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1 **Strategies for increasing uptake of vaccination in pregnancy in high-income countries: A**
2 **systematic review**

3

4 **Kate Alexandra Bisset^{a,b}, Pauline Paterson^{a*}**

5

6 a. The Vaccine Confidence Project, London School of Hygiene & Tropical Medicine, Keppel St,
7 London WC1E 7HT, United Kingdom

8 b. Imperial College Healthcare NHS Trust, South Wharf Road, St Mary's Hospital, London, W2 1NY,
9 United Kingdom

10

11 * Corresponding author at: London School of Hygiene & Tropical Medicine, Keppel Street, London
12 WC1E 7HT, United Kingdom. Phone: +44 (0)20 7927 2830, Fax: +44 (0)20 7436 5389

13

14 **Email addresses**

15 kate.bisset2@nhs.net

16 pauline.paterson@lshtm.ac.uk

17

18 **Abbreviations¹**

19

20 **Abstract**

21

¹ **Abbreviations**

EPHPP = Effective Public Health Practice Project, GP = General Practitioner, NHS = National Health Service, PHE = Public Health England, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = Randomised Control Trials, WHO = World Health Organization

22 *Introduction:* Vaccination in pregnancy is an effective method to protect against disease for the
23 pregnant woman, foetus and new born infant. In England, it is recommended that pregnant women
24 are vaccinated against pertussis and influenza. Improvement in the uptake of both pertussis and
25 influenza vaccination among pregnant women is needed to prevent morbidity and mortality for both
26 the pregnant women and unborn child.

27

28 *Aim:* To identify effective strategies in increasing the uptake of vaccination in pregnancy in high-
29 income countries and to make recommendations for England.

30

31 *Methods:* A systematic review of peer reviewed literature was conducted using a keyword search
32 strategy applied across six databases (Medline, Embase, PsychInfo, PubMed, CINAHL and Web of
33 Science). Articles were screened against an inclusion and exclusion criteria and papers included
34 within the review were quality assessed.

35

36 *Results and conclusions:* Twenty-two articles were included in the review. The majority of the papers
37 included were conducted in the USA and looked at strategies to increase influenza vaccination in
38 pregnancy. There is limited high quality evidence for strategies in high-income countries to increase
39 coverage of pertussis and influenza vaccination in pregnancy. A number of strategies have been
40 found to be effective; reminders about vaccination on antenatal healthcare records, midwives
41 providing vaccination, and education and information provision for healthcare staff and patients.
42 Future interventions to increase vaccination in pregnancy should be evaluated to ensure efficacy
43 and to contribute to the evidence base.

44

45 **Key Words:**

46 Pertussis vaccine; influenza vaccine; pregnancy; vaccine hesitancy; maternal vaccination; strategies.

47

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54

55 **1. Introduction**

56

57 Vaccination in pregnancy protects the pregnant woman, foetus and new born infant from harmful
58 diseases [1-4]. For high-income countries, World Health Organisation (WHO) [5] recommends
59 pregnant women are vaccinated against influenza and pertussis. In England, influenza vaccination in
60 pregnancy has been offered since 2010 [6]. In April 2012, a pertussis outbreak occurred in England
61 with 9,300 confirmed cases of pertussis and the death of 14 infants under three months old [7]. This
62 prompted the Department of Health (DH) to offer the pertussis vaccine to all pregnant women from
63 October 2012 to protect babies who are too young to be immunised [8]. The pertussis vaccination in
64 pregnancy has been found to be 90 per cent effective at protecting infants in the first months after
65 birth [9], safe to mother and foetus [2, 10] and is recommended by WHO [11] to prevent premature
66 infant mortality. The vaccination is offered from 16 to 32 weeks gestation [6], and is also available
67 up until delivery but does not offer the same level of protection to the infant [6].

68

69 Pregnant women and infants are more at risk of morbidity and mortality from influenza than the
70 general population [3-5, 12, 13, 14]. Between 2009 and 2012 influenza caused one out of 11
71 maternal deaths [14]. Influenza in pregnant women can also have an impact on the growth and
72 development of the foetus [4] and delivery complications, such as low birth weight and premature
73 birth [14]. Infants under six months old are more at risk of severe complications and mortality from

74 contracting the influenza virus [15]. Infants in England are unable to receive the flu vaccination until
75 they are six months old and only if they are in a clinical risk group, or ages two to seventeen years
76 old otherwise [6].

