**Understanding factors influencing vaccination acceptance during pregnancy globally**: **A literature review**

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**Abstract**

Maternal vaccination has been evaluated and found to be extremely effective at preventing illness in pregnant women and new-borns, however, uptake of such programmes has been low in some areas.

To analyse factors contributing to uptake of vaccines globally, a systematic review on vaccine hesitancy was carried out by The Vaccine Confidence Project in 2012. In order to further analyse factors contributing to uptake of maternal immunisation, a further search within the broader systematic review was conducted using the terms 'Prenan\*' or 'Matern\*'. Forty-two articles were identified. Pregnancy-related articles were further screened to identify those focused on concerns, trust and access issues regarding maternal vaccination reported by pregnant women and healthcare workers. Thirty-five relevant articles were included which were then searched using the snowballing technique to identify additional relevant references cited in these articles. A search alert was also conducted from February to April 2015 in PubMed to ensure that no new relevant articles were missed. A total of 155 relevant articles were included.

Most of the literature which was identified on hesitancy surrounding vaccination during pregnancy reports on determinants of influenza vaccine uptake in North America. Research conducted in low-income countries focused primarily on tetanus vaccine acceptance. The main barriers cited were related to vaccine safety, low knowledge about the vaccines, their efficacy, availability and/or the diseases they prevent, and the absence of recommendations from healthcare workers. From the point of view of healthcare workers, barriers included inadequate training, inadequate reimbursement and increased workload. Twenty-seven out of 46 (59%) articles mentioning ethnicity reported lower rates of coverage among ethnic minorities.

Barriers to vaccination in pregnancy are complex and vary depending on context and population. There are wide gaps in knowledge regarding the attitudes of healthcare workers and how ethnicity and gender dynamics influence a pregnant woman’s decision to vaccinate.

**Keywords:** Vaccine hesitancy,maternal immunisation, maternal vaccination, pregnancy, racial/ethnic minorities.

**Introduction**

Over the past two decades, tremendous progress has been made in halving worldwide maternal and child deaths, supported by the drive to meet Millennium Development Goals (MDGs) by 2015. One of the targets of UN The Sustainable Development Goals (SDGs) aims to continue this momentum by reducing the global maternal mortality ratio to less than 70 per 100,000 live births ([2](#_ENREF_2)).

Maternal vaccination programmes have been evaluated and found to be extremely effective at preventing illness in pregnant women and new-borns ([3](#_ENREF_3), [4](#_ENREF_4)).The pertussis vaccine is given as part of a combined product: diphtheria/tetanus/acellular pertussis/inactivated polio vaccine (dTaP/ IPV) ([5](#_ENREF_5)). Influenza and dTaP/IPV vaccinations during pregnancy are now offered in many countries, including Australia, Belgium, Canada, China, France, Germany, India, Mexico, the Netherlands, Poland, Spain, Slovenia, Switzerland, Turkey, the UK and the USA. The Monovalent maternal tetanus vaccination is implemented as part of the routine immunization program in most developing countries. And, Group B Streptococcus (GBS) vaccines are currently being developed for use in pregnancy.

Pertussis and influenza are preventable diseases with potentially severe consequences for new-born infants and in the case of influenza, for pregnant women. Infants under the age of six months are vulnerable to transmission of pertussis and influenza infection from others, especially their mothers. The most common clinical syndromes due to pertussis, requiring intensive care admission in infants, are apnoea, pneumonia and seizures. Most deaths are associated with the presence of pneumonia ([6](#_ENREF_6)).

Globally, there remain approximately 600,000 infection-related neonatal deaths per year ([7](#_ENREF_7)) and mortality reduction in new-born infants under one year of age has been gradual, especially in the highest burden countries in Africa ([8](#_ENREF_8)), declining on average three percent per year since 1990 ([9](#_ENREF_9)). The relative proportion of new-born deaths now accounts for about 44% of the total under-five mortality and new-borns are projected to make up 55% of all under-five mortality by 2035 ([10](#_ENREF_10)). If the present rate of decline continues, it will be over a century before an African new-born baby has the same survival probability as one born in Europe or North America in 2013—three times longer than this decline took in industrialised countries before neonatal intensive care began ([8](#_ENREF_8)).

