

1 **Interventions to increase the uptake of seasonal influenza vaccination among**
2 **pregnant women: A systematic review**

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Highlights

- This is the first review to identify and evaluate interventions aimed at increasing maternal influenza vaccine 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.

18 ABSTRACT

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

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

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

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

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

45

46 **1. Background**

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

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

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

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

78

79 **2. Methods**

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

82 2.1. Search strategy

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

90 #1: vaccin*(truncation) OR immuni*

91 #2: influenza* OR flu

92 #3: preg* OR matern*

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

95 2.2. Eligibility criteria

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

103 2.3. Study selection

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

111 2.4. Data analysis

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

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

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

128 2.5. Evidence quality assessment

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

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

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

153

154 **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.

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

181 *3.2.3. Types of interventions*

182 All included studies involved at least one of the three previously identified
183 intervention components with most studies (n=8) using only one component (58-
184 61,63-66). Three studies used provider-based interventions only (63,65,66), five
185 studies used pregnant woman-focused interventions only (58-61,64), and three studies
186 used a combination of the three types of intervention components (62,67,68) (Table
187 2).

188 *3.2.4. Use of standard care group*

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

192 *3.2.5. Outcome measures*

193 Six studies ascertained the vaccination status through medical records from hospital
194 databases (58,60,63,65-67), four studies used self-reported data (61,62,64,68), and
195 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

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

222 *3.3.1.2. Observational studies*

223 The quality assessment of the seven observational studies is described in Table 4. For
224 all studies, exposure was ascertained from existing interventions implemented to
225 improve influenza vaccination rate among pregnant women; outcome assessment was
226 based on either a medical records or vaccination billing record an in-person interview
227 by the research staff. The response rates of questionnaires in two studies were low
228 (64,68). Only one study compared the confounders between the different participant
229 groups (65). The overall quality scores for the observational studies ranged from 3 to
230 7 out of a maximum of 9.

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

241 participants recruited after the change in the vaccination recommendations (64-67).

242 Thus, in these studies, the groups observed over time may not be comparable.

243 3.4 Effect of various interventions in increasing influenza vaccine uptake

244 *3.4.1. Provider-focused interventions*

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

254 Two studies involved delivering either electronic reminders (63) or manually
255 attaching notifications to antenatal records (65). Both studies compared provider
256 reminders and recall systems alone with historical controls and reported a significant
257 increase in the influenza vaccination rate. The RD generated from Klatt et al. (63) was
258 0.19 (95% CI 0.14 to 0.25) while that from Sherman et al. (65) was 0.37 (95% CI 0.32
259 to 0.41). Mouzoon et al. (66) evaluated the combined effect of implementing standing
260 orders, giving provider feedback, and provider education on vaccination rates over six
261 influenza seasons from 2003–04 to 2008–09. The RD increased with each successive
262 influenza season ranging from 0.19 (95% CI 0.17 to 0.20) to 0.44 (95% CI 0.42 to
263 0.46).

264 3.4.2. *Pregnant woman-focused interventions*

265 Interventions to increase demand for influenza vaccination aim to enhance the self-
266 initiation and motivation of pregnant women to seek out influenza vaccine. Education
267 and promotion materials targeting pregnant women can be disseminated by mass
268 media campaigns, via the Internet, through posters and leaflets, through lectures and
269 workshops, and by personalized reminder and recall systems. Five (45%) studies (58-
270 61,64) assessed the effect of pregnant woman-focused interventions alone while two
271 studies also included other intervention components (62,68). Four of the five studies
272 assessing the sole effect of pregnant woman-focused interventions were RCTs (58-
273 61), and the other was a historical control study (64).