77

78 1.1 Vaccination rates in England

79

80 Pertussis vaccination coverage in pregnancy in England has recently been increasing. Latest figures
81 from Public Health England (PHE) indicate that 73.8 per cent of women were vaccinated in
82 pregnancy between January and March 2017 [15]. However, previous years saw a dip in vaccination
83 rates during the summer months. PHE have hypothesised that this is due to an increase in pertussis
84 vaccination during flu season when influenza vaccination is also being promoted.

85

86 Despite improvements in pertussis vaccination uptake in pregnancy, there have been 18 infant
87 deaths related to pertussis in England since the programme began in 2012 [16]. For 16 of these
88 deaths, the mother had not been vaccinated against pertussis during her pregnancy and for the
89 other two infant deaths, the vaccination was administered too close to delivery to effectively protect
90 the new born child [16]. Vaccination uptake also differs across regions in England, with some areas
91 reporting lower uptake than others.

92

93 Influenza vaccination rates during pregnancy in England were 44.9 per cent in 2016/17 season [17].

94 While this has increased from 42.3 per cent in the previous year (2015/16) [17] it compares
95 unfavourably to uptake of influenza vaccination in 65 year olds (70.5%, 2016/17) [17] and other
96 countries in the UK (for example, Scotland 61.5%, 2016/17) [18].

97

98 Caution should be taken when interpreting these pregnancy vaccination rates as data collection can
99 be difficult due to the complexities of recording pregnancy and non-pregnancy accurately and in a
100 timely manner on electronic health records [16].

101

102 1.2 Current research on determinants of vaccination uptake in pregnancy

103

104 Only a small portion of existing published research on determinants of vaccination uptake relates to
105 vaccination in pregnancy [19, 20]. Wilson et al [19] conducted a literature review, which specifically
106 focused on vaccine hesitancy in pregnancy. This paper found that the main factors reported to
107 contribute to vaccine hesitancy were [19]:

- 108 • Concerns about the safety of vaccination in pregnancy
- 109 • Low knowledge about vaccine efficacy, the diseases and availability of vaccine
- 110 • A healthcare worker not recommending the vaccination

111

112 It is important to understand the factors that influence the decision to receive a vaccination to
113 support the development of strategies and interventions to increase coverage of vaccination in
114 pregnancy. While Wilson et al's [19] review provides insight into the reasons pregnant women may
115 be hesitant to receive a vaccination, it does not analyse the strategies that could help to increase
116 uptake.

117

118 A systematic review has been published to look at strategies to increase influenza vaccination in
119 pregnancy in 2016 [21]. While this review by Wong et al [21] identified a number of strategies to
120 increase influenza vaccination in pregnancy, it did not include pertussis vaccination. Also, the review
121 only included papers up to August 2014. In order to make recommendations to an English setting on
122 strategies to improve vaccination uptake in pregnant women in England, pertussis vaccination must

123 also be reviewed, especially since pertussis has different recommendations around the timing of
124 vaccination in pregnancy compared with the influenza vaccine [6].

125

126 The reason for selecting England rather than the UK as a whole is due to the Health and Social Care
127 Act (2012) [22], which resulted in commissioning arrangements for vaccination delivery differing
128 across the UK. However, it is expected that the findings of this paper will translate to other high-
129 income countries.

130

131 1.3 Aims and objectives

132

133 The aim of this systematic review is to identify strategies that are effective in increasing the uptake
134 of vaccination in pregnancy in high-income countries and to make recommendations for England.

135

136 Objectives

137 • To identify and describe interventions to increase uptake of vaccination in pregnancy in
138 high-income countries

139

140 • To explore the effectiveness of any identified interventions and/or strategies to increase
141 uptake of vaccination in pregnancy

142

143 • To make recommendations on strategies to increase vaccination uptake in pregnancy in
144 England

145

146

147 2. Methods

148

149 2.1 Systematic Review Search Strategy

150

151 The search strategy was developed around vaccination type, pregnancy and keywords to identify
152 strategies or interventions to increase vaccination uptake (table 1 for search terms). The search term
153 ‘maternal’ was excluded from the search strategy due to the large number of irrelevant papers this
154 generated in preliminary literature searches (which focused more on child vaccinations rather than
155 vaccinations in pregnancy).

