standard care: routine antenatal care; intervention 1: influenza education pamphlet; intervention 2: influenza education pamphlet and a verbalized benefit statement: "vaccinating the pregnant woman also benefits the young infant"	Pregnant women in 3 antenatal outpatient clinics USA N = 133; standard care n = 49; intervention 1 n = 48; intervention 2 n = 36	Intervention 1 35/48 (72.9%) Intervention 2 31/36 (86.1%) Standard care: 23/49 (46.9%)	Intervention 1 0.26 [0.07, 0.45] Intervention 2 0.39 [0.21, 0.57]	Both intervention groups had higher vaccination rates than standard care group (χ^2 = 13.74, df = 1, p < 0.001) The difference between the two treatment groups was not statistically significant (χ^2 = 2.127, df = 1, p = 0.145)	None; study reports no significant differences in age, parity, trimester, ethnicity, marital status, employment status, education attainment, income, prenatal site, ever had influenza or ever had flu vaccine at baseline among groups.	Not provided.

Table 1
Characteristics of included studies

Author	Study design, period and methods	Participants, setting and sample size	Reported vaccine coverage rates	Computed RD (95% CI)	Authors reported results	Confounders adjusted for	Difference in vaccination rate after adjustment
Moniz (60)	RCT Recruitment: 2 influenza seasons Sep 2010 – Feb 2012; follow-up: 12 weeks after enrollment Standard care: routine antenatal care and 12 weekly text messages about general preventive health in pregnancy; intervention: standard care, 12 weekly text messages about general preventive health in pregnancy and the importance of influenza vaccination in pregnancy	Pregnant women in an antenatal outpatient clinic USA N = 204; standard care n = 100; intervention n = 104	Intervention: 34/104 (32.7%) Standard care: 31/100 (31.0%)	0.02 [-0.11, 0.14]	There was no difference in influenza vaccination rate between standard care and intervention groups (difference = 1.7%, 95% CI -11.1% to 14.5%)	None; study reports no significant difference in age, ethnicity, education attainment, marital status, income, or insurance at baseline between groups.	Not provided.

Table 1
Characteristics of included studies

Author	Study design, period and methods	Participants, setting and sample size	Reported vaccine coverage rates	Computed RD (95% CI)	Authors reported results	Confounders adjusted for	Difference in vaccination rate after adjustment
Stockwell (58)	RCT Recruitment: 1 Feb 2011 – 15 Aug 2011; 19 Sep 2011 – 31 Dec 2011 Standard care: routine automated telephone appointment reminders; intervention: standard care plus text messages involving pregnant woman-focused education and reminders	Pregnant women in 5 primary care outpatient clinics USA N = 1153; standard care n = 577; intervention n = 576	Intervention: 284/576 (49.3%) Standard care: 269/577 (46.6%)	0.03 [-0.03, 0.08]	The cumulative vaccination rates were 49.3% in the intervention group versus 46.6% in the standard care group (relative rate [RR] = 1.06; 95%CI = 0.94, 1.19; difference = 2.7%; 95% CI = –3.2%, 8.6%). After adjusting for gestational age and number of clinic visits, women who received intervention were more likely to receive an influenza vaccination (adjusted odds ratio [AOR] = 1.30; 95% CI = 1.003, 1.69). The greatest effect was observed among women in third trimester when intervention was implemented (AOR = 1.88, 95% CI 1.12 to 3.15)	Gestational age and number of clinic visits	After adjusting for confounders, women who received the intervention rose from 6% to 30% more likely to be vaccinated (adjusted odds ratio [AOR] = 1.30; 95% confidence interval [CI] = 1.003, 1.69).

