International Journal of Infectious Diseases 92 (2020) 1–12

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

Vaccinating pregnant women against influenza needs to be a priority for all countries: An expert commentary

Philippe Buchy[a,*], Selim Badur[b], George Kassianos[c], Scott Preiss[d], John S. Tam[e]

[a] GSK, 23 Rochester Park, Singapore 139234, Singapore
[b] GSK, Büyükdere Caddesi No:173 1. Levent Plaza B Blok, 34394 Istanbul, Turkey
[c] President of the British Global & Travel Health Association, Chairman of RAISE Pan- European Committee on Influenza, National Immunisation Lead Royal College of General Practitioners, United Kingdom, Board Director of the European Working Group on Influenza
[d] GSK, 20 Avenue Fleming, 1300 Wavre, Belgium
[e] Chairman of the Asia Pacific Alliance for the control of influenza (APACI); Adjunct Professor, Department of Applied Biology and Chemical Technology, Hong Kong Polytechnic University, 11 Yuk Choi Rd, Hung Hom, Hong Kong

ARTICLE INFO

Article history:
Received 1 November 2019
Received in revised form 12 December 2019
Accepted 13 December 2019

Keywords:
Influenza
Maternal immunisation
Pregnancy
Infant
Vaccine
Coverage

ABSTRACT

Background: In 2012, the World Health Organization recommended influenza vaccination for all pregnant women worldwide and the prioritisation of pregnant women in national influenza vaccination programmes. Nevertheless, vaccination rates in pregnant women often remain much lower than national targets.
Objectives: To assess the benefits and risks associated with influenza infection and vaccination during pregnancy, and to consider obstacles that work against influenza vaccine uptake during pregnancy.
Results: There is strong evidence that maternal and foetal outcomes can be compromised if women develop influenza infections during pregnancy. Influenza vaccines have been administered to millions of pregnant women and have demonstrated benefits in terms of disease prevention in mothers and their infants. There is a consensus amongst several recommending authorities that influenza vaccines may be safely administered during all stages of pregnancy. Healthcare professionals are recognised as the most important influencers of vaccine uptake, being well placed to recommend vaccination and directly address safety concerns.
Conclusions: Despite data supporting the value of influenza vaccination during pregnancy, vaccine uptake remains low globally. Low uptake appears to be largely due to ineffective communication with pregnant women about the risks and benefits of influenza vaccination. A graphical abstract is available online.

Introduction

Pregnancy and early infancy are periods of increased vulnerability to some infections for both mother and child (Jones and Heath, 2014). Due to physiological and immunological changes, pregnancy may increase susceptibility to infection and increase the risk of serious outcomes of infections, such as hepatitis E, herpes simplex virus, influenza, listeriosis, and malaria (Kourtis et al., 2014; Sappenfield et al., 2013). Changes in the immune system during pregnancy are mediated by hormones, cytokines, and immune cells, as well as structural changes such as remodelling of the endometrium (Vojtek et al., 2018). Despite these changes, pregnant women are still able to respond with antibody responses and immune memory following natural infection and vaccination that is similar to non-pregnant women (Vojtek et al., 2018), although cellular responses may be impaired (Shah et al., 2019).

Cardiopulmonary changes occurring during pregnancy, such as increased heart rate, stroke volume and oxygen consumption and reduced pulmonary capacity, may increase the risk of hypoxemia and contribute to increased severity of influenza infection in pregnant women (Vojtek et al., 2018). The increased vulnerability of pregnant women to influenza was illustrated during the 1918 and 2009 pandemics (Kourtis et al., 2014; Sakala et al., 2016). Mortality amongst pregnant women was 27% during the 'Spanish flu' pandemic in 1918 (Kourtis et al., 2014). Between April and August of the 2009 A (H1N1) influenza pandemic, 30 pregnant women died in the United States (US), accounting for 5% of all influenza-related deaths in the US during that period, although this demographic only represented approximately 1% of the overall population (Siston et al., 2010). Available data suggest that influenza complications may be more common during the second and third trimesters (Siston et al., 2010).

* Corresponding author.
E-mail address: philippe.x.buchy@gsk.com (P. Buchy).

https://doi.org/10.1016/j.ijid.2019.12.019

Young children are most vulnerable to infectious disease between birth and 6 months of age (Jones and Heath, 2014). Although overall mortality has been greatly reduced in children below 5 years of age over the last three decades, only minimal reductions have been achieved in very young infants (GBD 2015 Child Mortality Collaborators, 2016). In 2015, 2.6 million out of a total of 5.8 million children who died before 5 years of age worldwide, died in the neonatal period (0–27 days of age) (GBD 2015 Child Mortality Collaborators, 2016; Giles et al., 2018).

In the first months of life, the adaptive immune system of infants is unable to mount a fully protective response to many pathogens, because foetal and neonatal T cells are skewed towards Th2 immune responses that are not very effective against intracellular pathogens (Levy, 2007). During this period, infants rely on maternally transferred immunoglobulin G (IgG) antibodies present at birth in full-term infants for protection against many infectious diseases, but this defence may not be optimal in preterm infants. Transferred maternal immunity is important in the context of influenza because influenza vaccines are not currently licensed for use in children younger than 6 months of age.

Maternal immunisation builds on the concept that maternal levels of pathogen-specific antibodies are boosted and provide protection for the infant until it can mount its own effective immune response to immunisation. The transfer of maternal antibodies from immunised mothers across the placenta to the foetus is initiated at around week 17 of pregnancy and increases with gestation, so that by week 33 the foetal antibody levels often match, and in many cases exceed maternal levels due to active transplacental antibody transport (Jones and Heath, 2014). After delivery, maternal antibodies may be transferred to the infant via the breastmilk (Rasmussen et al., 2014). Since the level of protective maternal antibodies in the infant wanes by 2–3 months after birth, elevated baseline maternal antibody levels confer an extended period of maternally derived infant immune protection (Eick et al., 2011; Jones and Heath, 2014).

The successful prevention of infectious disease in young infants after maternal immunisation has been demonstrated for other infectious diseases. Maternal immunisation has greatly contributed to the elimination of neonatal tetanus (96% reduction in mortality), and has reduced the incidence of pertussis infections in infants younger than 8 weeks by up to 90% (Giles et al., 2018).

In 2012, the World Health Organization (WHO) recommended influenza vaccination for all pregnant women worldwide (WHO, 2012). Despite WHO recommendations to prioritise pregnant women in national influenza vaccination programmes (WHO, 2012), vaccination rates in pregnant women have often remained much lower than proposed by national targets. This paper discusses the benefits and risks associated with influenza vaccination during pregnancy, and considers obstacles that need to be overcome in order to improve influenza vaccination coverage in expectant mothers. This commentary draws together the results of important randomised clinical trials, observational studies, and meta-analyses that have been conducted to examine different aspects of maternal vaccination, and explores solutions to improve influenza vaccine coverage during pregnancy.

Risks associated with influenza infection for the mother, the foetus, and the infant: the burden of disease

Influenza increases morbidity, severe disease, and hospitalisations in pregnant women

Influenza is a frequent viral infection that is estimated to affect 11% of pregnant women (Fiore et al., 2009; Irving et al., 2000). Compared with the general population, pregnant women are at increased risk of serious illness due to influenza virus infection, although risk estimates vary widely between studies, possibly reflecting virus virulence in individual seasons, access to healthcare, and physician thresholds for hospital admission (Meijer et al., 2015). A systematic review of 100 studies, of which 96 were observational in design, showed that 5–87% of pregnant women with influenza were hospitalised, of whom 0–22% had severe disease defined as intensive care admission or death (Meijer et al., 2015). Among pregnant women with influenza-associated intensive care admission, mortality ranged from 0 to 33% (Meijer et al., 2015). A recent meta-analysis using individual-level data from previous studies found that pregnancy increased the risk of influenza-related hospitalisation by seven-fold (adjusted odds ratio (aOR) 6.80, 95% confidence interval (CI) 6.02–7.68), and that the risk was increased in older mothers and women with any cardio-respiratory disease (Mertz et al., 2019).

A hospital database study in the US reported that hospitalised pregnant women were more likely to have a respiratory illness during influenza season if they also had a high-risk condition for which influenza vaccination is recommended (aOR 3.2, 95% CI 3.0–3.5) (Cox et al., 2006). Risks associated with influenza infection for the mother, the foetus, and the infant are summarised in Figure 1.

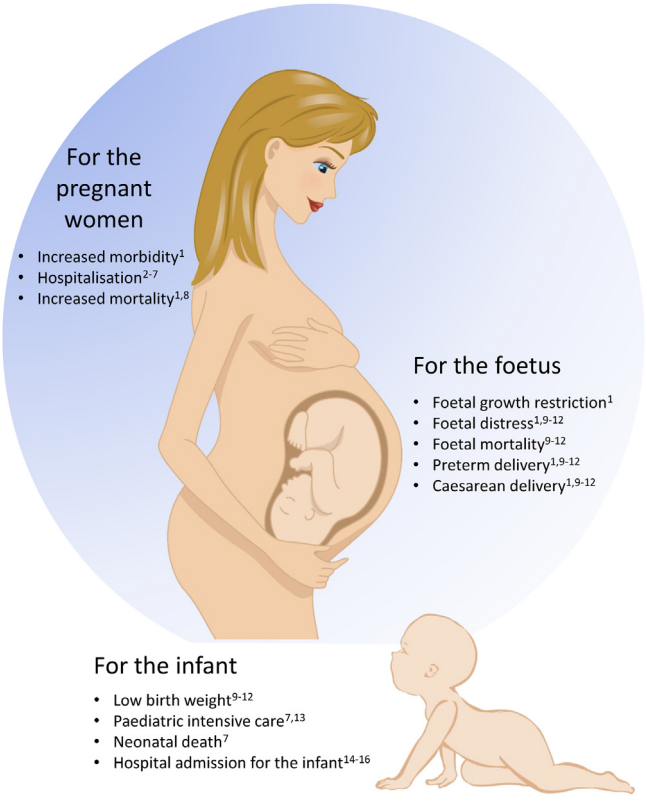

Figure 1. Adverse outcomes of influenza infection in pregnant women, the foetus, and the infant.
Legend: [1](Moniz and Beigi, 2014); [2](Prasad et al., 2019); [3](Neuzil et al., 1998); [4](Mazagatos et al., 2018); [5](Mosby et al., 2011); [6](Haberg et al., 2013); [7](Creanga et al., 2010); [8](Tempia et al., 2015); [9](Meijer et al., 2015); [10](Cox et al., 2006); [11](Martin et al., 2013); [12](Ribeiro et al., 2018); [13](Chaves et al., 2014); [14](Poehling et al., 2006); [15](Nelson et al., 2014); [16](Zhang et al., 2017).