274 Stockwell et al. (58) assessed the combined effect of providing reminders and
275 education via mobile phone text messages to increase seasonal influenza vaccination
276 uptake among urban, low-income pregnant women. Although, the complete case
277 analysis showed an insignificant increase [RD = 0.03, 95% CI -0.03 to 0.08] in the
278 vaccination rate, after adjustment for gestational age and the number of clinic visits,
279 participants in the intervention group were 30% more likely to be vaccinated [AOR =
280 1.30, 95% CI 1.003 to 1.69] and to be vaccinated early in the 3rd trimester [AOR =
281 1.88, 95% CI 1.12 to 3.15].

282 Education has been shown to be effective in changing various health behaviors in
283 pregnant women (71-73). Four studies assessed the effectiveness of influenza
284 vaccination education. Frew et al. (61) found that neither gain- nor loss-framed
285 messages increased the likelihood of vaccination in minority women [RD = -0.14,
286 95% CI -0.33 to 0.06 and RD = -0.15, 95% CI -0.33 to 0.05, respectively]. Moniz et

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

295 *3.4.3. Interventions to enhance access to influenza vaccination*

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

307 *3.4.4. Bundled interventions*

308 McCarthy et al. (62) found that implementing an education campaign that involved
309 putting provider reminders in the antenatal progress notes, providing influenza
310 vaccination education to health care providers, developing an information brochure on
311 influenza immunization for pregnant clients, and increasing vaccine stocks
312 significantly increased the influenza vaccination rate among pregnant women [RD =
313 0.10, 95% CI 0.01 to 0.19]. Similarly, Panda et al. (68) found that implementing a
314 vaccine promotion intervention that included education and reminders to both
315 providers and pregnant women and the provision of vaccine at antenatal clinics
316 significantly increased influenza vaccine uptake [RD = 0.12, 95% CI 0.07 to 0.17].
317 Ogburn et al. (67) evaluated two combined interventions over two consecutive
318 influenza seasons. In 2003-04, they provided education to providers and extended
319 locations for vaccination service and in 2004-05, standing vaccination orders were
320 added. The increase in vaccination after the 2003-04 influenza season was minimal
321 [RD = 0.03, 95% CI 0.00 to 0.05] but after standing orders were implemented, the
322 vaccination rate increased substantially [RD = 0.36, 95% CI 0.30 to 0.43].

323

324 **4. Discussion**

325 **4.1. Summary of evidence**

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

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

333 Researchers in five studies reported a statistically significant difference in the
334 vaccination rate of more than 0.20 (59,64-67), three studies showed a statistically
335 significant difference of 0.10 to 0.19 (62,63,68), and three RCTs had no significant
336 effect of the interventions (58,60,61). In general, higher quality studies showed a
337 decrease in statistical significance and effect size. The overall quality and amount of
338 evidence for the effectiveness of strategies to increase influenza vaccination uptake
339 among pregnant women varied and the risks of bias in the observational studies is
340 substantial. RCTs typically provide the best evidence for the efficacy of interventions.
341 Unfortunately, the interventions in three of the four RCTs included in this review
342 failed to increase the vaccination rate, even though two were adequately powered (58-
343 60).

344 The quality of evidence was low among observational studies. Three cohort studies
345 that showed a positive effect of provider-focused interventions (63,65,66) had
346 relatively high quality scores. In particular, interventions involving provider
347 reminders and/or recall only were associated with an increase in maternal vaccination
348 uptake (63,65). Although the evidence should be interpreted with caution given the
349 risk of bias, studies promoting vaccination in other target groups support this finding
350 (71-73). In addition, an extensive systematic review found that provider reminders and
351 recall systems are effective in increasing childhood vaccinations, influenza
352 vaccinations among children and adults, and adult hepatitis B, pneumococcus, and
353 tetanus vaccine uptake (30). Provider attitudes and practices matter because studies

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

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

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

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

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

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

398 The effectiveness of influenza vaccination programs depends on their content.
399 However a clear description of the content of many interventions, such as the wording
400 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