Table 1
Characteristics of included studies

Author	Study design, period and methods	Participants, setting and sample size	Reported vaccine coverage rates	Computed RD (95% CI)	Authors reported results	Confounders adjusted for	Difference in vaccination rate after adjustment
Yudin (64)	Historical control study Standard care: fall 2006; intervention: fall 2007 Standard care: routine antenatal care; intervention: routine antenatal care and a pregnant woman-focused education pamphlet	Postpartum women in an antenatal outpatient clinic Canada N = 240; standard care (2006) n = 58; intervention (2007) n = 182	Intervention: 103/ 182 (56.6%) Standard care: 11/ 58 (19.0%)	0.38 [0.25, 0.50]	56% of women reported receiving influenza vaccine during current pregnancy, significantly higher than the 19% of women who reported receiving vaccine in the sample in 2006 ($p < 0.001$)	None.	Not provided.

C. Interventions with bundled components

Table 1
Characteristics of included studies

Author	Study design, period and methods	Participants, setting and sample size	Reported vaccine coverage rates	Computed RD (95% CI)	Authors reported results	Confounders adjusted for	Difference in vaccination rate after adjustment
McCarthy (62)	Historical control study Standard care: 2 consecutive weeks in Jul 2010; intervention: 2 consecutive weeks in Jul 2011 Standard care: routine antenatal care; intervention: routine antenatal care and a multicomponent education campaign involving provider education, provider reminders, pregnant woman-focused education and increased vaccine access	Postpartum women in a tertiary hospital Australia N = 439; standard care (2010) n = 199; intervention (2011) n = 240	Intervention: 96/ 240 (40.0%) Standard care: 60/ 199 (30.2%)	0.10 [0.01, 0.19]	Influenza vaccine coverage increased from 30% in 2010 audit to 40% in 2011 (p = 0.03)	None.	Not provided.

Table 1
Characteristics of included studies

Author	Study design, period and methods	Participants, setting and sample size	Reported vaccine coverage rates	Computed RD (95% CI)	Authors reported results	Confounders adjusted for	Difference in vaccination rate after adjustment
Ogburn (67)	Retrospective cohort study Standard care: 1 Oct 2002 – 31 Mar 2003; intervention 1: 1 Oct 2003 – 31 Mar 2004; intervention 2: 1 Oct 2004 – 31 Mar 2005 Standard care: routine antenatal care; intervention 1 (2003-04): routine antenatal care, provider-focused education, increase availability of vaccine in clinic, and a screening protocol for nurses; intervention 2 (2004-05): intervention 1 plus standing orders allowing nurses to administer vaccine without involvement of provider	Pregnant women in an antenatal outpatient clinic USA N = 602 Standard care (2002-03) n = 190 Intervention 1 (2003-04) n = 220 Intervention 2 (2004-05) n = 192	Intervention: 2003-04 7/220 [4] (3.2%) 2004-05 71/192 [4] (37.0%) Standard care: 2002-03 1/190 [4] (0.5%)	2003-04 0.03 [0.00, 0.05] 2004-05 0.36 [0.30, 0.43]	The overall vaccination rate was 0.5% in 2002-03, 3% in 2003-04 (p = 0.07), and 37% in 2004-05 (p < 0.001)	None; study reports no significant difference in age, gravidity, gestational age, prenatal care clinic type among groups.	Not provided.

Table 1
Characteristics of included studies

Author	Study design, period and methods	Participants, setting and sample size	Reported vaccine coverage rates	Computed RD (95% CI)	Authors reported results	Confounders adjusted for	Difference in vaccination rate after adjustment
Panda (68)	Prospective interventional study Standard care: influenza season 2007–2008; intervention: 2008-2009 Standard care: routine antenatal care; intervention: routine antenatal care and a multicomponent education program which involved provider-focused education and reminders, pregnant woman- focused education and reminders and provision of vaccine at antenatal clinics	Postpartum women in a tertiary hospital USA N = 1000; standard care (2007-08) n = 520; intervention (2008-09) n = 480	Intervention: 149/ 480 (31.0%) Standard care: 99/ 520 (19.0%)	0.12 [0.07, 0.17]	Influenza vaccination rates increased from 19% to 31% after intervention. Pregnant women with comorbidities were more likely to be vaccinated than healthy pregnant women.	None.	Not provided.