A study in New Zealand performed during 2012–2015 reported that the risk of hospitalisation following influenza infection in pregnancy was higher for Māori women compared with women of European or other ethnicity (rate ratio (RR) 3.2, 95% CI 1.3–8.4), and for pregnant women infected with influenza A virus (RR for H3N2 3.0, 95% CI 1.8–5.0), but not influenza B virus (RR 1.8, 95% CI 0.7–4.6) (Prasad et al., 2019). The same study also reported that pregnant women experienced higher rates of influenza hospitalisation compared with non-pregnant women (RR 3.4, 95% CI 2.5–4.7), but no increased risk of hospitalisation was observed post-partum (RR 0.7, 95% CI 3.0–7.7). Complementing these data, a US (nested) case–control study using healthcare insurance claims data reported that during an influenza season, women in the second and third trimesters had a higher risk of hospitalisation for cardiopulmonary events than those in the post-partum period (OR 3.41, 95% CI 3.09–3.76) (Neuzil et al., 1998). The cohort study found that the incidence of hospitalisation due to a cardiopulmonary event was significantly higher among pregnant women during influenza seasons (influenza attributable risk 10.48, 95% CI 6.70–14.26 for the third trimester). In a Spanish study of the 2010–2016 influenza seasons, pregnant women had a relative risk of hospitalisation with severe influenza that was nearly eight times higher than that of non-pregnant women of reproductive age (Mazagatos et al., 2018). Several studies have also reported that influenza infection during pregnancy during the 2009 A(H1N1) influenza pandemic was associated with an increased risk of hospital admission (Creanga et al., 2010; Haberg et al., 2013; Mosby et al., 2011).

In 1999–2009 in South Africa, the estimated mean annual seasonal influenza-associated mortality rates were elevated for pregnant versus non-pregnant women (12.6 vs 7.3 deaths per 100 000 person years (PY)). This elevated mortality rate in pregnancy was further exacerbated by concomitant HIV infection (74.9 deaths in HIV-positive vs 1.5 deaths in HIV-negative per 100 000 PY) and by the 2009 A(H1N1) pandemic (19.3 vs 9.4 deaths per 100 000 PY for pregnant vs non-pregnant women, respectively) (Tempia et al., 2015). Of note, a meta-analysis of 33 datasets that included participant-level data of 186 656 individuals confirmed that pregnant women were at higher risk of hospital admission (OR 6.80, 95% CI 6.02–7.68), but did not find that pregnancy was a risk factor for influenza-related intensive care admission or death, except in those with an underlying immunocompromising condition or diabetes and in older mothers. A cohort study of pregnant and not pregnant women would need to be conducted to address the discrepancies between the results of previous ecological studies and this meta-analysis (Mertz et al., 2019).

Influenza infection may harm the foetus

A systematic review and meta-analysis reported on 10 studies that evaluated foetal outcomes in women with pandemic A(H1N1) infection during pregnancy (He et al., 2017). Maternal influenza infection was significantly associated with low birth weight (RR 1.71, 95% CI 1.03–2.84), and stillbirth (RR 2.36, 95% CI 1.05–5.31), and lower 5-minute APGAR (Activity, Pulse, Grimace, Appearance, Respiration) score (not significant) compared with newborn infants of women without influenza (He et al., 2017).

Pregnant women hospitalised with a respiratory illness have an increased risk of foetal distress, foetal mortality, preterm delivery, low weight, and need for caesarean section compared with hospitalised pregnant women without respiratory illness (Cox et al., 2006; Martin et al., 2013; Ribeiro et al., 2018). Infants born to pregnant women with influenza who were admitted to an intensive care unit were more likely to have adverse outcomes compared to infants born to women with influenza who were not admitted to intensive care (Newsome et al., 2019). In line with this finding, a Norwegian study found that mild influenza illness during pregnancy was not associated with an increased risk of pre-eclampsia, preterm birth, or the foetus being small for gestational age (Laake et al., 2018). In contrast, influenza infection in pregnancy during the 2009 A(H1N1) influenza pandemic was associated with increased foetal mortality and increased preterm and emergency caesarean deliveries (Haberg et al., 2013; Mosby et al., 2011).

Influenza is a severe disease in infants less than 6 months of age

The burden of influenza among infants less than 6 months of age who are the target of maternal immunisation programmes is less well described (Fell et al., 2017). Observational studies consistently show that children aged younger than 6 months have a high risk of hospital admission due to influenza (Chaves et al., 2014; Nelson et al., 2014; Poehling et al., 2006; Zhang et al., 2017). Estimates of the incidence of hospitalisation for laboratory-confirmed seasonal influenza in this age group range from 6.2 to 73.0 per 10 000 infants under 6 months (except for one study for which the rate was 250 per 10 000 infants) (Fell et al., 2017). Few studies have reported long-term morbidity or mortality rates after influenza infection in young infants. A population-based study that used hospital laboratory surveillance data in the US from 2003 to 2012 reported that the influenza-related hospitalisation rate was highest in infants less than 3 months of age (328 per 100 000 infants, range 84–644, vs 117 per 100 000 range 45–194 in 3 to <6 month-olds) (Chaves et al., 2014). Among all infants less than 12 months of age hospitalised with influenza, 10% required admission to intensive care and 4% needed mechanical ventilation. The risk of intensive care admission was significantly higher in infants aged less than 3 months compared to 6–12-month-old infants (aOR 1.40, 95% CI 1.04–1.88) (Chaves et al., 2014). The presence of high-risk conditions in the infant, such as lung disease, cardiovascular disease, or neurological and neuromuscular disorders, significantly increased the risk of intensive care admission (Chaves et al., 2014).

Immunogenicity, effectiveness, and safety of influenza vaccines in pregnant women, foetuses, newborns, and infants

Immunogenicity of influenza vaccination in pregnant women and antibodies in newborns and infants

Most studies have shown that the antibody response to influenza vaccine is similar in pregnant and non-pregnant women (Haberg et al., 2013; Mak et al., 2008), although there is some debate as to the optimal timing of vaccination in pregnancy. A meta-analysis of 16 studies found that the response to influenza vaccination was 1.33–1.96-fold higher in women vaccinated during the third trimester of pregnancy than at earlier time points, with evidence suggesting that vaccination later in pregnancy increased antibody transfer to the foetus by 1.21–1.64-fold (Cuningham et al., 2019). However, earlier vaccination provides longer protection against influenza for the pregnant woman, and averting infection early in pregnancy may have positive benefits for the foetus. For example, the rate of low birth weight is lower among infants of women vaccinated earlier rather than later in pregnancy (Katz et al., 2018). Conversely, antibody waning by the time of delivery may result in lower cord antibody levels and increase the risk of maternal influenza during the post-partum period, with transmission to the infant. The timing of the influenza season with respect to pregnancy and vaccination may also impact the effectiveness of

vaccination. Re-vaccination later in pregnancy may be necessary for women who receive influenza vaccination during the first trimester (Cuningham et al., 2019).

Vaccine-induced influenza-specific maternal antibodies appear to have high transplacental transfer rates (87–99%), depending on the IgG antibody subtype. The half-life of maternal vaccine-derived antibodies in the infant circulation is 43–53 days, which is similar to the half-life of transplacental antibodies derived from naturally acquired maternal influenza infections (Englund et al., 1993; Mak et al., 2008).

A randomised study found that a single dose of high-dose inactivated monovalent 2009 A(H1N1) influenza vaccine administered during the second or third trimester induced influenza haemagglutinin inhibition (HAI) titres of ≥1:40 (considered as seroprotective) in 93% of pregnant women (Jackson et al., 2011). HAI titres in cord blood were 1.81–2.96-fold higher than in maternal blood samples at delivery.

Maternal vaccine-induced antibodies appear to persist for at least 3 months in infants (Cuningham et al., 2019; Jackson et al., 2011; Kostinov et al., 2018).

A US prospective, observational cohort study during the 2002–2005 influenza seasons found that infants born to influenza-vaccinated mothers had higher antibody titres at birth and at 2–3 months old, but not at 6 months old, compared with infants of unvaccinated mothers (Eick et al., 2011).

Efficacy and effectiveness of influenza vaccine in pregnant women and their infants

The efficacy and effectiveness of maternal influenza vaccination in preventing maternal influenza, adverse foetal outcomes, and influenza infection in their infants have been explored in observational studies and in a small number of randomised controlled trials (RCTs).