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

443

444 **5. Conclusions**

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

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

456

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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 <u>Standard care:</u> 2007–2008 influenza season; <u>intervention:</u> 2008-2009 influenza season	Pregnant women in an antenatal outpatient clinic USA <u>Standard care:</u> routine antenatal care; <u>intervention:</u> routine antenatal care and a provider electronic reminder	<u>Intervention:</u> 393/ 645 (60.9%) <u>Standard care:</u> 267/ 639 (41.8%) N = 1280; standard care (2007) n = 638; intervention (2008) n = 645	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)	<p>Retrospective cohort study</p> <p><u>Standard care:</u> vaccination rates in 1998–2002; <u>intervention:</u> vaccination rates during influenza seasons 2003-2004 to 2008-2009</p> <p><u>Standard care:</u> routine antenatal care; <u>intervention:</u> routine antenatal care and provider-focused interventions including provider education, standing orders, and provider feedback</p>	<p>Pregnant women in a multispecialty medical organization</p> <p>USA</p> <p>N = 21292; standard care (1998-2003) n = 8813</p> <p>intervention 1 (2003-04) n = 2231;</p> <p>intervention 2 (2004-05) n = 2035;</p> <p>intervention 3 (2005-06) n = 2040;</p> <p>intervention 4 (2006-07) n = 2111;</p> <p>intervention 5 (2007-08) n = 2039;</p> <p>intervention 6 (2008-09) n = 2023</p>	<p><u>Interventions:</u> <u>2003-04</u> <u>2003-04</u> 427/ 2023 (21.1%)</p> <p><u>2004-05</u> <u>2004-05</u> 579/ 1893 (30.6%)</p> <p><u>2005-06</u> <u>2005-06</u> 633/ 1945 (32.5%)</p> <p><u>2006-07</u> <u>2006-07</u> 603/ 1488 (40.5%)</p> <p><u>2007-08</u> <u>2007-08</u> 949/ 2039 (46.5%)</p> <p><u>2008-09*</u> <u>2008-09*</u> 760/ 2032 (37.4%)</p>	<p>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.</p>	<p>None.</p>	<p>Not provided</p>	
			<p><u>Standard care:</u> <u>1998-2002</u> 222/ 8813 (2.5%)</p>				