[1] Although the study appears to meet the criteria for a randomized controlled trial, no study design is specified and no trial registry is available
[2] No trial registry is available
[3] The number of vaccinated participants was estimated based on the odds ratios provided by the authors
[4] The number of vaccinated participants was estimated based on the percentages provided by the authors

Table2

Table 2
Strategies used to improve influenza vaccination uptake among pregnant women

	Interventions to overcome provider/ system barriers (Physician-focused intervention)				Interventions to increase demand (Pregnant woman-focused intervention)		Interventions to enhance vaccination access	
Study	Provider reminder/ recall	Standing orders	Provider feedback	Provider education	Pregnant woman reminder/ recall	Pregnant woman education	Extend service location	Increase stock
Frew (61)						√		
Klatt (63)	√							
McCarthy (62)	√			√		√		√
Meharry (59)						√		
Moniz (60)						√		
Mouzoon (66)		√	√	√				
Ogburn (67)		√		√			√	
Panda (68)	√			√		√	√	
Sherman (65)	√							
Stockwell (58)					√	√		
Yudin (64)						√		

Table3

Table 3
Quality assessment of the reviewed randomized controlled trials using the GRADE criteria

	Risk of Bias									
Study	**Random sequence generation**	**Allocation concealment**	**Blinding of participants & outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of evidence**
Frew (61)	No information provided, unclear	No information provided, unclear	Participants: No Assessors: Unclear	Quote: "… resulting in our final retention of 46% of the recruited study population". Comments: The proportion of missing outcomes compared with observed event risk was high enough to induce clinically relevant bias in intervention effect estimates. Per-protocol analysis was done.	Quote: "Using seasonal influenza immunization as our primary outcome variable". Comments: The study protocol is not available but the study likely included all pre-specified primary outcomes.	Quote: "... the potential for participatory bias as women who were agreeable to participating in the study were included and therefore may not be representative of the actual population …". Comments: The study may be affected by volunteer bias.	No serious inconsistency (only one RCT included)	No serious indirectness	Insufficient number of participants in both arms (80% power)	**LOW**

Table 3
Quality assessment of the reviewed randomized controlled trials using the GRADE criteria

	Risk of Bias									
Study	**Random sequence generation**	**Allocation concealment**	**Blinding of participants & outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of evidence**
Meharry (59)	Quote: "Pregnant women were randomly assigned to one of the three groups, based upon the chronological entry into the study and the Web-based random number generator". Comments: Done.	Quote: "The study number was paired with a predetermined random-assigned intervention". Comments: Likely not done.	Participants: No Assessor: Yes Quote: "Proof of vaccination was obtained by the clinic RN or prenatal instructor outside the research team and therefore unaware of the random assignment".	Quote: "Two women transferred out of the system and were lost to follow up …", Comments: The proportion of missing outcomes compared with observed event risk was not enough to induce clinically relevant bias in intervention effect estimates. Per-protocol analysis was done.	Quote: "The primary outcome measure was influenza vaccine uptake (vaccination)". Comments: The study protocol is not available but the study likely included all pre-specified primary outcomes.	Quote: "Potential participants in the prenatal clinics were approached by the principal investigator in the waiting rooms (site 1 and 2) or by one of three registered nurses (RNs) in the patient work- up room (site 3), prior to their appointment". Comments: The study may be affected by volunteer bias.	No serious inconsistency.	No serious indirectness.	Sufficient number of participants in both arms (80% power).	**MODERATE**

Table 3
Quality assessment of the reviewed randomized controlled trials using the GRADE criteria