A Norwegian national registry study of 117 000 pregnancies during the 2009–2010 A(H1N1) pandemic reported that vaccination of pregnant women decreased the risk of influenza diagnosis during pregnancy by 70% (Haberg et al., 2013).

Investigators of a US study with a trivalent inactivated influenza vaccine reported an approximately 50% reduction in risk of acute respiratory illness associated with laboratory-confirmed influenza among pregnant women, similar to the protection observed among all adults during two influenza seasons (Thompson et al., 2014). In a recent Danish cohort study, influenza vaccine efficacy against laboratory-confirmed influenza was 63.9% (95% CI 29.1–81.6%) in pregnant women and 56.8% (95% CI 25.0–75.1%) in infants aged <6 months (Molgaard-Nielsen et al., 2019). The retrospective PREVENT (Pregnancy Influenza Vaccine Effectiveness Network) study demonstrated 40% protection against laboratory-confirmed influenza-associated hospitalisation during pregnancy between 2010 and 2016 (Thompson et al., 2019). Data from a RCT in Bangladesh showed that women vaccinated in the third trimester of pregnancy had significantly fewer respiratory illnesses with fever than controls (vaccine efficacy 28.9%, 95% CI 6.9–45.7%) (Zaman et al., 2008).

Partial protection provided by vaccination against influenza has also been demonstrated in HIV-infected pregnant women (Madhi et al., 2014). Vaccine efficacy against laboratory-confirmed influenza among HIV-infected women vaccinated during pregnancy was 57.7% (95% CI 0.6–82.1%) compared with 50.4% (95% CI 14.5–71.2%) among HIV-uninfected controls (Madhi et al., 2014). Pandemic and seasonal influenza vaccination during pregnancy has been associated with reduced low birth weight and reduced preterm births (Giles et al., 2019; Nunes et al., 2016a). A meta-analysis of 16 studies of foetal outcomes after A(H1N1) vaccination during pregnancy found a lower risk of stillbirth among women who had been vaccinated at any time during pregnancy (adjusted hazard ratio 0.80, 95% CI 0.6–0.92), although the quality of the evidence prohibited a definite conclusion (Zhang et al., 2018).

A RCT of influenza vaccine versus placebo in 3693 pregnant women administered at either 17–25 weeks or 26–34 weeks of pregnancy, found that vaccine efficacy against laboratory-confirmed influenza in infants did not differ significantly by gestational age at vaccination (Katz et al., 2018). The study reported no statistically significant differences between the early and late-vaccinated cohorts in terms of confirmed maternal influenza during pregnancy, low birth weight, small-for-gestational age, or preterm birth.

A prospective, active-controlled, observer-blind, randomised phase 4 trial evaluated vaccine efficacy against laboratory-confirmed influenza in the infants of pregnant women in Mali vaccinated during the third trimester with a trivalent inactivated influenza vaccine (Tapia et al., 2016). Cumulative vaccine efficacy was 67.9% (95% CI 48.4–89.8%) after the first 4 months of follow-up, diminishing thereafter (57.3%, 95% CI 30.6–74.4% during the 5th month). A placebo-controlled RCT of trivalent inactivated influenza vaccine in pregnant women found that vaccine efficacy in infants was highest until 8 weeks of age (85.6%, 95% CI 38.3–98.4%), decreasing to 30.3% (95% CI −154.9–82.6%) by 16–24 weeks of age (Nunes et al., 2016b). In the US, the effectiveness of influenza vaccine given to pregnant women was 45–92% at preventing seasonal influenza-related hospitalisations in infants aged <6 months (Benowitz et al., 2010; Poehling et al., 2011). In England during the 2013–2014 influenza season, vaccination prevented 71% of influenza infections in infants aged <6 months and prevented 64% of infant hospitalisations due to influenza (Dabrera et al., 2014). Infants under 6 months of age born to US mothers who where immunised during pregnancy were less likely to have a medically attended acute respiratory illness during the peak of the 2004–2005 influenza season, when compared with infants born to non-immunised mothers matched by age and date of delivery (10.9% vs 31%, $p < 0.001$) (Mak et al., 2008). A meta-analysis of four RCTs and five observational studies found that influenza vaccination during pregnancy reduced laboratory-confirmed influenza in infants by 48% (95% CI 33–59%), and reduced influenza-associated hospitalisation by 72% (95% CI 39–87%) (Nunes and Madhi, 2018). Other studies in developing countries (Bangladesh, Nepal, Mali, and South Africa) have reported that maternal vaccination reduces influenza disease and severe pneumonia episodes among infants (Omer et al., 2018; Zaman et al., 2008).

Safety of influenza vaccines in pregnant women and foetuses

Influenza vaccines have been used in pregnant women in the US since the 1950s (Jones and Heath, 2014). Prior to the 2009 influenza pandemic, studies of vaccination in pregnancy were limited due to theoretical safety concerns and reluctance to enrol pregnant women in clinical trials. However, during the 2009 A(H1N1) pandemic, the risk of disease outweighed expected adverse events and studies in pregnant women were initiated.

A retrospective observational cohort study in the US with 75 900 vaccinated and 148 000 unvaccinated pregnant women concluded that receipt of a trivalent inactivated influenza vaccine during pregnancy was not associated with an increased risk of adverse events in the 42 days post vaccination, supporting its safety for mothers (Nordin et al., 2013). In 2009–2010, 2.4 million pregnant women were vaccinated in the US, and no patterns of adverse outcomes for mother or child were identified (Munoz, 2012). Similarly, a Danish cohort study of 7000 influenza vaccinated women reported no evidence of an increased risk of foetal death associated with exposure to an adjuvanted pandemic

2009 A(H1N1) influenza vaccine during pregnancy (Pasternak et al., 2012). A US prospective RCT of two licensed seasonal trivalent inactivated influenza vaccines came to similar conclusions (Munoz et al., 2018).

An Australian cohort study investigating the safety of a trivalent inactivated influenza vaccine found no evidence suggesting that adverse events following vaccination are more common in pregnant women compared to non-pregnant women controls of similar age (Regan et al., 2015). In a similar way, a Thai cohort study reported that adverse events following immunisation with a trivalent inactivated influenza vaccine in pregnant women occurred with a similar frequency to those reported by healthy adults in other studies, and that adverse events were generally mild and self-limiting. No influenza vaccine-associated serious adverse events were reported (Asavapiriyanont et al., 2018).

Systematic reviews of the safety of influenza vaccination in pregnancy emphasise that inactivated influenza vaccine can be safely and effectively administered during any trimester of pregnancy, and that no study to date has demonstrated an increased risk of either maternal complications or adverse foetal outcomes associated with inactivated influenza vaccination (Bratton et al., 2015; Fell et al., 2015; McMillan et al., 2015; Nunes et al., 2016a; Polyzos et al., 2015). A WHO review of the safety of influenza vaccines concluded that no adverse effects on pregnancy outcomes have been reported for non-adjuvanted or adjuvanted influenza vaccines (WHO, 2014). Of note, as for other live-attenuated vaccines, live-attenuated influenza vaccines are contraindicated during pregnancy (ACIP, 2011).

Numerous large studies and meta-analyses have demonstrated that inactivated influenza vaccines do not increase the risk of foetal death, adverse foetal outcomes, adverse birth outcomes, low birth weight, spontaneous abortion, or congenital malformations (Jeong et al., 2019; Ludvigsson et al., 2015; Madhi et al., 2014; McHugh et al., 2019; McMillan et al., 2015; Omer et al., 2015; Steinhoff et al., 2017).

A case–control study showed an association between spontaneous abortion and vaccination with inactivated influenza vaccine within a 28-day exposure period, but only among women who had received an A(H1N1)-containing vaccine in the previous influenza season (aOR 7.7, 95% CI 2.2–27.3) (Donahue et al., 2017). The interpretation of this finding is difficult in view of the study design, which cannot be easily compared with other available data. The implications for vaccinating pregnant women are not known given that the composition of seasonal vaccines changes annually (Chambers et al., 2017). Further investigation is required, but these results did not lead to changes to the recommendations of the Advisory Committee on Immunization Practices for vaccinating pregnant women.

The effect of maternal influenza vaccination on the immune response of infants to subsequent influenza vaccination has not been explored in humans. Given that influenza vaccines are not currently recommended until 6 months of age, any theoretical interference by maternal antibody is likely to be minimal.

Some authorities recommend influenza vaccination only in the second or third trimesters because of theoretical concerns associated with administering vaccines during embryogenesis. While the large bodies of available evidence described above support the safety of influenza vaccination in early pregnancy, much of the data rely on observational studies potentially prone to confounding factors. Further studies are required to validate any potential association between seasonal influenza vaccination and spontaneous abortion, and to assess vaccine safety in early pregnancy. To this end, a US Mini-sentinel Post-Licensure Rapid Immunization Safety Monitoring (PRISM) project, created in 2009 to monitor the safety of the H1N1 vaccination programme, is establishing a framework to use claims data, birth certificate information, and vaccine information to evaluate pregnancy outcomes after influenza vaccination (Nguyen et al., 2012).

International and national recommendations and guidelines for maternal influenza immunisation

The WHO produces global vaccination recommendations that are adapted by individual countries based on local information about risk groups, disease burden, and cost-effectiveness. Importantly, contradictions that may occur between national guidelines, recommendations (based on post-marketing experience), and vaccine labels (based on pre-licensure clinical studies) may make messages on maternal vaccination appear ambiguous for healthcare providers (HCPs) and the public (Regan, 2016).