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 <u>Standard care</u> : 2003; <u>intervention</u> : 2005 <u>Standard care</u> : routine antenatal care; <u>intervention</u> : 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	<u>Intervention</u> : 445/ 863 (51.6%) <u>Standard care</u> : 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 <u>Recruitment:</u> Sep 2011 - May 2012; <u>intervention:</u> follow-up: Oct 2011 - May 2013 <u>Standard care:</u> standard vaccine information sheet; <u>intervention 1:</u> gain-framed messages targeting pregnant women to articulate maternal vaccination benefits; <u>intervention 2:</u> 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	<u>Intervention 1</u> 11/45 ³ (24.4%)	<u>Intervention 1</u> -0.14 [-0.33, 0.06]	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 <u>Recruitment:</u> 22 Sep 2011 – 2 Feb 2012; <u>follow-up:</u> Apr 2012 <u>Standard care:</u> routine antenatal care; <u>intervention 1:</u> influenza education pamphlet; <u>intervention 2:</u> 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	<u>Intervention 1</u> 35/48 (72.9%) <u>Intervention 2</u> 31/36 (86.1%)	<u>Intervention 1</u> 0.26 [0.07, 0.45] <u>Intervention 2</u> 0.39 [0.21, 0.57]	Both intervention groups had higher vaccination rates than standard care group ($\chi^2 = 13.74$, df = 1, p < 0.001) The difference between the two treatment groups was not statistically significant ($\chi^2 = 2.127$, 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 <u>Recruitment:</u> 2 influenza seasons Sep 2010 – Feb 2012; <u>follow-up:</u> 12 weeks after enrollment <u>Standard care:</u> routine antenatal care and 12 weekly text messages about general preventive health in pregnancy; <u>intervention:</u> 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	<u>Intervention:</u> 34/104 (32.7%) <u>Standard care:</u> 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 <u>Recruitment:</u> 1 Feb 2011 – 15 Aug 2011; 19 Sep 2011 – 31 Dec 2011 <u>Standard care:</u> routine automated telephone appointment reminders; <u>intervention:</u> 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	<u>Intervention:</u> 284/576 (49.3%) <u>Standard care:</u> 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).	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 <u>Standard care</u> : fall 2006; <u>intervention</u> : fall 2007 <u>Standard care</u> : routine antenatal care; <u>intervention</u> : 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	<u>Intervention</u> : 103/ 182 (56.6%) <u>Standard care</u> : 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 <u>Standard care:</u> 2 consecutive weeks in Jul 2010; <u>intervention:</u> 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	<u>Intervention:</u> 96/ 240 (40.0%) <u>Standard care:</u> 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)	<p>Retrospective cohort study</p> <p><u>Standard care</u>: 1 Oct 2002 – 31 Mar 2003; <u>intervention 1</u>: 1 Oct 2003 – 31 Mar 2004; <u>intervention 2</u>: 1 Oct 2004 – 31 Mar 2005</p> <p><u>Standard care</u>: routine antenatal care; <u>intervention 1</u> (2003-04): routine antenatal care, provider-focused education, increase availability of vaccine in clinic, and a screening protocol for nurses; <u>intervention 2</u> (2004-05): intervention 1 plus standing orders allowing nurses to administer vaccine without involvement of provider</p>	<p>Pregnant women in an antenatal outpatient clinic</p> <p>USA</p> <p>N = 602 Standard care (2002-03) n = 190</p> <p>Intervention 1 (2003-04) n = 220</p> <p>Intervention 2 (2004-05) n = 192</p>	<p><u>Intervention</u>: <u>2003-04</u> <u>2003-04</u> 7/220⁴ (3.2%)</p> <p><u>2004-05</u> <u>2004-05</u> 71/192⁴ (37.0%)</p> <p><u>Standard care</u>: <u>2002-03</u> 1/190⁴ (0.5%)</p>	<p><u>2003-04</u> 0.03 [0.00, 0.05]</p> <p><u>2004-05</u> 0.36 [0.30, 0.43]</p>	<p>The overall vaccination rate was 0.5% in 2002-03, 3% in 2003-04 ($p = 0.07$), and 37% in 2004-05 ($p < 0.001$)</p>	<p>None; study reports no significant difference in age, gravidity, gestational age, prenatal care clinic type among groups.</p>	<p>Not provided.</p>

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 <u>Standard care:</u> influenza season 2007–2008; <u>intervention:</u> 2008-2009 <u>Standard care:</u> routine antenatal care; <u>intervention:</u> 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	<u>Intervention:</u> 149/ 480 (31.0%) <u>Standard care:</u> 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

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

Study	Interventions to overcome provider/ system barriers (Physician-focused intervention)				Interventions to increase demand (Pregnant woman- focused intervention)		Interventions to enhance vaccination access	
	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)						✓		

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

Study	Risk of Bias									Quality of evidence
	Random sequence generation	Allocation concealment	Blinding of participants & outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Inconsistency	Indirectness	Imprecision	
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

Study	Risk of Bias									Quality of evidence
	Random sequence generation	Allocation concealment	Blinding of participants & outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Inconsistency	Indirectness	Imprecision	
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”.	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

Study	Risk of Bias									Quality of evidence
	Random sequence generation	Allocation concealment	Blinding of participants & outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Inconsistency	Indirectness	Imprecision	
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 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". 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 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

Study	Risk of Bias									Quality of evidence
	Random sequence generation	Allocation concealment	Blinding of participants & outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Inconsistency	Indirectness	Imprecision	
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: 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 ...”.	Quote: “We evaluated the impact of influenza vaccine text message reminders in a low-income obstetric population”.	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

