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

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Abbreviations\textsuperscript{1}

Abstract

\textsuperscript{1} Abbreviations
Introduction: Vaccination in pregnancy is an effective method to protect against disease for the pregnant woman, foetus and new born infant. In England, it is recommended that pregnant women are vaccinated against pertussis and influenza. Improvement in the uptake of both pertussis and influenza vaccination among pregnant women is needed to prevent morbidity and mortality for both the pregnant women and unborn child.

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

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

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

Key Words: Pertussis vaccine; influenza vaccine; pregnancy; vaccine hesitancy; maternal vaccination; strategies.
1. Introduction

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

Pregnant women and infants are more at risk of morbidity and mortality from influenza than the general population [3-5, 12, 13, 14]. Between 2009 and 2012 influenza caused one out of 11 maternal deaths [14]. Influenza in pregnant women can also have an impact on the growth and development of the foetus [4] and delivery complications, such as low birth weight and premature birth [14]. Infants under six months old are more at risk of severe complications and mortality from
contracting the influenza virus [15]. Infants in England are unable to receive the flu vaccination until they are six months old and only if they are in a clinical risk group, or ages two to seventeen years old otherwise [6].

1.1 Vaccination rates in England

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

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

Influenza vaccination rates during pregnancy in England were 44.9 per cent in 2016/17 season [17]. While this has increased from 42.3 per cent in the previous year (2015/16) [17] it compares unfavourably to uptake of influenza vaccination in 65 year olds (70.5%, 2016/17) [17] and other countries in the UK (for example, Scotland 61.5%, 2016/17) [18].
Caution should be taken when interpreting these pregnancy vaccination rates as data collection can be difficult due to the complexities of recording pregnancy and non-pregnancy accurately and in a timely manner on electronic health records [16].

1.2 Current research on determinants of vaccination uptake in pregnancy

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

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

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

A systematic review has been published to look at strategies to increase influenza vaccination in pregnancy in 2016 [21]. While this review by Wong et al [21] identified a number of strategies to increase influenza vaccination in pregnancy, it did not include pertussis vaccination. Also, the review only included papers up to August 2014. In order to make recommendations to an English setting on strategies to improve vaccination uptake in pregnant women in England, pertussis vaccination must
also be reviewed, especially since pertussis has different recommendations around the timing of vaccination in pregnancy compared with the influenza vaccine [6].

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

1.3 Aims and objectives

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

Objectives

- To identify and describe interventions to increase uptake of vaccination in pregnancy in high-income countries
- To explore the effectiveness of any identified interventions and/or strategies to increase uptake of vaccination in pregnancy
- To make recommendations on strategies to increase vaccination uptake in pregnancy in England

2. Methods
2.1 Systematic Review Search Strategy

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

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

2.2 Study Selection

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

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

Studies that used cocooning or postnatal vaccination of mothers and family members of the child were also excluded as this method is not recommended in England and the aim of this systematic review was to review strategies to increase vaccination in pregnancy, not postnatal vaccination.
The outcome measure ‘intention to vaccinate’ was also excluded as this does not measure actual vaccination behaviour and research has shown that not all people that ‘intend to vaccinate’ go on to get the vaccine [23].

2.3 Analysis

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

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

- Selection bias
- Design
- Confounding
- Blinding
- Data collection
- Withdrawal and opt out of participants
- Intervention integrity
- Analysis
Papers were awarded a score of ‘weak’, ‘moderate’ or ‘strong’ based on their design and analysis. Each paper’s assessment is presented in appendix 2 and the quality score is reported in appendix 1 and 2.

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

3. Results

3.1 Literature search

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

3.2 Main findings

The majority of the included studies focused on influenza vaccination in pregnancy (18/22) and of these, 12 were conducted in the USA. The other four studies focusing on influenza vaccination in
pregnancy occurred in Australia, Canada, Hong Kong and UK. Only four studies looked at strategies to increase pertussis vaccination and all occurred in the USA.

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

**Randomised control trials**

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

**Observational studies**

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

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

Also, many of the observational studies were retrospective cohort studies (appendix 1). It was difficult to ascertain whether changes in vaccination status in observational studies were due to the intervention, as the control group vaccination rates were taken at a different time period to the
intervention group. External confounding factors may have influenced the uptake of vaccinations in the study population, such as greater public awareness of pertussis or influenza.

*Recording vaccination status*

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

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

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

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

Intervention components in the papers that showed a significant increase in vaccination uptake in
pregnant women can be seen in table 3. Of these 12 papers, 11 focused on influenza vaccination in pregnancy and one on pertussis [44].

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

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

Midwives vaccinating pregnant women

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

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

Text message reminders

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

Information and education for patients

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

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

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

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

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

4. Discussion

4.1 Findings

The aim of the systematic review was to identify strategies that were effective in increasing uptake of pertussis and influenza vaccination in pregnant women in high-income countries.
The majority of the published articles identified in the review looked at strategies to increase seasonal influenza vaccination in pregnancy and were conducted in the USA. There were limited articles that aimed to evaluate strategies to increase pertussis vaccination in pregnancy, which may be due to recommendations for universal pertussis vaccination being released more recently than the recommendations around seasonal influenza vaccination in pregnancy.

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

4.2 Support for intervention themes identified in the systematic review

There are no other systematic or literature views that solely focus on strategies to increase both pertussis and influenza vaccination uptake in pregnancy in high-income countries. However, one systematic review [21], published in 2016, did look at strategies to increase influenza vaccination in pregnancy and found similar results suggesting the use of vaccination reminders in healthcare systems and patient information pamphlets can increase vaccine coverage. The authors of this systematic review [21] also conclude that there is a lack of high quality evidence around interventions to increase vaccination coverage in pregnancy. It is a public health priority to address vaccination uptake in pregnancy, given the benefit to infants and pregnant women [21].
While there is limited evidence on strategies to increase vaccination uptake, by looking at previous research into vaccine hesitancy, it appears the reasons women report for not wanting to receive vaccination in pregnancy links in with the intervention themes identified in our findings. For example, two literature reviews [20, 49] have looked at factors that influence vaccine hesitancy in pregnancy. Both papers found that concerns regarding vaccine safety and efficacy were identified as barriers to vaccination, as well as not receiving a recommendation from a healthcare professional and lack of knowledge about vaccination in pregnancy.

Midwives providing vaccination

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

Staff education and training

Lack of conversation with a healthcare professional about influenza and pertussis vaccination in pregnancy has been identified as a barrier to vaccination in previous original research into vaccine hesitancy [51-53]. Survey data has found that 16 - 24 per cent of women had a meaningful discussion with their GP about pertussis vaccination in pregnancy [54, 55]. Cross-sectional survey data suggests the principal reason for accepting pertussis vaccination was encouragement or recommendation from a health professional. A meaningful conversation with a health professional has been identified as a facilitator to influenza and pertussis vaccination [49, 51, 53-56] with 73 - 96 per cent [51, 55] of women accepting vaccination if a health professional (especially an NHS health
professional [51]) recommends it. This previous research supports the findings of this paper that education and training for staff and reminders on health records could increase vaccine uptake.

Information and education for patients

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

4.3 Limitations

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

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

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

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

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

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

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

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

**Contributors**

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

**Declarations of interest**

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KB - Declarations of interest: none

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August 2017].


exposure on rates of hospital admissions and physician visits because of respiratory illness among


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Table 1 Search terms

Table 2 Inclusion and exclusion criteria for papers

Table 3 Effective interventions in increasing vaccination uptake in pregnant women
Figures

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

Figure 2 Effective strategies to increase vaccination in pregnancy