	Risk of Bias									
Study	**Random sequence generation**	**Allocation concealment**	**Blinding of participants & outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of evidence**
Moniz (60)	Quote: "Participants were randomized to the two study arms with equal frequency using a permuted block design with random block sizes of two, four, and six". Comments: Done.	Quote: "The randomization sequence was generated and group assignments were placed in sequentially numbered, sealed, opaque envelopes by a researcher (L.A. M.) uninvolved in participant recruitment or clinical care". Comments: Done.	Participants: No Assessors: Yes Quote: "Health care providers were blind to the groups to which participants were randomized".	Quote: "The final intention-to-treat analysis included 204 participants ... For the per-protocol analysis, 18 patients in the General group and 28 patients in the Flu group were deemed nonevaluable … or they were lost to follow-up". Comments: The proportion of missing outcomes compared with observed event risk was not enough to induce clinically relevant bias in intervention effect estimates. Both intention-to-treat and per-protocol analyses were done.	Quote: "The prespecified primary outcome was uptake of the influenza vaccine". Comments: The study protocol is not available but the study probably included all pre-specified primary outcomes.	Quote: "Approximately 2,100 obstetric patients received care in the Magee Outpatient Clinic during the study's enrollment periods. Of these, 216 were enrolled in the study". Comments: There may be a risk of volunteer bias but insufficient information was provided.	No serious inconsistency.	No serious indirectness.	Sufficient number of participants in both arms (80% power).	**HIGH**

Table 3
Quality assessment of the reviewed randomized controlled trials using the GRADE criteria

	Risk of Bias									
Study	**Random sequence generation**	**Allocation concealment**	**Blinding of participants & outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality of evidence**
Stockwell (58)	Quote: "Eligible women were individually randomized to the text messaging intervention or to usual care using 1:1 allocation stratified by clinic site, using the random sample algorithm … with a randomly generated start point". Comments: Done.	Comments: Insufficient information about the sequence generation process to permit judgment, unclear.	Participants: No Assessors: Unclear	Quote: "Five women at less than 14 weeks gestational age were removed from further analysis, as were 28 women who were vaccinated after randomization but before the intervention, and 1 duplicate patient. The remaining 1153 women constituted the analytical group …". Comments: The proportion of missing outcomes compared with observed event risk was not enough to induce clinically relevant bias in intervention effect estimates. Per-protocol analysis was done.	Quote: "We evaluated the impact of influenza vaccine text message reminders in a low-income obstetric population". Comments: The study protocol is not available but the study likely included all pre-specified primary outcomes.	The study appears to be free of other sources of bias.	No serious inconsistency.	No serious indirectness.	Sufficient number of participants in both arms (80% power).	**MODERATE**

Table4

Table 4
Quality assessment of the reviewed observational studies using the Newcastle-Ottawa scale for cohort studies [a]

Quality assessment criteria	Klatt (63)	McCarthy (62)	Mouzoon (66)	Ogburn (67)	Sherman (65)	Panda (68)	Yudin (64)
(1) Selection							
• Representativeness of exposed cohort	*	*	*	*	*	*	*
• Selection of non-exposed cohort	--	--	--	--	--	--	--
• Ascertainment of exposure	*	*	*	*	*	*	*
• Demonstration that outcome of interest was not present at start of study	--	--	--	--	--	--	--
(2) Comparability[a]							
• Comparability of cohorts on the basis of design and analysis	--	--	--	--	*	--	--
• Comparability of cohorts on the basis of design and analysis	--	--	--	--	*	--	--
(3) Outcome							
• Assessment of outcome	*	--	*	*	*	--	--
• An adequate follow up period for outcome of interest	*	*	*	*	*	*	*
• Adequate follow up of cohorts	*	*	*	*	*	--	--
Overall quality score (Maximum score = 9/9)	**5/9**	**4/9**	**5/9**	**5/9**	**7/9**	**3/9**	**3/9**

[a] Each asterisk represents if an individual criterion within the subsection was fulfilled
[b] All criteria receive a maximum score of "one star" except for comparability of study groups and an extra star may be allocated for the control of any additional confounding factors.