156

157 The following six databases were searched: Medline, Embase, PsychInfo, PubMed, CINAHL and Web
158 of Science using the same search terms (table 1 and figure 1) for peer reviewed journal articles. The
159 search was conducted on 4th August 2017.

160

161 2.2 Study Selection

162

163 The papers were screened according to the inclusion and exclusion criteria detailed in table 2. We
164 did not exclude studies based on their design but included all types of studies (e.g. Randomised
165 Control Trials (RCTs), observational).

166

167

168 Papers that purely focused on pandemic flu vaccination were excluded since pandemic flu
169 vaccination is only available during a pandemic outbreak and strategies to increase vaccination
170 uptake differ to those to increase seasonal influenza vaccination uptake.

171

172 Studies that used cocooning or postnatal vaccination of mothers and family members of the child
173 were also excluded as this method is not recommended in England and the aim of this systematic
174 review was to review strategies to increase vaccination in pregnancy, not postnatal vaccination.

175

176 The outcome measure 'intention to vaccinate' was also excluded as this does not measure actual
177 vaccination behaviour and research has shown that not all people that 'intend to vaccinate' go on to
178 get the vaccine [23].

179

180 2.3 Analysis

181

182 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [24] flow
183 diagram guidance was used to display studies that were identified by the database search and met
184 inclusion and exclusion criteria (see figure 1). Papers were assessed using the Effective Public Health
185 Practice Project's (EPHPP) Quality Assessment Tool for Quantitative studies [25, 26] (appendix 2).
186 This assessment tool was selected as it allows RCTs and observational studies to be assessed easily
187 within one tool and has been shown to have excellent inter-rater agreement for the quality grade
188 awarded to papers within systematic reviews [27].

189

190 The EPHPP framework [25] assesses the quality of studies against the following criteria:

- 191 • Selection bias
- 192 • Design
- 193 • Confounding
- 194 • Blinding
- 195 • Data collection
- 196 • Withdrawal and opt out of participants
- 197 • Intervention integrity
- 198 • Analysis

199

200 Papers were awarded a score of 'weak', 'moderate' or 'strong' based on their design and analysis.
201 Each paper's assessment is presented in appendix 2 and the quality score is reported in appendix 1
202 and 2.

203

204 Where sufficient data was provided in the papers, and the assumptions were met, a risk difference
205 and a Chi-Squared test for proportions was calculated for each paper (appendix 1). This was done to
206 allow for a comparison to be made between the effect of the interventions in each paper. The types
207 of interventions identified in the papers were too heterogeneous to conduct a meta-analysis. The
208 components of the interventions in these studies were described (appendix 1).

209

210

211 **3. Results**

212

213 3.1 Literature search

214

215 The database search identified 1,062 articles. After duplicates were removed the total number of
216 articles was 687 (figure 1). Articles were initially screened by title and abstract to assess relevancy
217 and were also assessed against the inclusion and exclusion criteria. Forty-three articles (including
218 three articles found through snowballing technique) appeared relevant to the research question and
219 were assessed against the inclusion and exclusion criteria by full text, at which point a further 21
220 were excluded. Twenty-two papers were included in this review (figure 1).

221

222 3.2 Main findings

223

224 The majority of the included studies focused on influenza vaccination in pregnancy (18/22) and of
225 these, 12 were conducted in the USA. The other four studies focusing on influenza vaccination in

226 pregnancy occurred in Australia, Canada, Hong Kong and UK. Only four studies looked at strategies
227 to increase pertussis vaccination and all occurred in the USA.

228

229 Nine studies included in the review were RCTs and the remaining 13 were observational studies
230 (appendix 1).

231

232 *Randomised control trials*

233

234 Of the nine RCTs, three were assessed as 'strong' [28, 29, 30], three 'moderate' [31, 32, 33] and
235 three 'weak' [34, 35, 36] in quality. The weak-quality studies had methodological flaws with
236 allocation concealment, blinding and power.

237

238 *Observational studies*

239

240 None of the observational studies presented high quality evidence. Of the 13 papers identified, five
241 were graded as 'moderate' (38.5%) [36-40], and eight as 'weak' evidence (61.5%) [35, 41-47
242 (appendix 2).

243

244 Fifty-four per cent of the observation studies (7/13) assessed the impact of strategies or
245 interventions that had multiple components so it was difficult to determine which specific elements
246 of the interventions resulted in an increase of vaccination uptake in pregnant women [35, 38-41, 43,
247 45]. Elements of each intervention are detailed in appendix 1.