Childhood deaths associated with influenza are most frequent in infants under the age of six months; Influenza can also cause bacterial pneumonia and otitis media. Maternal influenza infection has been associated with an increased risk of hospitalisation relative to non-pregnant women of the same age: in an analysis of acute respiratory illness visits within a managed-care organization, non-pregnant women had ten excess visits per 1,000 compared with 23.7 excess visits per 1,000 among pregnant women ([11](#_ENREF_11)). Recent evidence also argues that there could be a direct effect of influenza infection on the foetal brain; Aronsson (2001) ([12](#_ENREF_12)) reported that mice that were prenatally infected with human influenza had influenza viral ribonucleic acid (RNA) in the brain.

Influenza and pertussis vaccine uptake in pregnancy are around 40% ([13](#_ENREF_13)) and 62.3% ([14](#_ENREF_14)) respectively in England. In comparison, vaccine uptake in pregnancy is much lower in other countries, such as Australia ([15](#_ENREF_15)), China ([16](#_ENREF_16)), Nigeria ([17](#_ENREF_17)) and the USA ([18](#_ENREF_18)). These lower uptake rates have been reported as being due to challenges such as lack of knowledge on the part of health care workers (HCW) and pregnant women related to the safety and efficacy of vaccines provided during pregnancy ([19](#_ENREF_19)), complex delivery arrangements involving different HCW, challenges in data collection and reporting ([20](#_ENREF_20)) and because the vaccines were newly introduced. Pregnant women and HCW also report feeling confused by mixed messages regarding vaccination and medication in pregnancy.

Maternal and neonatal tetanus (MNT) are among the most common lethal consequences of unclean deliveries and umbilical cord care practices in many countries ([21](#_ENREF_21)). However, on the basis of cause-of-death trends (2000–2012), tetanus had the largest relative decrease, of more than two-thirds from 1.3 deaths (per 1000 live births) to 0.4. This decrease is associated with substantial increases in tetanus toxoid vaccination ([22](#_ENREF_22)) and may also relate to improved cleanliness, cord care practices and education ([23](#_ENREF_23)).  High vaccination uptake however, must be sustained as neonatal tetanus is an acute disease presenting initially with loss of ability to suck, followed by generalized rigidity and painful muscle spasms as the disease progresses. Most (90%) cases of neonatal tetanus develop symptoms during the first 3–14 days of life with the majority presenting at 6–8 days. Mortality is very high: in the absence of medical treatment, case fatality approaches 100% ([24](#_ENREF_24)).

In terms of new vaccines in the pipeline, preclinical and human phase I studies of Group B Streptococcus (GBS) vaccine have been completed demonstrating the safety and immunogenicity of the vaccine. Phase III vaccine trials are still needed to determine the clinical efficacy of maternal GBS vaccination ([25](#_ENREF_25)) but acceptability of this vaccine would be extremely important as GBS is the leading cause of meningitis in the early new-born period. Infants who survive GBS meningitis often [face lifelong moderate to severe sequelae](http://www.ncbi.nlm.nih.gov/pubmed/22689869), such as school failure, loss of digits, deafness, and intellectual impairment. GBS carriage by mother may also be causally related to stillbirth, spontaneous abortion and preterm birth ([26](#_ENREF_26)). Though there is very little data on neonatal GBS disease worldwide, studies in African countries have indicated [incidence as high as 1.21 per 1000 live births](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2742968/) ([27](#_ENREF_27)).

Some of these challenges are due to “vaccine hesitancy”. Vaccine-hesitant individuals may refuse some vaccines, but agree to others or delay vaccines and are influenced by a number of factors including issues of **confidence, complacency** and **convenience**/access ([1](#_ENREF_1)).

