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Maternal vaccination for the prevention of influenza: current status and hopes for the future

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Abstract

Influenza is an important cause of morbidity and mortality among pregnant women and young infants, and influenza infection during pregnancy has also been associated with adverse obstetric and birth outcomes. There is substantial evidence – from randomized trials and observational studies – that maternal influenza immunization can protect pregnant women and their infants from influenza disease. In addition, there is compelling observational evidence that prevention of influenza in pregnant women can also protect against certain adverse pregnancy outcomes, including stillbirth and preterm birth. In this article we will review and evaluate the literature on both the burden of influenza disease in pregnant women and infants, as well as the multiple potential benefits of maternal influenza immunization for mother, fetus, and infant. We will also review key clinical aspects of maternal influenza immunization, as well as identify remaining knowledge gaps, and discuss avenues for future investigation.

Keywords

Influenza; pregnancy; vaccine; seasonal; pandemic; maternal immunization; infant; stillbirth; preterm birth

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1. Introduction

Influenza virus infections have long been recognized as an important cause of morbidity and mortality in pregnant women. Based on observations of increased disease severity in pregnant women during the 1918 [1] and 1957 [2] influenza pandemics, pregnant women were first prioritized for routine influenza vaccination in the United States (US) as early as 1960 [3]. Following several decades of more limited recommendations in the US [4], starting in 1995 the Advisory Committee on Immunization Practices (ACIP) reintroduced healthy pregnant women as a group to be considered for routine influenza vaccination [5]. In 2004 this recommendation was expanded to all pregnant women regardless of gestational age [6]. Multiple other countries have since also begun to recommend routine influenza immunization of healthy pregnant women. For countries that are planning to initiate or expand their seasonal influenza immunization programs, in 2012 the World Health Organization (WHO) recommended that pregnant women receive the “highest priority” for vaccination [7].

The reasons for more severe influenza disease during pregnancy, particularly during pandemics, remain incompletely characterized. Physiologic changes associated with pregnancy, including increases in minute ventilation and oxygen consumption, with a concomitant decrease in functional residual capacity may predispose to more severe illness due to respiratory pathogens. Sequential changes in the number, phenotype and function of various immune cell populations also occur over the course of a normal pregnancy [8,9] – these changes may increase the susceptibility to or pathogenicity of certain infections, including influenza. For example, previous studies have found that natural killer (NK) and T lymphocyte responsiveness is attenuated during pregnancy [8,10], and pregnancy-related hormonal changes may create a bias toward the type 2 phenotype of CD4+ T helper cells [11] – both of these changes could contribute to an impaired immune response to influenza virus infection. Importantly, these observations likely oversimplify the interaction between influenza viruses and the immune system during pregnancy. For example, in animal models, fatal or severe influenza virus infections during pregnancy have actually been associated with over-exuberant inflammatory responses [12,13]; these observations have since been replicated using lymphocytes from pregnant women receiving inactivated influenza vaccine [14].

Regardless of the mechanisms of enhanced severity of influenza virus infection during pregnancy, maternal influenza immunization has the potential to confer tremendous benefit, to mother, infant, and potentially also the fetus. First, influenza vaccination during pregnancy can directly protect the expectant mother against influenza disease; this could also decrease the risk of maternal to infant transmission of influenza. Second, maternal immunization could also simultaneously benefit the developing fetus, potentially by curtailing the systemic inflammatory effects of maternal influenza virus infection [15], or by preventing rare cases of trans-placental infection [16]. Third, due to the normal trans-placental transfer of maternal antibodies from mother to fetus, vaccination during pregnancy can also indirectly provide protection to the newborn infant, at a time when the infant is otherwise ineligible to receive childhood influenza vaccine.

In this article we will review the published literature on the epidemiology of influenza disease in pregnant women and young infants (<6 months of age), the impact of influenza virus infection on the developing fetus, as well as the numerous benefits of maternal influenza immunization for mothers and their infants. We will also discuss issues pertaining to the quality of the existing data, the likely impact of forthcoming data from two completed randomized controlled trials of maternal influenza immunization on the current evidence base, and highlight key areas of future research. Finally, we will provide an overview of key clinical aspects of maternal influenza immunization, including the optimal timing and type of influenza vaccination in pregnancy, the safety of influenza vaccination during pregnancy, and strategies for improving influenza vaccine acceptance and coverage among pregnant women.

2. Burden of influenza in pregnant women

2.1 Pandemic influenza

During influenza pandemics pregnant women have been observed to be at elevated risk for severe disease (e.g. hospitalization and death). Prior to the development of rapid diagnostic tests and population-based surveillance programs, this association was only recognized in large hospital-based case series. For example, during the 1918 influenza pandemic, pregnant women in the US and United Kingdom (UK) had high rates of secondary bacterial pneumonia and a higher case fatality rate than the general population [1,17,18]. Similarly, during the 1957 pandemic, reviews of cases in the US and UK showed that pregnant women comprised a disproportionate fraction of influenza deaths among women of child-bearing age [19,20].