248

249 Also, many of the observational studies were retrospective cohort studies (appendix 1). It was
250 difficult to ascertain whether changes in vaccination status in observational studies were due to the
251 intervention, as the control group vaccination rates were taken at a different time period to the

252 intervention group. External confounding factors may have influenced the uptake of vaccinations in
253 the study population, such as greater public awareness of pertussis or influenza.

254

255 *Recording vaccination status*

256

257 All of the studies used either self-reported vaccination status or electronic health records to record
258 whether a vaccination had been received during pregnancy. There are problems with both of these
259 measures for assessing outcome; self-reporting is susceptible to response bias (although perhaps
260 less so than self-reporting of vaccinations in childhood, since vaccination during pregnancy would
261 have happened fairly recently), and assessment of electronic records were only able to detect if
262 vaccination had been received in the facility where the study took place. Only one study [39]
263 included 'vaccination received elsewhere' in electronic medical records. The use of electronic health
264 records is likely to underestimate vaccine coverage but it is uncertain how self-reported vaccination
265 status would impact results in the papers. For both of these methods it is likely to have a non-
266 differential impact on the intervention and control groups so this was not recorded as a significant
267 weakness when grading these papers (appendix 2).

268

269 3.3 Strategies and interventions to increase uptake of pertussis and influenza vaccination in
270 pregnancy

271

272 We have grouped the effective interventions into three main themes, illustrated in figure 2. We
273 describe these interventions in more detail below.

274

275 Fifty-five per cent (12/22) of papers found significant improvement (at 95% significance level) in
276 vaccination coverage following interventions or strategies to increase uptake (appendix 1).

277 Intervention components in the papers that showed a significant increase in vaccination uptake in

278 pregnant women can be seen in table 3. Of these 12 papers, 11 focused on influenza vaccination
279 in pregnancy and one on pertussis [44].

280

281 The observational studies that were graded as moderate or strong quality [36-40] found a risk
282 difference of between 9.85 - 36.90 per cent between intervention and control groups for
283 vaccination. The highest difference between the control and intervention groups were found for
284 strategies that included education for staff and allowing midwives to provide vaccination with a risk
285 difference of 36.45 per cent (95% CI: 29.21%, 43.72%; $p < 0.001$) [39], and adding a reminder to
286 health records about vaccination, risk difference 36.90 per cent (95% CI: 32.10%, 41.40%; $p < 0.001$)
287 [36] (appendix 1).

288

289 One RCT found a modest risk difference of 11.12 per cent (95% CI: 2.80%, 19.38%; $p < 0.01$) between
290 the intervention and control group for a 1-2-1 brief education session for pregnant women including
291 information on safety, vaccine recommendations and benefits of vaccination [30] (appendix 1). The
292 other RCT found a risk difference of 39.17 per cent (95% CI: 17.76%, 56.27%; $p < 0.001$) between the
293 intervention and control group, with the intervention comprising of a patient information pamphlet
294 with a statement about the importance of vaccination to protect the baby from influenza (appendix
295 1) [32].

296

297 *Midwives vaccinating pregnant women*

298

299 In the USA, the majority of vaccination is not provided by midwives. Where healthcare institutions
300 had implemented a 'standing order', allowing midwives to administer pertussis or influenza
301 vaccination, without seeking permission from a physician or referring to a General Practitioner (GP)
302 or physician to administer vaccine, vaccination coverage increased [39, 42, 45].

303

304 *Reminders on medical records*

305

306 Adding a reminder to medical records (electronic or paper) to prompt antenatal care staff to discuss
307 and offer vaccination was shown to increase vaccination coverage [33, 37, 38, 44-46].

308

309 *Text message reminders*

310

311 Three RCTs focusing specifically on text messaging to pregnant women found a lack of significant
312 effect of text message reminders as method of increasing vaccination in pregnancy [29, 31, , 33].

313

314 *Information and education for patients*

315

316 Information and education was important for both staff and patients separately. Information for
317 patients was found to be effective at increasing vaccine coverage when administered through
318 education sessions, posters or pamphlets [30, 32, 38, 40].