The Strategic Advisory Group of Experts (SAGE) on Immunization established a Working Group dealing with vaccine hesitancy in March 2012 ([28](#_ENREF_28)) The working group drafted a “Model of determinants of vaccine hesitancy” ([Fig. 1](http://www.sciencedirect.com/science/article/pii/S0264410X14001443#fig0005)) organized around three key domains: 1. Contextual influences – including historic, socio-cultural, environmental, health system/institutional, economic or political factors; 2. Individual and group influences – including influences arising from personal perception of the vaccine or influences of the social/peer environment; and, 3. Vaccine and vaccination-specific issues which are directly related to the characteristics of the vaccine or the vaccination process ([Fig. 1](http://www.sciencedirect.com/science/article/pii/S0264410X14001443#fig0005)). This model includes a broad selection of factors that have been identified as potential influencers of vaccine hesitancy drawn from the collective experience and insights of the SAGE WG members ([1](#_ENREF_1)). The model has been used in this literature review to categorise concerns surrounding vaccination during pregnancy.

To address some of these issues, communication strategies around the safety and effectiveness of the inactivated influenza and acellular pertussis vaccines in pregnancy have targeted pregnant women and HCW in some settings ([29](#_ENREF_29), [30](#_ENREF_30)). However, a Vaccine Hesitancy literature review conducted by The Vaccine Confidence Project in 2012 found only 42 out of 1164 articles focusing on vaccination during pregnancy and there have only been four systematic literature reviews conducted on factors associated with vaccination uptake during pregnancy. All of these reviews focused solely on the influenza vaccine. Two were published in 2010 ([31](#_ENREF_31), [32](#_ENREF_32)), one in 2011 ([33](#_ENREF_33)) and one in 2014 (with a search that was performed up to November 2013) ([34](#_ENREF_34)). The Bulifon et al. (2010) article identified influences on decision-making for influenza A/H1N1v vaccination among pregnant women ([31](#_ENREF_31)). The lack of information on influenza vaccination for pregnant women and confusing information relating to the risk of adverse foetal events following vaccination were reported. In France, these concerns led to the vaccine being discredited by the mass media and in the population before it became available. The Guthmann et al. (2010) article focused on reasons for the low uptake of the influenza vaccine in all groups in France, including pregnant women ([32](#_ENREF_32)). Bish et al. (2011) carried out a systematic literature review to examine the psychological and demographic factors associated with uptake of vaccination globally during the 2009 pandemic ([35](#_ENREF_35)) and Yuen et al (2014) carried out a literature review of factors influencing uptake of influenza vaccination during pregnancy in North America ([34](#_ENREF_34)).

With reference to the barriers to vaccination during pregnancy mentioned above and in the SAGE working Group Model of Determinants of Vaccine Hesitancy, the aim of this literature review was to analyse factors influencing uptake of vaccines in pregnancy, focusing on maternal and HCW concerns, trust and access issues.

**Methods**

Search Strategy

To analyse factors leading to uptake of all vaccines globally, a systematic review on vaccine hesitancy was carried out by The Vaccine Confidence Project in 2012 ([1](#_ENREF_1)):

*Systematic review on vaccine hesitancy search strategy*

A search strategy was developed in Medline and then adapted as required by differential indexing across several multidisciplinary mainstream and regional databases including: Medline, Embase Classic & Embase, PsychInfo, Cochrane, CINAHL Plus, Web of Science, IBSS, LILACS, AfricaWideInfo and IMEMR. The strategy included an extensive list of keywords (Table 1) and related MeSH/subject headings in an effort to capture the many dimensions and expressions of vaccine confidence, trust and hesitancy.

In order to analyse factors influencing uptake of vaccines in pregnancy, a further search was conducted, within the broader systematic review, using the terms 'Prenan\*' or 'Matern\*'. Forty-two articles were identified. The pregnancy-related articles were then screened to identify those which focused on maternal and HCW concerns, trust and access issues regarding vaccination. Thirty-five relevant articles were included which were then searched using the snowballing technique ([36](#_ENREF_36)) to identify relevant references cited in these articles. The snowballing technique was also used on articles recommended by peers as well as articles identified in a PubMed search as the original search conducted by the Vaccine Confidence Project commenced in 2012 and more relevant articles may have been published since then.