The 2009 H1N1 influenza A pandemic was the first time that the impact of pandemic influenza on pregnant women could be evaluated using modern surveillance tools. Similar to previous pandemics, pregnancy was recognized early in the 2009 pandemic as a potential risk factor for hospitalization and influenza complications [21,22]. In a large meta-analysis, Van Kerkhove et al. analyzed observational data reported from ten countries and computed a relative risk (RR) of 6.8 (95% confidence interval (CI), 4.5–12.3) for hospitalization and 1.9 (95% CI, 0.0–2.6) for death among pregnant women with laboratory-confirmed 2009 H1N1 influenza, compared with women of child-bearing age [23]. Notably, the RR for death was not statistically significant, and this was because higher case fatality rates among pregnant women were not consistently observed in all countries. For example, in one analysis of data from the Emerging Infections Program (EIP), a collaborative surveillance project between the US Centers for Disease Control and Prevention (CDC) and 10 US states, Creanga et al. found that, compared with non-pregnant women of child-bearing age, pregnant women actually had shorter lengths of stay, fewer were given a diagnosis of pneumonia at discharge, and they were less likely to be admitted to the intensive care unit (ICU), to require mechanical ventilation, or to die from pandemic influenza [24]. Some of the country-level differences in outcomes for pregnant women could have been due to differences in the quality of obstetric and critical care services, population-specific thresholds for seeking care and hospitalization for respiratory illness, and importantly, the level of awareness among clinicians of the risks of novel influenza virus infections in pregnant women and the

consequent tendency toward prescription of antivirals and preemptive hospitalization. In any case, similar to the 1918 and 1957 pandemics, in pooled analyses from multiple countries pregnant women constituted a disproportionate fraction of total deaths among women of child-bearing age during the 2009 pandemic [23,25].

2.2 Seasonal influenza

During non-pandemic seasons pregnant women have incidence rates of acute respiratory illness (ARI) and influenza virus infection comparable to age-matched non-pregnant women [26–32]. However, pregnant women experience a disproportionately high burden of severe disease due to seasonal influenza. For example, in one analysis of four inter-pandemic seasons (2005–2006 to 2007–2008) in the US, pregnant women accounted for 2.9% of all adults hospitalized with laboratory-confirmed influenza [33] – not only did this proportion far exceed the fraction of the US population that is pregnant at any given time, but in a subsequent analysis, Creanga et al. found that these hospitalizations accounted for a disproportionate 23.5% of all the influenza-associated hospitalizations among reproductive-aged women over a similar time period [24].

Multiple observational studies have sought to quantify the excess burden or risk of severe influenza disease – as measured by hospitalizations or deaths – among pregnant women relative to non-pregnant women (Table 1). Notably, most of these analyses were conducted prior to the development of modern quality criteria for the assessment of epidemiologic studies, and are therefore vulnerable to important biases; however, dismissal of all previous studies based on these criteria overlooks the important insights afforded by this substantial body of evidence. For example, in one of the first such studies, Neuzil et al. used data from the Tennessee Medicaid Program from 20 influenza seasons (1974–1993) to compute the incidence rate of cardiopulmonary hospitalizations during influenza season among pregnant and non-pregnant women – they found that compared to both non-pregnant and postpartum women (who had incidence rates of 6.37 and 5.62 per 10,000 women-months respectively), pregnant women had significantly elevated rates of hospitalization, and these rates increased with gestational age (incidence rates of 6.46, 12.58, and 21.74 per 10,000 women-months in the first, second, and third trimesters respectively) [34]. Compounding this elevated risk for hospitalizations, two analyses of pregnancy hospitalizations in the US spanning 1998–2008 found that hospitalizations associated with a cardiopulmonary diagnosis during influenza season were longer and costlier than those for other diagnoses [35,36].

Neuzil et al. also used incidence rates among postpartum women during the peri-influenza period to determine the influenza-attributable risk for each group – this risk was 1.91 among non-pregnant women, rose successively through each trimester of pregnancy up to 10.48 among women in the third trimester, and was heightened further in the presence of other comorbidities (Figure 1, adapted from Table 2 in Neuzil et al.) [34]. Similar population-based analyses in Canada have yielded comparable results [37–39]. Notably, one older study did not identify an excess burden of medical visits for ARI among pregnant women except during one epidemic season [40] – importantly, this analysis was limited to a shorter time period and did not stratify outcomes by trimester, and therefore may have been

underpowered to detect an association. Thus, the bulk of the evidence indicates that there is a substantial healthcare burden attributable to influenza disease during pregnancy.