In 2012, the WHO recommended that all pregnant women worldwide receive influenza vaccination regardless of stage of pregnancy. For the first time, the WHO also emphasised pregnant women as the highest priority group in countries considering initiating or expanding seasonal influenza vaccination programmes (WHO, 2012). In 2014, 115 of 194 WHO Member States (59%) had a national influenza immunisation policy, with 85 of these countries (44%) having influenza vaccination programmes aimed specifically at pregnant women. Recommendations made by a selection of authorities worldwide are provided in Table 1. The inclusion of pregnant women in a national influenza vaccination policy was found to be more likely in high- or upper middle-income countries (Ortiz et al., 2016).

The Advisory Committee on Immunization Practices of the US Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists recommend that women who are or will be pregnant during the influenza season receive an inactivated influenza vaccine as soon as it is available (ACOG, 2018; Fiore et al., 2009). Both authorities emphasise that any of the licensed, recommended, age-appropriate inactivated influenza vaccines can be given safely during any trimester. They also recommend that obstetricians and gynaecologists, as well as other HCPs, should counsel pregnant women about the safety and benefits of influenza immunisation for themselves and their foetuses and advocate for the benefits of passive immunity from maternal immunisation for their newborns (ACOG, 2018).

An extensive review conducted by the European Centre for Disease Prevention and Control concluded that the vaccination of pregnant women against influenza could reduce the number of influenza-related hospitalisations and deaths in pregnant women and potentially reduce the burden of influenza in children younger than 6 months, for whom influenza vaccination and antiviral treatment are not indicated (ECDC, 2012).

Current influenza vaccination coverage

In the European Union, recommendations to vaccinate pregnant women have been adopted by an increasing number of countries (91% in 2014–2015 compared with 40% in 2008–2009) (Jorgensen et al., 2018). Among a few ($n = 11$) countries with readily available vaccine coverage data, the median influenza vaccine coverage rate in pregnant women was 8.7%, compared to 34.4% amongst older adults also at risk (Jorgensen et al., 2018). In the US 2017–2018 influenza season, vaccine uptake before or during pregnancy was 49.1% (Kahn et al., 2018), which is lower that the Healthy People 2020 target of 80% (Healthy-People.gov, 2019). One study in Hong Kong found 1.7% influenza vaccine uptake amongst pregnant women (2010–2011 season) (Yuet Sheung Yuen et al., 2013). By contrast, a hospital survey in Brazil in 2010 found that maternal influenza vaccine uptake was 95.7% following a government vaccination campaign (Kfouri Rde and Richtmann, 2013). However, it is not known whether the results are generally applicable across

Table 1
Influenza vaccine recommendations during pregnancy (non-exhaustive).

Country (recommending body)	Influenza vaccine recommendation	Reference
World Health Organization	All pregnant women worldwide regardless of stage of pregnancy	WHO (2012)
Australia (Australian Technical Advisory Group on Immunisation)	Pregnant women are strongly recommended to receive influenza vaccine in each pregnancy	ATAGI (2018)
Australia, New Zealand (Royal Australian and New Zealand College of Obstetricians and Gynaecologists)	All pregnant women regardless of gestation, and in women planning pregnancy	RANZCOG (2011)
United Kingdom, Ireland, France, Spain, Portugal, Greece, Finland, Poland, Estonia, Latvia, Lithuania, Luxemburg, Liechtenstein, Romania, Hungary, Slovakia, Czech Republic, Slovenia, Malta	All pregnant women	ECDC (2018)
Cyprus, Belgium, Italy	Healthy pregnant women in their second and third trimesters	
Germany, Norway, Denmark, Sweden	All pregnant women in the second and third trimesters and during any trimester or women with clinical risk	
Argentina, Bahamas, Belize, Bermuda, Bolivia, Brazil, Cayman Islands, Colombia, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Guatemala, Mexico, Nicaragua, Panama, Paraguay, Peru, St. Lucia, Suriname, Turks and Caicos, Uruguay, Venezuela	Targeted for influenza vaccination	Ropero-Alvarez et al. (2016)
United States (Advisory Committee on Immunization Practices, the American College of Obstetricians and Gynecologists)	Influenza vaccination recommended for all pregnant women	ACOG (2018)
Canada	All pregnant women	NACI (2018)
China (Chinese Center for Disease Control and Prevention)	All pregnant women or women who plan to become pregnant during the influenza season	Feng et al. (2015)
Taiwan (Centers for Disease Control and Prevention)	All pregnant women	CDC (2017)
Japan (obstetric and gynaecological societies)	All pregnant women	JNC (2019)
Thailand (Ministry of Public Health)	Healthy pregnant women in the second and third trimesters	Muangchana et al. (2010)
South Africa (National Department of Health)	All pregnant women at all stages of pregnancy, including the post-partum period	NICD (2018)

Brazil or whether the high uptake rate has been sustained. Very high influenza vaccine coverage rates among pregnant women have also been achieved in Argentina (>95% between 2011 and 2014) after a national influenza vaccination campaign in 2010 and the introduction of mandatory free influenza vaccination for all at-risk groups in 2011 (Vizzotti et al., 2015). During this period, no deaths were recorded due to influenza in vaccinated pregnant women, and there were no reports of serious adverse events related to vaccination (Vizzotti et al., 2015).

Obstacles to influenza vaccination in pregnancy and lessons learned from countries that have succeeded in improving vaccine coverage

Barriers to maternal influenza immunisation

Barriers to antenatal influenza immunisation are multifactorial and stem from vaccine manufacturers, HCPs, pregnant women, and the wider society (Text Box 1).

Vaccine manufacturers

Manufacturers are reluctant to develop, evaluate in RCTs, and market vaccines for pregnant women (Jones and Heath, 2014), and may provide overly cautious product labelling, or labelling that does not reflect WHO and/or national public health advisory group recommendations (Proveaux et al., 2016; Roberts and Gruber, 2015; Top et al., 2016). Until recently, no vaccine label had included a specific indication during pregnancy because no licensed vaccine had been studied in pregnant women in pre-licensure RCTs (Roberts and Gruber, 2015). Furthermore, a 2016 study found that only 10% of reviewed product information documents endorsed influenza vaccination during pregnancy (Proveaux et al., 2016). A study of 141 HCPs from 49 countries reported that wording in influenza vaccine product labels influenced decisions to recommend vaccination. Negatively framed statements in the product label indicating the absence of data or cautionary use in pregnancy (as opposed to more positively framed statements) were perceived by HCPs to contradict WHO and national immunisation recommendations, which may impact their decision to recommend antenatal influenza immunisation (Top et al., 2016). Appropriately worded vaccine labelling is helpful for providers, but strongly worded national recommendations, reimbursement, and application of standard of care has more impact in increasing vaccine uptake (Top et al., 2016). In Europe, influenza vaccine labels are more permissive and carry stronger language recommending vaccination in pregnancy than labels in the US (GSK group of companies, 2019a, 2019b). Nevertheless, vaccine uptake in Europe is substantially lower (around 10%) than the US (40–50%) (Jorgensen et al., 2018; Kahn et al., 2018), suggesting that factors other than the label are equally important.

HCPs

The failure of HCPs to recommend and offer influenza vaccination to pregnant women, reluctance of HCPs who do not normally administer vaccines (e.g., midwives) to vaccinate pregnant women, financial barriers or lack of incentives, a lack of national guidelines, and lack of strong, clear recommendations by health authorities have been identified as HCP barriers to antenatal influenza vaccination (Ishola et al., 2013; Jones and Heath, 2014; Li et al., 2018; Lutz et al., 2018; MacDougall and Halperin, 2016; Maertens et al., 2016; Prospero et al., 2019). The absence of clear recommendations results in hesitancy/fear amongst prescribers, which potentially places pregnant women and young children at risk if vaccination is withheld.

Pregnant women

The main barriers to antenatal influenza vaccination reported by pregnant women include safety concerns for the foetus, objections to drugs in pregnancy, poor understanding of the

Box 1. Barriers to maternal influenza vaccination.

Manufacturers

- Reluctance of manufacturers to develop, test in RCTs, and market vaccines for pregnant women (Jones and Heath, 2014)
- Regulatory barriers (product information labelling) (Proveaux et al., 2016; Roberts and Gruber, 2015; Top et al., 2016)

HCPs

- Poor sensitisation of care providers (Koul and Mir, 2018)
- Failure to offer influenza vaccination to pregnant women (Ishola et al., 2013; Jones and Heath, 2014; MacDougall and Halperin, 2016; Maertens et al., 2016; Prospero et al., 2019)
- Reluctance of HCPs who do not normally administer vaccines (e.g., midwives) to pregnant women (Ishola et al., 2013; MacDougall and Halperin, 2016; Maertens et al., 2016; Prospero et al., 2019)
- Lack of strong, clear recommendations by health authorities (Ishola et al., 2013; MacDougall and Halperin, 2016; Maertens et al., 2016; Prospero et al., 2019)
- The logistics of vaccine acquisition, storage, administration, and tracking (Ishola et al., 2013; Koul and Mir, 2018; MacDougall and Halperin, 2016; Maertens et al., 2016; Prospero et al., 2019)
- Financial barriers (e.g., inadequate reimbursement) (Lutz et al., 2018)
- Lack of national guidelines (Li et al., 2018)

Pregnant women

- Concerns regarding the safety and welfare of the foetus (D'Alessandro et al., 2018; Henninger et al., 2013; Meharry et al., 2013; Moniz and Beigi, 2014; Wilson et al., 2015)
- Objections to drugs in pregnancy (Ishola et al., 2013; MacDougall and Halperin, 2016; Maertens et al., 2016; Prospero et al., 2019)
- Lack of knowledge about the severity and burden of influenza disease (D'Alessandro et al., 2018; Ishola et al., 2013; Li et al., 2018; MacDougall and Halperin, 2016; Maertens et al., 2016; Prospero et al., 2019)
- Lack of awareness of beneficial effect of vaccination (Koul and Mir, 2018; Li et al., 2018)