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

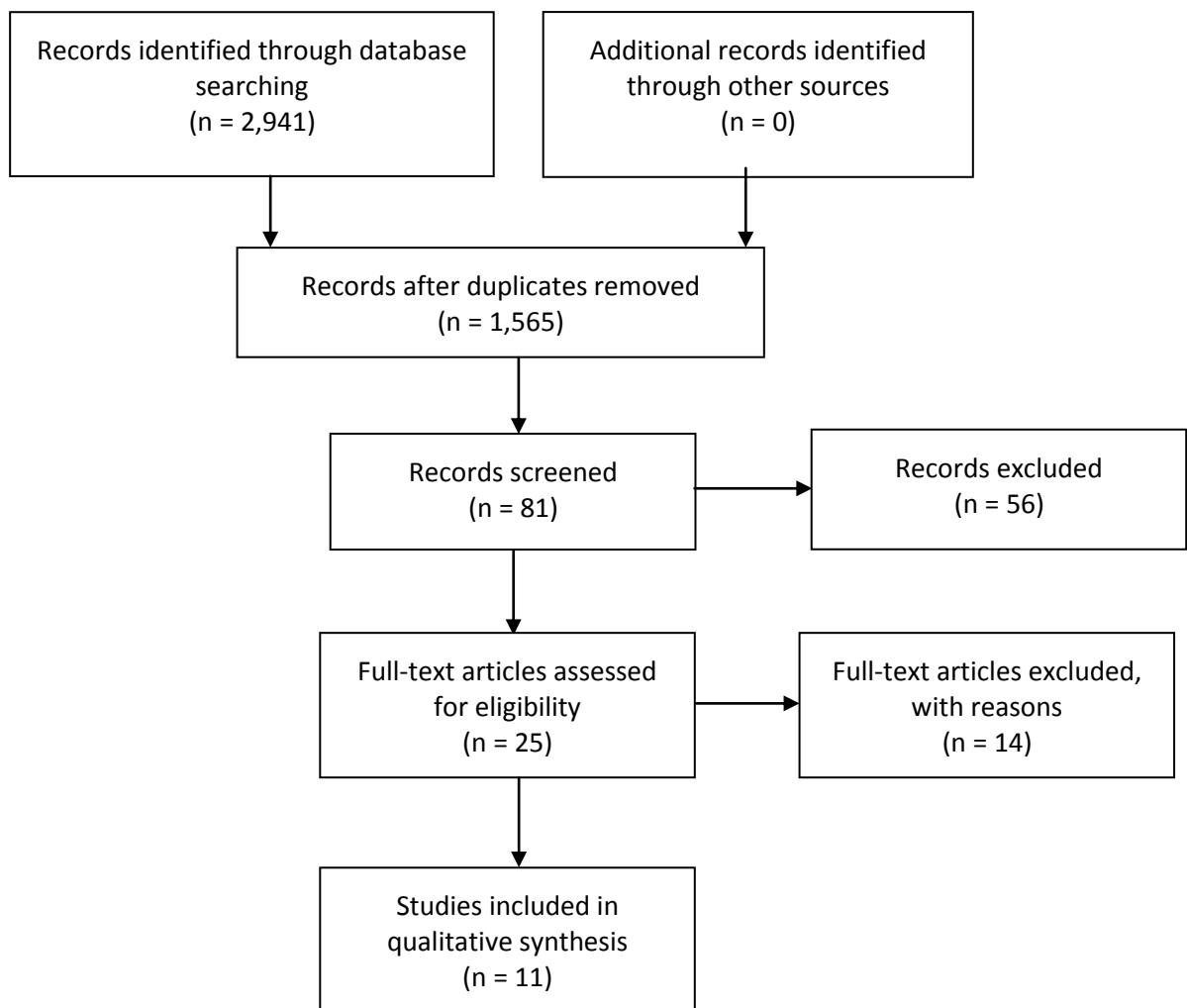


Figure2

Figure 2
Risk of bias summary

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Frew 2014	?	?	-	?	-	+	-
Meharry 2013	+	-	-	+	+	+	-
Moniz 2013	+	+	-	+	+	+	?
Stockwell 2012	+	?	-	?	+	+	+

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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