The PubMed search commenced on 19/02/2015 and ran until 22/04/2015 with the following terms: *(vaccin\* OR immuni\*) AND (pregnan\* OR maternal) AND (attitude OR awareness OR access OR predictors OR factors OR determinants OR refusal OR hesitancy OR acceptance)* (all dates were included).

Study Selection

Once retrieved, peer-reviewed articles were screened by title and abstract according to a set of inclusion and exclusion criteria (Table 2).

Data Analysis

Data was extracted from included articles and analysed in Excel.

**Results**

Thirty-eight out of 42 articles were included from the 2012 systematic literature review ([1](#_ENREF_1)). An additional 239 articles were found after using the snowballing technique with these articles (Figure 2). Fourteen articles were added from peer recommendations and 111 from the additional PubMed search alert. A total of 364 articles were screened by title and abstract. One hundred and eighty-three articles were excluded by title and abstract, two were not available by full text and one was not able to be translated (from Hungarian) due to copyright issues relating to the article*.* One hundred and seventy-eight articles were screened by full text and 61 were excluded by full text, resulting in 117 articles. There were a total of 155 articles including the relevant articles from the earlier vaccine hesitancy search (2012) ([1](#_ENREF_1)).These articles included 113 focusing on the influenza vaccine (A(H1N1), seasonal influenza or both), 16 on tetanus, seven on dTaP/ IPV, two on group b streptococcus (GBS) and 17 on any vaccine given in pregnancy.

Main findings

Almost all of the studies (113/155, 73%)focused on the influenza vaccine and of these, 73/113 (65%) were conducted in North America. *S*tudies focusing on the tetanus vaccine were focused mainly in Asia and Africa (8/16, 50% and 4/16, 25% respectively) (Figure 3).

There has been an increase in articles focusing on the determinants of influenza vaccination uptake in pregnancy since 2008, peaking at 26 articles in 2011. This has since declined to just seven in 2014 and three as of 21st April 2015. Most articles focusing on the tetanus vaccine (14/16, 88%) were published between 1970 and 2005 ([17](#_ENREF_17), [37-49](#_ENREF_37)). There were very few articles focusing on dTaP/ IPV with the most (4/7, 57%) published in 2014 and 2015 ([18](#_ENREF_18), [50](#_ENREF_50), [51](#_ENREF_51)) (Figure 4).

Sample sizes of pregnant women surveyed/interviewed in the included articles were between 17 and 6000.Nine articles reported on the number of women intending to vaccinate.

The main concerns cited in the included articles were regarding the safety of vaccines in pregnancy (64/155, 41%). Other frequently cited barriers were: concerns about the efficacy or the belief that the vaccine is not necessary (28/155, 18%); low knowledge about the vaccines and/or the diseases they prevent (among both pregnant women and HCW) (22/155, 14%); no recommendations from HCW (17/155, 10%); and access/availability issues (6/155, 4%). From the point of view of the HCW, barriers included inadequate reimbursement ([52](#_ENREF_52)) ([53](#_ENREF_53)) ([54](#_ENREF_54)) and training ([55](#_ENREF_55)) and increased workload ([56](#_ENREF_56)) (6/155, 4%). Other barriers were conflicting advice ([57-59](#_ENREF_57)), cost ([18](#_ENREF_18), [60](#_ENREF_60)) and religion ([61](#_ENREF_61)) (Figure 5).