Societal

- Social norms (Ishola et al., 2013; MacDougall and Halperin, 2016; Maertens et al., 2016; Prospero et al., 2019)
- Opinions of family and friends (Ishola et al., 2013; MacDougall and Halperin, 2016; Maertens et al., 2016; Prospero et al., 2019)
- Poor antenatal care (Pathirana et al., 2015)
- Low income and high parity (Pathirana et al., 2015)

severity and burden of influenza disease, and low awareness of the benefits of vaccination (Henninger et al., 2013; Ishola et al., 2013; Koul and Mir, 2018; Li et al., 2018; MacDougall and Halperin, 2016; Maertens et al., 2016; Meharry et al., 2013; Moniz and Beigi, 2014; Prospero et al., 2019; Wilson et al., 2015). A US study identified 25 different barriers to antenatal vaccination by pregnant women. These were primarily related to vaccine safety concerns followed by perceptions of low risk of disease and beliefs that influenza was a mild disease (Lutz et al., 2018). HCP recommendations were highlighted as the most important predictor of maternal immunisation uptake (Lutz et al., 2018). Studies in China and in several developing countries in Africa and Asia, identified similar findings, with poor influenza vaccine uptake in pregnancy associated primarily with low awareness of the risks of influenza infection and the benefits and safety of seasonal influenza vaccination (Li et al., 2018; Pathirana et al., 2015).

An Italian study reported correlations between education level, pregnancy stage, and willingness to receive antenatal immunisations, including a strong association between low educational attainment and perceived vaccine safety concerns (D'Alessandro et al., 2018).

Societal

Societal barriers to antenatal vaccination include social norms and the opinions of family and friends, as well as poor antenatal care, low income, high parity, and poor sensitization of care (Ishola et al., 2013; Koul and Mir, 2018; MacDougall and Halperin, 2016; Maertens et al., 2016; Pathirana et al., 2015; Prospero et al., 2019). Inadequate financial and human resources are also major barriers to maternal immunisation in low-income countries, and translate to inadequate vaccination services delivery and logistics management (Koul and Mir, 2018).

Solutions to improve uptake of influenza vaccination in pregnancy

Improvements in antenatal influenza vaccine uptake require a combination of regulatory reform, improved vaccine accessibility such that all HCPs involved in prenatal care can be involved in discussion and decision-making around influenza vaccination, HCP endorsement of vaccination, and patient and HCP education on the benefits of antenatal vaccination, preferably delivered together in a multichannel approach, as outlined in Text Box 2 and below.

Vaccine accessibility

Influenza vaccines are unique in that they are adjusted seasonally, and vaccines recommended for the northern and southern hemispheres frequently differ. Manufacturers usually register one vaccine in countries with clear seasonality, which means that influenza vaccines may not be available all year round. Strategies to provide year-round vaccine availability could include local vaccine production, alternating between northern and southern hemisphere vaccines throughout the year, or extending the shelf-life of influenza vaccines (Lambach et al., 2015). The latter

Box 2. Proposed solutions to improve antenatal influenza vaccination.

Regulatory processes

- Improved processes for the development, approval, and labelling of vaccines for pregnant women (Roberts and Gruber, 2015; Vojtek et al., 2018)

Vaccine accessibility

- Convenient location of vaccination clinic (Wiley et al., 2013)
- Vaccination available at the antenatal clinics (Wiley et al., 2013)
- Free vaccination

Influenza vaccine endorsement by HCPs

- HCPs recommend vaccination to pregnant women (Wiley et al., 2013; Wilson et al., 2015)
- Enabling of HCPs through training, reimbursement, and management of workload (Wilson et al., 2015)
- Pregnant women having face-to-face consultations with HCPs (McCarthy et al., 2015)
- Internet and text messaging as information sources about influenza vaccination (McCarthy et al., 2015)

Education on benefits of antenatal influenza vaccination

- Improved awareness of maternal immunisation among HCPs who do not traditionally administer vaccinations (Healy et al., 2015; Maltezou et al., 2019)
- Prenatal vaccine education of expectant mothers (Kfouri Rde and Richtmann, 2013; O'Leary et al., 2019; Vojtek et al., 2018)

Multichannel approaches

- Governments willing to invest in and support prevention by vaccination. Multichannel approaches involving community awareness campaigns, community pharmacy programmes, primary care incentive schemes, positive reinforcement of HCPs, IT support, medical education, and strategic weekly influenza group teleconferencing (Baxter, 2013)
- Awareness of non-medical media perception of vaccine benefits and safety (Wilcox et al., 2018)
- Strategy to counter vaccine refusal (O'Leary et al., 2019)
- Knowledge of local disease epidemiology, involvement of the consumer, HCP recommendation, equitable access to maternal vaccination, and systems for disease surveillance, programme evaluation, and safety monitoring (Krishnaswamy et al., 2019)
- Reminders about vaccination on antenatal healthcare records, midwives providing vaccination, education and information provision for HCPs and patients (Bisset and Paterson, 2018)

has allowed the availability of vaccines in Australia nearly all year around, reducing the period during which vaccine is no longer available to around 1 month of the year (ATAGI, 2019).

Optimally located vaccination clinics improve influenza vaccine accessibility and vaccination uptake, as reported in an Australian study (Wiley et al., 2013).

Influenza vaccine endorsement by HCPs

A lack of HCP recommendation is one of the most common reasons for not receiving immunisations (Johnson et al., 2008; Wiley et al., 2013). Other factors associated with vaccination uptake include perceived severity of influenza infections, overall caution toward antenatal vaccination, and willingness to accept the vaccine if recommended. Foetal safety concerns are negatively associated with vaccination uptake, but an Australian study found that 68% of women who expressed concern agreed that they would have accepted the vaccine if their HCP had recommended it (Wiley et al., 2013). Another Australian study reported that expectant mothers preferred face-to-face consultations with HCPs and internet and text messaging as information sources about influenza vaccination, highlighting how different means of communication can be used to boost vaccine uptake (Johnson et al., 2008; McCarthy et al., 2015).

Education on the benefits of antenatal vaccination influences uptake

HCP recommendations are essential to increase vaccination coverage, and HCPs responsible for antenatal care need to be educated on the main aspects of maternal immunisation and be convinced about its clear benefits for pregnant women and infants (Wilson et al., 2015). This also applies to HCPs who are not traditionally providing antenatal immunisations, and emphasises that effective communication strategies are needed to improve antenatal vaccination awareness among obstetricians, midwives, and general practitioners. However, education of HCPs alone is unlikely to be sufficient, as parental vaccine hesitancy also needs to be addressed through specific public awareness campaigns (Healy et al., 2015). The impact of education on vaccination uptake is exemplified by an educational intervention at a large maternity hospital in Greece, where education resulted in an increase in antenatal influenza vaccination rate from below 2% to 20% (Maltezou et al., 2019). Furthermore, a study from Brazil found that maternal acceptance of influenza vaccination in pregnancy improved following a government campaign and HCP endorsements during prenatal visits. Close to 70% of women who refused influenza vaccination during pregnancy stated that they would have accepted immunisation if they had been informed about the neonatal protection provided by influenza vaccination (Kfouri Rde and Richtmann, 2013).

A survey among US obstetricians and gynaecologists found that HCPs perceive vaccine refusal in pregnancy as common, and that emphasizing the risk of disease to the foetus or infant may be an effective strategy to increase antenatal influenza vaccine uptake (O'Leary et al., 2019).

Multichannel approach

The Stockport multichannel approach, which was rolled out during the 2010–2011 influenza season in Stockport, UK, is an example of a successful multichannel approach to increasing antenatal vaccination. It included a community awareness campaign, a community pharmacy programme, a general practitioner incentive scheme, positive reinforcement from enthusiastic and confident HCPs, information technology support (e.g., follow-up reminders, data entry, database quality control), medical education, and strategic weekly influenza group teleconferencing (Baxter, 2013). Following the introduction of the programme, influenza vaccine coverage increased from 65.1% to 79.7% among at-risk populations, and from 53.0% to 63.4% among populations not at risk (Baxter, 2013).

Key elements essential for successful implementation of maternal immunisation programmes in low- and middle-income countries are knowledge of local disease epidemiology, involvement of the consumer, HCP endorsement, equitable access to maternal vaccination, and systems for disease surveillance, programme evaluation, and safety monitoring (Krishnaswamy et al., 2019).

In high-income countries, strategies that boost antenatal influenza vaccination rates include reminders about vaccination on antenatal healthcare records, midwives providing vaccination, and education and information provision for HCPs and patients (Bisset and Paterson, 2018; Vojtek et al., 2018).

Whereas the existence of recommendations for maternal immunisation is a pre-requisite, they are not always sufficient to ensure that HCPs feel confident to recommend vaccination to pregnant women, nor do they ensure that pregnant women are aware of the value of such vaccination. To improve confidence, further progress in generating data acceptable for label updates is needed, and requires collaboration between manufacturers, regulators, and public health authorities (Roberts and Gruber, 2015; Vojtek et al., 2018).

Conclusions

There is strong evidence that maternal and foetal outcomes can be compromised if women develop influenza infections during pregnancy, although estimates of the magnitude and extent of harm vary between studies. The risks associated with influenza in pregnancy were highlighted during the A(H1N1) pandemic and the vast majority of studies that evaluated risk were conducted during that period. However, available data suggest similar trends for seasonal influenza infections that occur during pregnancy. Influenza vaccines have been administered to millions of pregnant women and their clinical benefit has been demonstrated. The consensus amongst many recommending authorities is that they are safe in mothers and their infants regardless of the stage of pregnancy during which they are administered. Continued surveillance of adverse events and pregnancy outcomes after influenza vaccination is needed to address specific concerns and data gaps, and to provide ongoing reassurance to authorities, HCPs and women of the positive benefit–risk ratio for vaccination.