Figure1

Figure 1
Flow diagram of the process and results of study selection

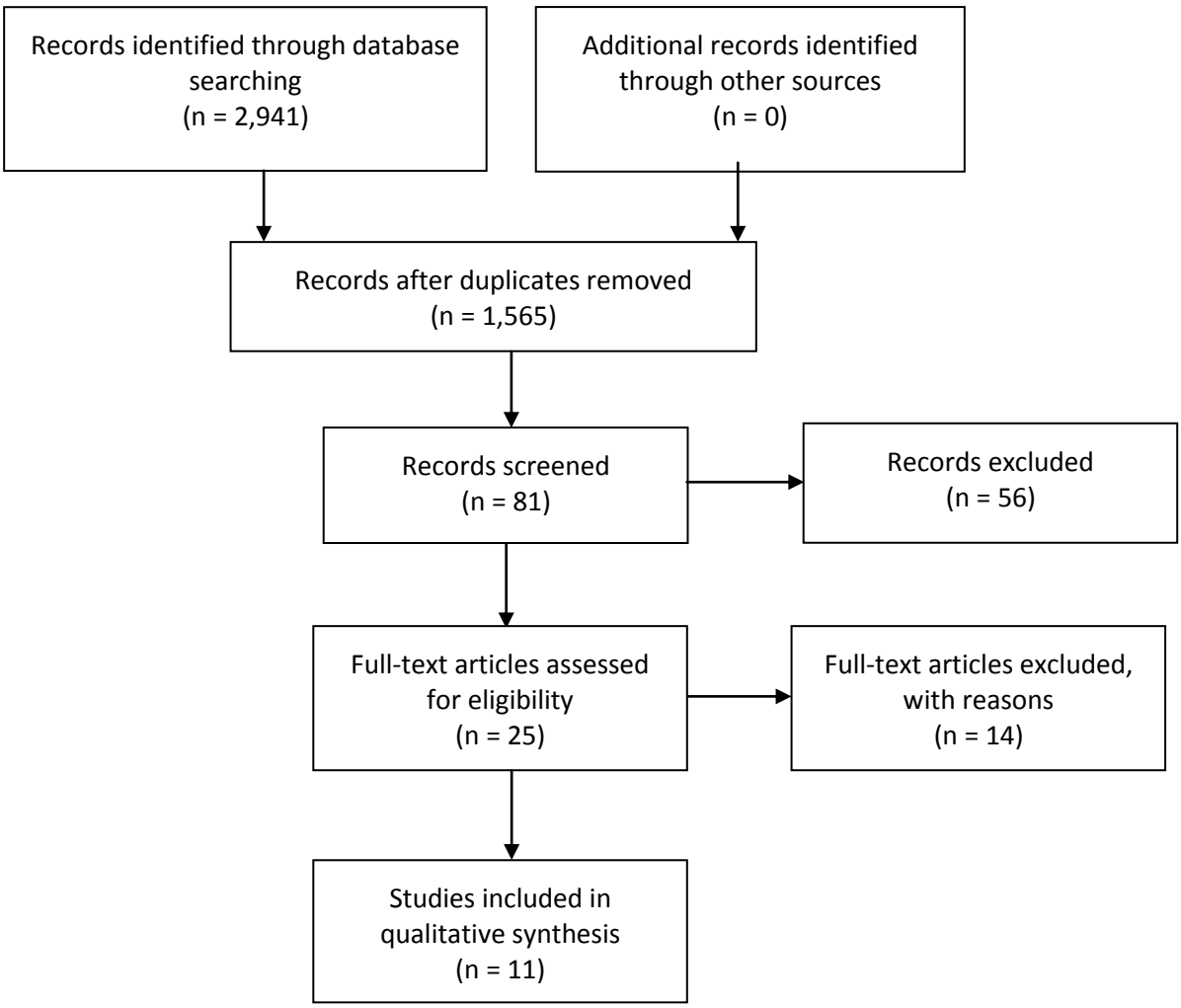
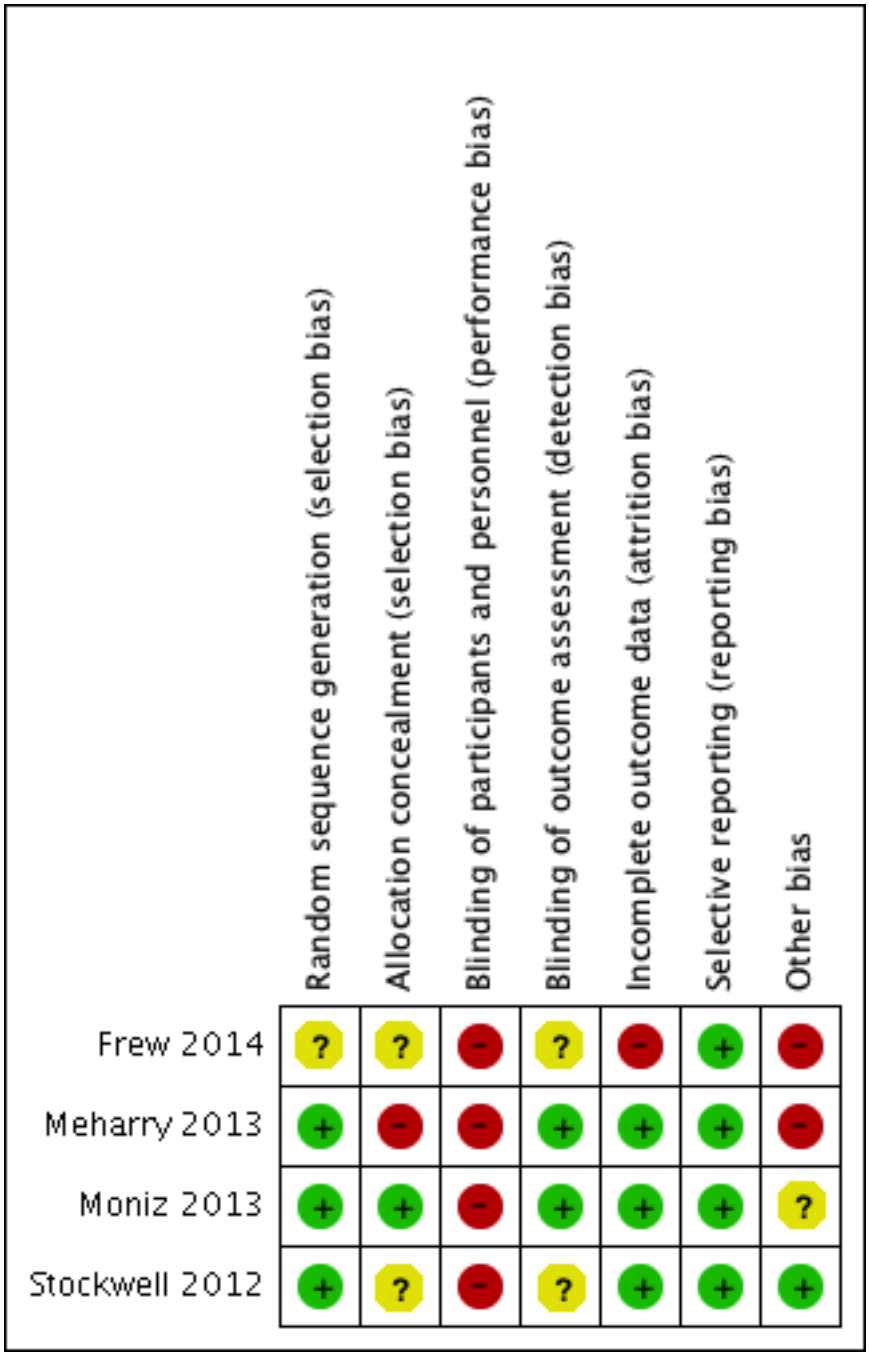


Figure2

Figure 2
Risk of bias summary



Entry with “Yes” (+) answers indicating a low risk of bias, “No” (-) answers indicating a high risk of bias, and “Unclear” (?) answers indicating an unknown risk of bias

supplementary file

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