When these varied concerns were mapped against the SAGE Working Group model of determinants of vaccine hesitancy (Figure 1), for all vaccines, more than half were grouped under ‘risks/benefits (perceived/heuristic)’ which includes safety concerns (83/155, 54%). The role of healthcare professionals was the second biggest category of issues (26/155, 17%) and included concerns such as no recommendation from the HCW. Inadequate knowledge of why, where, what and when vaccines are needed was also a barrier to vaccination (25/155, 16%). The main concerns regarding the influenza, dTaP/ IPV and group b streptococcus vaccine fell into the ‘risk/benefit (perceived/heuristic)’ category (mostly regarding the safety of the vaccine). The main concerns regarding the tetanus vaccine fell into the ‘knowledge of why/where/what/when vaccines are needed’ category (Figure 6).

One hundred and eleven out of 155 (72%) articles focused on attitudes towards vaccination in pregnancy among pregnant women/women who had recently given birth, 29/155 (19%) on attitudes of HCW and 15/155 (10%) on the attitudes of both. The main vaccine of focus was influenza both groups (i.e. pregnant women/mothers and HCWs). There have been no studies on HCW about attitudes towards tetanus vaccination provided during pregnancy. Articles focusing on attitudes of HCW were more likely to cite barriers regarding ‘knowledge of why/where/what/when vaccines are needed’ (7/29, 24%) than those focusing on pregnant women (15/111, 14%). (Note that these figures do not include the articles that focused on both pregnant women/new mothers and HCW).

These concerns were grouped into larger overarching categories according to the SAGE Working Group model of determinants (Fig.1). Most concerns fell into the ‘Individual/social group influences’ category (106/155, 68%), followed by ‘Vaccine & vaccine-specific issues’ (37/155, 24%) and ‘Contextual issues’ (11/155, 7%).

Only 46/155 (30%) articles mentioned ethnicity as a factor influencing vaccine uptake. Of these, the majority (38/155, 25%) focused on the influenza vaccine. Twenty-seven out of 46 (59%) articles reported lower rates of vaccination coverage among ethnic minorities ([45](#_ENREF_45), [57](#_ENREF_57), [61-84](#_ENREF_61)). Only 8/46 (17%) reported higher uptake rates among ethnic minorities and 11/46 (24%) reported no difference. One hundred and nine articles (70%) did not mention ethnicity as a factor related to vaccination uptake.

Five articles found that agreement/advice from the pregnant woman’s husband/partner significantly affected her likelihood to vaccinate ([47](#_ENREF_47), [48](#_ENREF_48), [85-87](#_ENREF_85)). In Canada, advice from a spouse was frequently considered important in the immunized group ([88](#_ENREF_88)). In the Ivory Coast, the agreement of the husband is considered necessary because he is the head of the family, the decision maker, and controls the money ([47](#_ENREF_47)). In Pakistan, unmarried females are not encouraged to get themselves vaccinated ([48](#_ENREF_48)). In Turkey, 37.9% of the study group stated that they made their decisions on their own, 10.5% said their vaccination decisions were made by their spouses and 51.5% said they decided with their spouses ([87](#_ENREF_87)) and in the USA, women cited their partner’s dissuasive role; often due to the latter’s lack of knowledge or own lower vaccine uptake ([85](#_ENREF_85)).

The recommendation from a HCW to receive vaccination during pregnancy was reported in most articles to increase vaccination uptake. In a study by Walker et al. (2011), it was found that women who were offered influenza vaccination by a HCW were more likely to be vaccinated (71%) than women who were not offered the vaccine (14%) and they were more likely to have positive attitudes about vaccine effectiveness and safety ([89](#_ENREF_89)).

**Discussion**

The aim of this literature review was to analyse factors contributing to uptake of vaccines in pregnancy, focusing on maternal and HCW concerns, trust and access issues.

The largest number of articles focused on the influenza vaccine and the primary focus on the influenza vaccine was in North America and most were published in 2011. This can be explained by the 2009 A (H1N1) pandemic. The number of articles focusing on the influenza vaccine has since declined and could be because it has now been six years since the last influenza pandemic*.*

The articles focusing on the tetanus vaccine were primarily in research on low-income countries and were mostly published between 1970 and 2005. ([90](#_ENREF_90)). There were very few articles focusing on dTaP/ IPV. This is surprising considering the relatively recent introduction of the vaccine during pregnancy in many countries.