Multichannel efforts focused on improved education on the benefits of antenatal influenza vaccination aimed at both pregnant women and HCPs, supported by effective IT solutions, appear to be important for boosting the uptake of influenza vaccination in pregnancy. The number and quality of interactions between pregnant women and the healthcare system needs to increase, with presentation of consolidated and consistent messages on vaccination during pregnancy. Low vaccine uptake does not appear to be due to a lack of data on the benefits of antenatal vaccination, but rather due to the ineffectiveness of communicating this information.

Authors' contributions

All authors reviewed the literature, provided substantial input, and reviewed the paper. PB led the manuscript development. All authors approved the final article and are accountable for all aspects of the work.

Declaration of interest

SB, PB, and SP are employees of the GSK group of companies and hold shares in the GSK group of companies. GK reports personal fees from the GSK group of companies, Seqirus, Sanofi Pasteur, MSD, AZ, and CDC/Kazakhstan, as well as travel expenses covered from ESWI, outside the submitted work. JST has nothing to disclose.

Funding

GlaxoSmithKline Biologicals SA funded all costs associated with the development and the publishing of the present manuscript.

Ethical approval

Not required.

Acknowledgements

The authors thank Rebecca Crawford (GSK, Singapore) for her support during the development of the publication. The authors would also like to thank Business & Decision Life Sciences platform for editorial assistance and manuscript coordination, on behalf of GSK. Nathalie Arts coordinated manuscript development and editorial support and Stefan Amisten provided medical writing support.

References

ACIP. General recommendations on immunization. recommendations of the advisory committee on immunization practices (ACIP). MMWR 2011;60 (2):1–64.

ACOG. ACOG committee opinion no. 732: influenza vaccination during pregnancy. Obstet Gynecol 2018;131(4):e109–14.

Asavapiriyanont S, Kittikraisak W, Suntarattiwong P, Ditsungnoen D, Kaoiean S, Phadungkiatwatana P, et al. Tolerability of trivalent inactivated influenza vaccine among pregnant women, 2015. BMC Pregnancy Childbirth 2018;18 (1):110.

ATAGI. Australian Technical Advisory Group on Immunisation (ATAGI). Australian immunisation handbook. Canberra: Australian Government Department of Health; 2018 Available from: https://immunisationhandbook.health.gov.au/. [Accessed 20 July 2019].

ATAGI. Australian Technical Advisory Group on Immunisation. Statement on the administration of seasonal influenza vaccines in 2019. 2019 April. Available from: https://www.health.gov.au/sites/default/files/atagi-advice-on-seasonal-influenza-vaccines-in-2019.pdf. [Accessed 22 November 2019]..

Baxter D. Approaches to the vaccination of pregnant women: experience from Stockport, UK, with prenatal influenza. Hum Vaccin Immunother 2013;9 (6):1360–3.

Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vazquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. Clin Infect Dis 2010;51(12):1355–61.

Bisset KA, Paterson P. Strategies for increasing uptake of vaccination in pregnancy in high-income countries: a systematic review. Vaccine 2018;36(20):2751–9.

Bratton KN, Wardle MT, Orenstein WA, Omer SB. Maternal influenza immunization and birth outcomes of stillbirth and spontaneous abortion: a systematic review and meta-analysis. Clin Infect Dis 2015;60(5):e11–9.

CDC. Taiwan Centers for Disease Control Emerging Infectious Disease Incident Team. What is the target of the flu vaccination program this year?. 2017 Available from: https://www.cdc.gov.tw/antirumorinfo.aspx?treeid=9B400D6-BAFE34857&nowtreeid=1BF9D4691CE7E7DD&tid=B9FC327FD934FBB7. [Accessed 31 July 2019].
Chambers CD, Xu R, Mitchell AA. Commentary on: "Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010-11 and 2011-12". Vaccine 2017;35(40):5323–4.
Chaves SS, Perez A, Farley MM, Miller L, Schaffner W, Lindegren ML, et al. The burden of influenza hospitalizations in infants from 2003 to 2012, United States. Pediatr Infect Dis J 2014;33(9):912–9.
Cox S, Posner SF, McPheeters M, Jamieson DJ, Kourtis AP, Meikle S. Hospitalizations with respiratory illness among pregnant women during influenza season. Obstet Gynecol 2006;107(6):1315–22.
Creanga AA, Johnson TF, Graitcer SB, Hartman LK, Al-Samarrai T, Schwarz AG, et al. Severity of 2009 pandemic influenza A (H1N1) virus infection in pregnant women. Obstet Gynecol 2010;115(4):717–26.
Cuningham W, Geard N, Fielding JE, Braat S, Madhi SA, Nunes MC, et al. Optimal timing of influenza vaccine during pregnancy: a systematic review and meta-analysis. Influenza Other Respir Viruses 2019;13(5):438–52.
D'Alessandro A, Napolitano F, D'Ambrosio A, Angelillo IF. Vaccination knowledge and acceptability among pregnant women in Italy. Hum Vaccin Immunother 2018;14(7):1573–9.
Dabrera G, Zhao H, Andrews N, Begum F, Green H, Ellis J, et al. Effectiveness of seasonal influenza vaccination during pregnancy in preventing influenza infection in infants, England, 2013/14. Euro Surveill 2014;19(45):20959.
Donahue JG, Kieke BA, King JP, DeStefano F, Mascola MA, Irving SA, et al. Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010-11 and 2011-12. Vaccine 2017;35(40):5314–22.
ECDC. Public health guidance: seasonal influenza vaccination of children and pregnant women. 2012 Available from: https://ecdc.europa.eu/en/publications-data/public-health-guidance-seasonal-influenza-vaccination-children-and-pregnant-women. [Accessed 31 July 2019].
ECDC. European Centre for Disease Prevention and Control. Seasonal influenza vaccination and antiviral use in EU/EEA Member States. 2018 Available from: https://ecdc.europa.eu/sites/portal/files/documents/seasonal-influenza-antiviral-use-2018.pdf. [Accessed 31 July 2019].
Eick AA, Uyeki TM, Klimov A, Hall H, Reid R, Santosham M, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. Arch Pediatr Adolesc Med 2011;165(2):104–11.
Englund JA, Mbawuike IN, Hammill H, Holleman MC, Baxter BD, Glezen WP. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. J Infect Dis 1993;168(3):647–56.
Fell DB, Johnson J, Mor Z, Katz MA, Skidmore B, Neuzil KM, et al. Incidence of laboratory-confirmed influenza disease among infants under 6 months of age: a systematic review. BMJ open 2017;7(9)e016526.
Fell DB, Platt RW, Lanes A, Wilson K, Kaufman JS, Basso O, et al. Fetal death and preterm birth associated with maternal influenza vaccination: systematic review. BJOG 2015;122(1):17–26.
Feng L, Yang P, Zhang T, Yang J, Fu C, Qin Y, et al. Technical guidelines for the application of seasonal influenza vaccine in China (2014-2015). Hum Vaccin Immunother 2015;11(8):2077–101.
Fiore AE, Shay DK, Broder K, Iskander JK, Uyeki TM, Mootrey G, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep 2009;58(RR-8):1–52.
GBD 2015 Child Mortality Collaborators. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1725–74.
Giles ML, Krishnaswamy S, Macartney K, Cheng A. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. Hum Vaccin Immunother 2019;15(3):687–99.
Giles ML, Krishnaswamy S, Wallace EM. Maternal immunisation: What have been the gains? Where are the gaps? What does the future hold?. F1000Res 2018;7.
GSK group of companies. Fluarix quadrivalent [package insert]. 2019 Available from: Food and Drug Administration website. https://www.fda.gov/media/115744/download. [Accessed 30 October 2019]..
GSK group of companies. Fluarix Tetra suspension for injection in pre-filled syringe. 2019 Available from: Electronic medicines compendium website. https://www.medicines.org.uk/emc/product/3021/smpc. [Accessed 30 October 2019].
Haberg SE, Trogstad L, Gunnes N, Wilcox AJ, Gjessing HK, Samuelsen SO, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. N Engl J Med 2013;368(4):333–40.
He J, Liu ZW, Lu YP, Li TY, Liang XJ, Arck PC, et al. A systematic review and meta-analysis of influenza A virus infection during pregnancy associated with an increased risk for stillbirth and low birth weight. Kidney Blood Press Res 2017;42(2):232–43.
Healthy-People.gov. Immunization and infectious diseases. 2019 Available from: https://www.healthypeople.gov/2020/data-search/Search-the-Data#objid=6362. [Accessed 29 October 2019].
Healy CM, Rench MA, Montesinos DP, Ng N, Swaim LS. Knowledge and attitiudes of pregnant women and their providers towards recommendations for immunization during pregnancy. Vaccine 2015;33(41):5445–51.
Henninger M, Naleway A, Crane B, Donahue J, Irving S. Predictors of seasonal influenza vaccination during pregnancy. Obstet Gynecol 2013;121(4):741–9.
Irving WL, James DK, Stephenson T, Laing P, Jameson C, Oxford JS, et al. Influenza virus infection in the second and third trimesters of pregnancy: a clinical and seroepidemiological study. BJOG 2000;107(10):1282–9.
Ishola Jr. DA, Permalloo N, Cordery RJ, Anderson SR. Midwives' influenza vaccine uptake and their views on vaccination of pregnant women. J Public Health (Oxf) 2013;35(4):570–7.
Jackson LA, Patel SM, Swamy GK, Frey SE, Creech CB, Munoz FM, et al. Immunogenicity of an inactivated monovalent 2009 H1N1 influenza vaccine in pregnant women. J Infect Dis 2011;204(6):854–63.
Jeong S, Jang EJ, Jo J, Jang S. Effects of maternal influenza vaccination on adverse birth outcomes: a systematic review and Bayesian meta-analysis. PLoS One 2019;14(8)e0220910.
JNC. Japan National Center for Child Health and Development. The Japan drug information institute in pregnancy. 2019 Available from: https://www.ncchd.go.jp/en/center/activity/JDIIP/faq.html. [Accessed 31 July 2019].
Johnson DR, Nichol KL, Lipczynski K. Barriers to adult immunization. Am J Med 2008;121(7 Suppl 2):S28–35.
Jones C, Heath P. Antenatal immunization. Hum Vaccin Immunother 2014;10(7):2118–22.
Jorgensen P, Mereckiene J, Cotter S, Johansen K, Tsolova S, Brown C. How close are countries of the WHO European Region to achieving the goal of vaccinating 75% of key risk groups against influenza? Results from national surveys on seasonal influenza vaccination programmes, 2008/2009 to 2014/2015. Vaccine 2018;36(4):442–52.
Kahn KE, Black CL, Ding H, Williams WW, Lu PJ, Fiebelkorn AP, et al. Influenza and Tdap vaccination coverage among pregnant women—United States, April 2018. MMWR Morb Mortal Wkly Rep 2018;67(38):1055–9.
Katz J, Englund JA, Steinhoff MC, Khatry SK, Shrestha L, Kuypers J, et al. Impact of timing of influenza vaccination in pregnancy on transplacental antibody transfer, influenza incidence, and birth outcomes: a randomized trial in rural Nepal. Clin Infect Dis 2018;67(3):334–40.
Kfouri Rde A, Richtmann R. Influenza vaccine in pregnant women: immunization coverage and associated factors. Einstein (Sao Paulo) 2013;11(1):53–7.
Kostinov MP, Cherdantsev AP, Kuselman AI, Akhmatova NK, Kostinova AM, Deryabina EV, et al. Prospective randomized open-label comparative study of immunogenicity after subunit and polymeric subunit influenza vaccines administration among mothers and infants. Hum Vaccin Immunother 2018;1–8.
Koul PA, Mir H. The biggest barrier to influenza vaccination in pregnant females in India: poor sensitization of the care providers. Vaccine 2018;36(25):3569–70.
Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med 2014;370(23):2211–8.
Krishnaswamy S, Lambach P, Giles ML. Key considerations for successful implementation of maternal immunization programs in low and middle income countries. Hum Vaccin Immunother 2019;1–9.
Laake I, Tunheim G, Robertson AH, Hungnes O, Waalen K, Haberg SE, et al. Risk of pregnancy complications and adverse birth outcomes after maternal A(H1N1)pdm09 influenza: a Norwegian population-based cohort study. BMC Infect Dis 2018;18(1):525.
Lambach P, Alvarez AM, Hirve S, Ortiz JR, Hombach J, Verweij M, et al. Considerations of strategies to provide influenza vaccine year round. Vaccine 2015;33(47):6493–8.
Levy O. Innate immunity of the newborn: basic mechanisms and clinical correlates. Nat Rev Immunol 2007;7(5):379–90.
Li R, Xie R, Yang C, Rainey J, Song Y, Greene C. Identifying ways to increase seasonal influenza vaccine uptake among pregnant women in China: a qualitative investigation of pregnant women and their obstetricians. Vaccine 2018;36(23):3315–22.
Ludvigsson JF, Strom P, Lundholm C, Cnattingius S, Ekbom A, Ortqvist A, et al. Maternal vaccination against H1N1 influenza and offspring mortality: population based cohort study and sibling design. BMJ 2015;351:h5585.
Lutz CS, Carr W, Cohn A, Rodriguez L. Understanding barriers and predictors of maternal immunization: identifying gaps through an exploratory literature review. Vaccine 2018;36(49):7445–55.
MacDougall DM, Halperin SA. Improving rates of maternal immunization: challenges and opportunities. Hum Vaccin Immunother 2016;12(4):857–65.
Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 2014;371(10):918–31.
Maertens K, Cabore RN, Huygen K, Hens N, Van Damme P, Leuridan E. Pertussis vaccination during pregnancy in Belgium: results of a prospective controlled cohort study. Vaccine 2016;34(1):142–50.
Mak TK, Mangtani P, Leese J, Watson JM, Pfeifer D. Influenza vaccination in pregnancy: current evidence and selected national policies. Lancet Infect Dis 2008;8(1):44–52.
Maltezou HC, Pelopidas Koutroumanis P, Kritikopoulou C, Theodoridou K, Katerelos P, Tsiaousi I, et al. Knowledge about influenza and adherence to the recommendations for influenza vaccination of pregnant women after an educational intervention in Greece. Hum Vaccin Immunother 2019;1–5.
Martin A, Cox S, Jamieson DJ, Whiteman MK, Kulkarni A, Tepper NK. Respiratory illness hospitalizations among pregnant women during influenza season, 1998-2008. Matern Child Health J 2013;17(7):1325–31.
Mazagatos C, Delgado-Sanz C, Oliva J, Gherasim A, Larrauri A. Spanish Influenza Surveillance S. Exploring the risk of severe outcomes and the role of seasonal influenza vaccination in pregnant women hospitalized with confirmed influenza, Spain, 2010/11-2015/16. PLoS One 2018;13(8)e0200934.