319

320 Three papers [28, 34, 48] used an educational video (providing information on the importance of
321 vaccination based on theoretic methods of behaviour change) as the intervention to increase
322 vaccination uptake and found no difference between the control and intervention arms of their
323 study. However, two of the papers [34, 48] had small sample sizes ($n < 35$ in each arm of the RCT),
324 meaning they are unlikely to be sufficiently powered to detect any effect. For one study the
325 educational video intervention did positively influence vaccination health beliefs but not actual
326 vaccine behaviour [28].

327

328 *Staff training and education*

329

330 Staff education was important to ensure that staff were equipped with the current information on
331 vaccination in pregnancy and current guidance on discussing vaccination with pregnant women [38,
332 40].

333

334 In summary, the intervention components supported by strong or moderate quality studies to
335 increase vaccination coverage in pregnancy:

- 336 • Provision of vaccination by midwives (rather than just physicians or in GP practices)
- 337 • Alerts on medical records to prompt staff to discuss vaccination
- 338 • Staff education and training
 - 339 - Information of efficacy, safety, benefits and timing of vaccination
- 340 • Education and information for patients
 - 341 - Information of efficacy, safety, benefits and timing of vaccination
 - 342 - Distribution of information and education materials within antenatal clinics and
 - 343 facilities
 - 344 - Education and information provided by healthcare staff
 - 345 - Information/referral to places to access vaccination

346

347

348 **4. Discussion**

349

350 4.1 Findings

351

352 The aim of the systematic review was to identify strategies that were effective in increasing uptake
353 of pertussis and influenza vaccination in pregnant women in high-income countries.

354

355 The majority of the published articles identified in the review looked at strategies to increase
356 seasonal influenza vaccination in pregnancy and were conducted in the USA. There were limited
357 articles that aimed to evaluate strategies to increase pertussis vaccination in pregnancy, which may
358 be due to recommendations for universal pertussis vaccination being released more recently than
359 the recommendations around seasonal influenza vaccination in pregnancy.

360

361 Of the articles that found effective strategies to increase vaccination uptake, it was difficult to
362 identify effectiveness by individual interventions, since many of the studies used multi-component
363 strategies to address low uptake of vaccination in their study population. However, assessing the
364 elements of strategies that significantly increased vaccine coverage, in high or moderate quality
365 papers, we identified that education and information for staff and patients, reminder alerts on
366 medical records and allowing midwives to also administer vaccination are effective strategies in
367 increasing vaccination uptake. There is currently no evidence to support the use of text messaging or
368 educational video-based interventions to increase vaccination uptake in pregnancy in high income
369 countries.

370

371 4.2 Support for intervention themes identified in the systematic review

372 There are no other systematic or literature views that solely focus on strategies to increase both
373 pertussis and influenza vaccination uptake in pregnancy in high-income countries. However, one
374 systematic review [21], published in 2016, did look at strategies to increase influenza vaccination in
375 pregnancy and found similar results suggesting the use of vaccination reminders in healthcare
376 systems and patient information pamphlets can increase vaccine coverage. The authors of this
377 systematic review [21] also conclude that there is a lack of high quality evidence around
378 interventions to increase vaccination coverage in pregnancy. It is a public health priority to address
379 vaccination uptake in pregnancy, given the benefit to infants and pregnant women [21].

380

381 While there is limited evidence on strategies to increase vaccination uptake, by looking at previous
382 research into vaccine hesitancy, it appears the reasons women report for not wanting to receive
383 vaccination in pregnancy links in with the intervention themes identified in our findings. For
384 example, two literature reviews [20, 49] have looked at factors that influence vaccine hesitancy in
385 pregnancy. Both papers found that concerns regarding vaccine safety and efficacy were identified as
386 barriers to vaccination, as well as not receiving a recommendation from a healthcare professional
387 and lack of knowledge about vaccination in pregnancy.

388

389 *Midwives providing vaccination*

390 Evidence from qualitative interviews suggests that women are left to make their own arrangements
391 with their GPs for pertussis vaccination during pregnancy and feel vaccination should be provided in
392 antenatal care [49]. Midwives providing vaccination could improve vaccination uptake [49, 50] and
393 midwives providing vaccination is currently being trialled in Lewisham and Greenwich National
394 Health Service (NHS) Trust in London [50]. This supports the findings of this systematic review, that
395 midwives providing the vaccine themselves could be an effective strategy to increase vaccination
396 uptake in pregnancy by increasing convenience.