The main concerns cited in the included articles were related to the safety of vaccines in pregnancy. While low knowledge about the vaccines, their efficacy, their availability and the diseases they prevent, were among the reasons for low vaccine uptake, as some studies reported, the role of the media regarding pregnant women’s knowledge about and decisions to vaccinate cannot be ignored ([86-88](#_ENREF_86), [91-93](#_ENREF_91)). Almost all articles mentioned that recommendations from a HCW to receive the vaccine had a large impact on vaccination uptake ([89](#_ENREF_89)).

When concerns were grouped into larger overarching categories of the SAGE model of determinants, most concerns fell into the ‘Individual/social group influences’ category (106/155, 68%). This demonstrates the extent that a pregnant woman’s social context and members of the local community, family and friends influence her decision to vaccinate. Five articles explicitly stated the husband/partner’s role in the decision to vaccinate.

Twenty-seven out of 46 (59%) articles reported lower vaccination uptake among ethnic minorities. One article ([81](#_ENREF_81)) on Ghana suggested that women from ethnic minorities are discriminated against due to their poor socio-economic position, languagebarriers that prevent them from understanding and communicating with HCW, access issues related to their geographical location and less health education.

Four literature reviews were found which focused on identifying factors associated with vaccination uptake in pregnancy. All four reviews focused on the influenza vaccine and the views of pregnant women. Two of the reviews ([31](#_ENREF_31), [32](#_ENREF_32)) focused on uptake in France.

Most of the literature focused on the views of pregnant women. Only 29/155 (19%) solely focused on views of the HCW. There is the need for more in-depth analysis on the barriers HCW cited to vaccination, including inadequate training, inadequate reimbursement and increased workload.

Although West Africa has the highest global burden of whooping cough thus far in 2015, with 500 cases reported in Liberia ([94](#_ENREF_94)), the dTaP/ IPV vaccine in pregnancy is not yet provided. The Middle East has had the highest burden of influenza ([95](#_ENREF_95)) but only one study was found within this literature review focusing on influenza vaccine uptake in the area (Turkey) ([87](#_ENREF_87)). As of March 2015, maternal and neonatal tetanus is still a public health problem in 23 countries, mostly in Africa as well as Afghanistan, Cambodia, Equatorial Guinea, Haiti, India, Indonesia, Iraq, Pakistan, Papua New Guinea, Philippines and Yemen. In the literature, tetanus vaccine uptake was reported in four African countries, as well as Bangladesh, India, Indonesia, Pakistan, Peru and Turkey([21](#_ENREF_21)).

**Conclusion**

This literature review has shown that both pregnant women and HCW cite safety concerns as a main barrier to obtaining/providing influenza and pertussis vaccines during pregnancy. However responses differed depending on geographical area. Regulatory agencies still don’t have a licensing pathway for many vaccines for pregnant women, manufacturers remain concerned about liability and providers perceive that pregnant women are unwilling to take vaccines ([26](#_ENREF_26)).

In low income countries, pregnant women were more likely to cite access issues as a barrier to vaccination.

The results show that barriers to vaccination in pregnancy are complex and vary depending on context and target population. There are wide gaps in knowledge regarding the attitudes of HCW to vaccination in pregnancy, which is significant considering the impact they have on a woman’s decision to vaccinate. It is also important to understand how ethnicity and gender dynamics in different cultural settings can influence a woman’s decision to vaccinate.

As the MDG era comes to an end, the development agenda beyond 2015 is widening to include important issues such as wellbeing and human capital and non-communicable diseases (NCDs). However, neither stillbirths nor neonatal deaths are mentioned in post-2015 documents ([96](#_ENREF_96)). Thus, previous momentum for new-borns risks being forgotten. The complex socio-political reasons for under-vaccination in certain communities globally, must be understood and acted upon if vaccines are to reach and protect pregnant women and their newborn from preventable disease.

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