McCarthy EA, Pollock WE, Tapper L, Sommerville M, McDonald S. Increasing uptake of influenza vaccine by pregnant women post H1N1 pandemic: a longitudinal study in Melbourne, Australia, 2010 to 2014. BMC Pregnancy Childbirth 2015;15:53.
McHugh L, Marshall HS, Perrett KP, Nolan T, Wood N, Lambert SB, et al. The safety of influenza and pertussis vaccination in pregnancy in a cohort of Australian mother-infant pairs, 2012-2015: the FluMum study. Clin Infect Dis 2019;68(3):402–8.
McMillan M, Porritt K, Kralik D, Costi L, Marshall H. Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. Vaccine 2015;33(18):2108–17.
Meharry PM, Colson ER, Grizas AP, Stiller R, Vazquez M. Reasons why women accept or reject the trivalent inactivated influenza vaccine (TIV) during pregnancy. Matern Child Health J 2013;17(1):156–64.
Meijer WJ, van Noortwijk AG, Bruinse HW, Wensing AM. Influenza virus infection in pregnancy: a review. Acta Obstet Gynecol Scand 2015;94(8):797–819.
Mertz D, Lo CK, Lytvyn L, Ortiz JR, Loeb M, Flurisk I. Pregnancy as a risk factor for severe influenza infection: an individual participant data meta-analysis. BMC Infect Dis 2019;19(1):683.
Molgaard-Nielsen D, Fischer TK, Krause TG, Hviid A. Effectiveness of maternal immunization with trivalent inactivated influenza vaccine in pregnant women and their infants. J Intern Med 2019;286(4):469–80.
Moniz MH, Beigi RH. Maternal immunization. Clinical experiences, challenges, and opportunities in vaccine acceptance. Hum Vaccin Immunother 2014;10(9):2562–70.
Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. Am J Obstet Gynecol 2011;205(1):10–8.
Muangchana C, Thamapornpilas P, Karnkawinpong O. Immunization policy development in Thailand: the role of the Advisory Committee on Immunization Practice. Vaccine 2010;28 Suppl 1:A104–9.
Munoz FM. Safety of influenza vaccines in pregnant women. Am J Obstet Gynecol 2012;207(3 Suppl):S33–7.
Munoz FM, Jackson LA, Swamy GK, Edwards KM, Frey SE, Stephens I, et al. Safety and immunogenicity of seasonal trivalent inactivated influenza vaccines in pregnant women. Vaccine 2018;36(52):8054–61.
NACI. National Advisory Committee on Immunization. Canadian Immunization Guide. Chapter on influenza and statement on seasonal influenza vaccine for 2018–2019. 2018 Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2018-2019.html. [Accessed 31 July 2019].
Nelson EA, Ip M, Tam JS, Mounts AW, Chau SL, Law SK, et al. Burden of influenza infection in hospitalised children below 6 months of age and above in Hong Kong from 2005 to 2011. Vaccine 2014;32(49):6692–8.
Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998;148(11):1094–102.
Newsome K, Alverson CJ, Williams J, McIntyre AF, Fine AD, Wasserman C, et al. Outcomes of infants born to women with influenza A(H1N1)pdm09. Birth Defects Res 2019;111(2):88–95.
Nguyen M, Ball R, Midthun K, Lieu TA. The Food and Drug Administration's Post-Licensure Rapid Immunization Safety Monitoring program: strengthening the federal vaccine safety enterprise. Pharmacoepidemiol Drug Safety 2012;21 Suppl 1:291–7.
NICD. South Africa National Institute for Communicable Diseases. Influenza. NICD recommendations for the diagnosis, prevention, management and public health response. 2018 Available from: http://www.nicd.ac.za/wp-content/uploads/2017/03/Influenza-guidelines-rev_-23-April-2018.pdf. [Accessed 31 July 2019].
Nordin JD, Kharbanda EO, Benitez GV, Nichol K, Lipkind H, Naleway A, et al. Maternal safety of trivalent inactivated influenza vaccine in pregnant women. Obstet Gynecol 2013;121(3):519–25.
Nunes MC, Aqil AR, Omer SB, Madhi SA. The effects of influenza vaccination during pregnancy on birth outcomes: a systematic review and meta-analysis. Am J Perinatol 2016a;33(11):1104–14.
Nunes MC, Cutland CL, Jones S, Hugo A, Madimabe R, Simoes EA, et al. Duration of infant protection against influenza illness conferred by maternal immunization: secondary analysis of a randomized clinical trial. JAMA Pediatr 2016b;170(9):840–7.
Nunes MC, Madhi SA. Influenza vaccination during pregnancy for prevention of influenza confirmed illness in the infants: a systematic review and meta-analysis. Hum Vaccin Immunother 2018;14(3):758–66.
O'Leary ST, Riley LE, Lindley MC, Allison MA, Albert AP, Fisher A, et al. Obstetrician-gynecologists' strategies to address vaccine refusal among pregnant women. Obstet Gynecol 2019;133(1):40–7.
Omer SB, Clark DR, Aqil AR, Tapia MD, Nunes MC, Kozuki N, et al. Maternal influenza immunization and prevention of severe clinical pneumonia in young infants: analysis of randomized controlled trials conducted in Nepal, Mali and South Africa. Pediatr Infect Dis J 2018;37(5):436–40.
Omer SB, Richards JL, Madhi SA, Tapia MD, Steinhoff MC, Aqil AR, et al. Three randomized trials of maternal influenza immunization in Mali, Nepal, and South Africa: methods and expectations. Vaccine 2015;33(32):3801–12.
Ortiz JR, Perut M, Dumolard L, Wijesinghe PR, Jorgensen P, Ropero AM, et al. A global review of national influenza immunization policies: analysis of the 2014 WHO/UNICEF joint reporting form on immunization. Vaccine 2016;34(45):5400–5.
Pasternak B, Svanstrom H, Molgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark. BMJ 2012;344:e2794.
Pathirana J, Nkambule J, Black S. Determinants of maternal immunization in developing countries. Vaccine 2015;33(26):2971–7.
Poehling KA, Edwards KM, Weinberg GA, Szilagyi P, Staat MA, Iwane MK, et al. The underrecognized burden of influenza in young children. N Engl J Med 2006;355(1):31–40.
Poehling KA, Szilagyi PG, Staat MA, Snively BM, Payne DC, Bridges CB, et al. Impact of maternal immunization on influenza hospitalizations in infants. Am J Obstet Gynecol 2011;204(6 Suppl 1):S141–8.
Polyzos KA, Konstantelias AA, Pitsa CE, Falagas ME. Maternal influenza vaccination and risk for congenital malformations: a systematic review and meta-analysis. Obstet Gynecol 2015;126(5):1075–84.
Prasad N, Huang QS, Wood T, Aminisani N, McArthur C, Baker MG, et al. Influenza-associated outcomes among pregnant, post-partum, and non-pregnant women of reproductive age. J Infect Dis 2019;219(12):1893–903.
Prospero E, Galmozzi S, Paris V, Felici G, Barbadoro P, D'Alleva A, et al. Factors influencing refusing of flu vaccination among pregnant women in Italy: healthcare workers' role. Influenza Other Respir Viruses 2019;13(2):201–7.
Proveaux T, Lambach P, Ortiz JR, Hombach J, Halsey NA. Review of prescribing information for influenza vaccines for pregnant and lactating women. Vaccine 2016;34(45):5406–9.
RANZCOG. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Influenza vaccination during pregnancy (and in women planning pregnancy). 2011 Available from: https://ranzcog.edu.au/RANZCOG_-SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Influenza-vaccination-in-pregnancy-(C-Obs-45)-Review-March-2017.pdf?ext=.pdf. [Accessed 31 July 2019].
Rasmussen SA, Watson AK, Kennedy ED, Broder KR, Jamieson DJ. Vaccines and pregnancy: past, present, and future. Semin Fetal Neonatal Med 2014;19(3):161–9.
Regan AK. The safety of maternal immunization. Hum Vaccin Immunother 2016;12(12):3132–6.
Regan AK, Tracey L, Blyth CC, Mak DB, Richmond PC, Shellam G, et al. A prospective cohort study comparing the reactogenicity of trivalent influenza vaccine in pregnant and non-pregnant women. BMC Pregnancy Childbirth 2015;15:61.
Ribeiro AF, Pellini ACG, Kitagawa BY, Marques D, Madalosso G, Fred J, et al. Severe influenza A(H1N1)pdm09 in pregnant women and neonatal outcomes, State of Sao Paulo, Brazil, 2009. PLoS One 2018;13(3)e0194392.
Roberts JN, Gruber MF. Regulatory considerations in the clinical development of vaccines indicated for use during pregnancy. Vaccine 2015;33(8):966–72.
Ropero-Alvarez AM, El Omeiri N, Kurtis HJ, Danovaro-Holliday MC, Ruiz-Matus C. Influenza vaccination in the Americas: progress and challenges after the 2009 A (H1N1) influenza pandemic. Hum Vaccin Immunother 2016;12(8):2206–14.
Sakala IG, Honda-Okubo Y, Fung J, Petrovsky N. Influenza immunization during pregnancy: benefits for mother and infant. Hum Vaccin Immunother 2016;12(12):3065–71.
Sappenfield E, Jamieson DJ, Kourtis AP. Pregnancy and susceptibility to infectious diseases. Infect Dis Obstet Gynecol 2013;2013:752852.
Shah NM, Imami N, Kelleher P, Barclay WS, Johnson MR. Pregnancy-related immune suppression leads to altered influenza vaccine recall responses. Clin Immunol 2019;108254.
Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 2010;303(15):1517–25.
Steinhoff MC, Katz J, Englund JA, Khatry SK, Shrestha L, Kuypers J, et al. Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial. Lancet Infect Dis 2017;17(9):981–9.
Tapia MD, Sow SO, Tamboura B, Teguete I, Pasetti MF, Kodio M, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. Lancet Infect Dis 2016;16(9):1026–35.
Tempia S, Walaza S, Cohen AL, von Mollendorf C, Moyes J, McAnerney JM, et al. Mortality associated with seasonal and pandemic influenza among pregnant and nonpregnant women of childbearing age in a high-HIV-prevalence setting-South Africa, 1999-2009. Clin Infect Dis 2015;61(7):1063–70.
Thompson MG, Kwong JC, Regan AK, Katz MA, Drews SJ, Azziz-Baumgartner E, et al. Influenza vaccine effectiveness in preventing influenza-associated hospitalizations during pregnancy: a multi-country retrospective test negative design study, 2010–2016. Clin Infect Dis 2019;68(9):1444–53.
Thompson MG, Li DK, Shifflett P, Sokolow LZ, Ferber JR, Kurosky S, et al. Effectiveness of seasonal trivalent influenza vaccine for preventing influenza virus illness among pregnant women: a population-based case-control study during the 2010-2011 and 2011-2012 influenza seasons. Clin Infect Dis 2014;58(4):449–57.
Top KA, Arkell C, Scott H, McNeil SA, Mannerfeldt J, Ortiz JR, et al. Effect of package insert language on health-care providers' perceptions of influenza vaccination safety during pregnancy. Lancet Glob Health 2016;4(10):e690–1.
Vizzotti C, Neyro S, Katz N, Juarez MV, Perez Carrega ME, Aquino A, et al. Maternal immunization in Argentina: a storyline from the prospective of a middle income country. Vaccine 2015;33(47):6413–9.
Vojtek I, Dieussaert I, Doherty TM, Franck V, Hanssens L, Miller J, et al. Maternal immunization: where are we now and how to move forward?. Ann Med 2018;50(3):193–208.
WHO. World Health Organisation. Vaccines against influenza WHO position paper—November 2012. Wkly Epidemiol Rec 2012;87(47):461–76.
WHO. World Health Organization Global Advisory Committee on Vaccine Safety. Safety of immunization during pregnancy. A review of the evidence. 2014 Available from: https://www.who.int/vaccine_safety/publications/safety_pregnancy_nov2014.pdf. [Accessed 31 July 2019].