397

398 *Staff education and training*

399 Lack of conversation with a healthcare professional about influenza and pertussis vaccination in
400 pregnancy has been identified as a barrier to vaccination in previous original research into vaccine
401 hesitancy [51-53]. Survey data has found that 16 - 24 per cent of women had a meaningful
402 discussion with their GP about pertussis vaccination in pregnancy [54, 55]. Cross-sectional survey
403 data suggests the principal reason for accepting pertussis vaccination was encouragement or
404 recommendation from a health professional. A meaningful conversation with a health professional
405 has been identified as a facilitator to influenza and pertussis vaccination [49, 51, 53-56] with 73 - 96
406 per cent [51, 55] of women accepting vaccination if a health professional (especially an NHS health

407 professional [51]) recommends it. This previous research supports the findings of this paper that
408 education and training for staff and reminders on health records could increase vaccine uptake.

409

410 *Information and education for patients*

411 It has been suggested that women may decline vaccination due to a lack of information and
412 awareness [54]. Additionally, safety concerns have been identified as a barrier for vaccination in
413 pregnancy [19, 52, 55] despite extensive research into vaccine safety [2, 10]. Qualitative evidence
414 from London suggests that many mothers trust the NHS and if the NHS are providing vaccination,
415 they are more likely to trust the vaccine [51]. It is important to ensure pregnant women are
416 provided with accurate information about safety, efficacy and the vaccination schedule in
417 pregnancy, which was identified as an effective strategy in this paper.

418

419 4.3 Limitations

420 Study limitations include the possibility of selection bias or subjective review. Due to funding
421 constraints, the papers were screened and assessed by only one researcher. As the papers were
422 selected from high-income countries, the directness (or generalisability) to England was not
423 considered a limitation. Although, the majority of papers (n=18) were published in the USA, where a
424 different healthcare payment system means that individuals (who are not eligible for social support)
425 are reliant on purchasing insurance to access healthcare and may need to pay for vaccinations if
426 these are not covered as part of their insurance policy. This may be an additional barrier to
427 vaccination that is not seen in England due to vaccination being provided for free by the NHS.

428

429 4.4 Recommendations

430

431 Based on the current evidence and given that vaccination in pregnancy is a public health priority, it
432 would be advisable that the NHS England and PHE work with Clinical Commissioning Groups and the
433 providers of antenatal care to put a number of strategies in place:

434

435 1. Implement an alert on health records to prompt healthcare professionals to discuss
436 vaccination with women during pregnancy. This should be on GP systems as well as
437 antenatal care systems.

438

439 2. Ensure staff have the knowledge and confidence to discuss vaccination with women
440 during pregnancy, via staff education and training.

441

442 3. Commissioners of vaccinations and antenatal services should work together to make it
443 possible for midwives to vaccinate pregnant women during antenatal appointments. This
444 will remove the additional barrier of mothers needing to make an appointment with their
445 GP to receive the vaccination.

446

447 4. Provide up-to-date vaccine information leaflets to pregnant women and have posters in GP
448 surgeries, antenatal clinics, and childcare facilities.

449

450 5. Further research and evaluation of strategies to increase uptake of pertussis and influenza
451 vaccination in pregnancy.

452

453

454 **5. Conclusions**

455

456 While there is limited high quality evidence for strategies in high-income countries to increase
457 coverage of pertussis and influenza vaccination in pregnancy, there are a number of strategies that
458 have been found to be effective; reminders about vaccination on antenatal healthcare records,
459 midwives providing vaccination, and education, and information provision for healthcare staff and
460 patients. We recommend that any future interventions to increase influenza and pertussis
461 vaccination in pregnancy are evaluated to ensure efficacy and to contribute to the evidence base.

462

463 **Contributors**

464 KB and PP contributed to the conception/design of the review. KB conducted the systematic review.
465 KB drafted the initial manuscript. KB and PP contributed to multiple reviews and feedback on the
466 manuscript and gave final approval before submission.

467

468 **Declarations of interest**

469 PP - The LSHTM research group “The Vaccine Confidence Project” has received primary research
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473 KB - Declarations of interest: none

474

475

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691

692 **Tables**

693 **Table 1** Search terms

694 **Table 2** Inclusion and exclusion criteria for papers

695 **Table 3** Effective interventions in increasing vaccination uptake in pregnant women

696

697

698 **Figures**

699 **Figure 1** Search process flow chart (adapted from PRISMA flow chart [24])

700 **Figure 2** Effective strategies to increase vaccination in pregnancy

701