Wilcox CR, Bottrell K, Paterson P, Schulz WS, Vandrevala T, Larson HJ, et al. Influenza and pertussis vaccination in pregnancy: portrayal in online media articles and perceptions of pregnant women and healthcare professionals. Vaccine 2018;36(50):7625–31.
Wiley KE, Massey PD, Cooper SC, Wood NJ, Ho J, Quinn HE, et al. Uptake of influenza vaccine by pregnant women: a cross-sectional survey. Med J Aust 2013;198(7):373–5.
Wilson RJ, Paterson P, Jarrett C, Larson HJ. Understanding factors influencing vaccination acceptance during pregnancy globally: a literature review. Vaccine 2015;33(47):6420–9.
Yuet Sheung Yuen C, Yee Tak Fong D, Lai Yin Lee I, Chu S, Sau-mei Siu E, Tarrant M. Prevalence and predictors of maternal seasonal influenza vaccination in Hong Kong. Vaccine 2013;31(45):5281–8.
Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med 2008;359(15):1555–64.
Zhang C, Wang X, Liu D, Zhang L, Sun X. A systematic review and meta-analysis of fetal outcomes following the administration of influenza A/H1N1 vaccination during pregnancy. Int J Gynaecol Obstet 2018;141(2):141–50.
Zhang X, Zhang J, Chen L, Feng L, Yu H, Zhao G, et al. Pneumonia and influenza hospitalizations among children under 5 years of age in Suzhou, China, 2005-2011. Influenza Other Respir Viruses 2017;11(1):15–22.