It may be argued that these previous analyses, which have used proxy outcomes for influenza disease (for example, diagnosis codes for respiratory or influenza-like illness (ILI) during influenza season), may have been confounded by inadequately captured exposures or outcomes – or ascertainment bias – as well as outcomes that should have been attributed to co-circulating non-influenza viruses – or misclassification bias. Certainly, varying degrees of these biases between studies makes direct comparisons of risk estimates more challenging. However, studies that minimize these biases by focusing only on laboratory-confirmed influenza have yielded results that are remarkably consistent, further strengthening the conclusions of previous analyses. For example, in the previous analyses of EIP data, more than 70% of the influenza hospitalizations among pregnant women were among those in the second or third trimester [24,33], recapitulating observations made during prior studies of both pandemic and seasonal influenza. Indeed, estimates of influenza disease incidence that are based on proxy outcomes may actually underestimate the true burden among pregnant women. This could be because, (1) respiratory illnesses (due to influenza) may be complicated by secondary diagnoses (including pregnancy complications) [35], which may supplant influenza diagnosis codes in administrative datasets, (2) identification of pregnant women in a cohort using records of livebirths or antenatal visits will systematically exclude women that acquired influenza earlier in their pregnancy and experienced pregnancy loss as a result [29], and (3) confounding by non-influenza viruses may actually dilute the observed severity of illness attributed to influenza [30].

Few studies have explored other severe outcomes of seasonal influenza among pregnant women with the specific aim of determining excess burden relative to non-pregnant women (Table 1). In their analysis of influenza hospitalizations Creanga et al. found that pregnant women had shorter lengths of stay than non-pregnant women, and that they were less likely to require mechanical ventilation or ICU admission, or be given a diagnosis of pneumonia at discharge [24]. Although these results challenge the findings of previous observational studies, they must be interpreted in context. With increasing recognition of pregnancy as a potential risk factor for severe influenza disease, especially since the 2009 pandemic, influenza vaccine coverage and rates of anti-viral prescription use among pregnant women have increased [24,41], and this could certainly account for temporal differences in the risk of severe disease. Similarly, any difference that may actually exist between pregnant and non-pregnant women may be diluted in more recent studies due to lowered thresholds for hospitalization of pregnant women, especially in later stages of pregnancy – indeed, in their study Creanga et al. found that 64% of pregnant women hospitalized for influenza had no other underlying medical conditions, whereas 71% of non-pregnant women had at least one condition recognized by the ACIP as a risk factor for severe influenza [24].

Mortality due to seasonal influenza among pregnant women has been inadequately characterized, and therefore the true burden is unknown. In fact, in a large meta-analysis, Mertz et al. found only one study reporting data on pregnancy as a risk factor for death due to seasonal influenza, and based on that they concluded that pregnancy conferred no increased risk [42]. Notably, previous studies that have attempted to quantify the association

between pregnancy and death due to seasonal influenza have almost certainly been underpowered to compute statistically meaningful risk estimates – Callaghan et al. reported only 40 maternal deaths attributable to influenza from 1998–2005 based on data from the CDC Pregnancy Mortality Surveillance System (PMSS) [43]. Similar analyses of PMSS data from 1979–1997 and 2006–2010 have not specifically reported influenza as a cause of death, precluding any assessment of influenza-associated mortality. In this context, previous clinical trials of maternal influenza immunization have also had inadequate sample sizes to detect any protective effect against death due to influenza [31,32] – however, a pooled analysis of the three recently completed clinical trials may be sufficiently powered to shed light on this issue [44]. More recently, Tempia et al. conducted an ecological study using vital statistics data in South Africa from 1999–2009 and estimated influenza-attributable mortality among HIV-uninfected and HIV-infected pregnant women [45]. They determined a relative risk of death of 2.4 due to seasonal influenza for HIV-uninfected pregnant women as compared with non-pregnant women [45]. To date, this is the only study of mortality due to seasonal influenza among pregnant women that has been conducted using modern epidemiologic tools.

Most of the evidence for the seasonal influenza disease burden among pregnant women comes from developed countries, particularly the US and Canada. More data are clearly needed from other regions, especially developing countries, in order to provide nuance to the existing evidence base for influenza disease in pregnancy given the known heterogeneity in influenza epidemiology between populations. For example, in a recent cost-effectiveness analysis conducted in Sweden using data from 2003–2009, investigators estimated only 9–48 influenza-attributable hospitalizations among pregnant women per season [46]. In contrast, in a similar analysis conducted using data spanning the same time period (2000–2009) in the UK, Jit et al. estimated 815 influenza-attributable hospitalizations per year among pregnant women [47]. Importantly, this variability in influenza hospitalization rates between countries may reflect methodologic heterogeneity and associated biases, or real differences in influenza disease burden, which together affect estimates of country-specific vaccine impact.

3. Effects of influenza virus infection during pregnancy on the fetus and newborn

3.1 Pandemic influenza

Observations of high rates of stillbirth or preterm delivery among pregnant women affected during the 1918 pandemic were the first indication that maternal influenza infection could have adverse effects on the developing fetus [1,17]. A weaker, and more inconsistent association between maternal infection and adverse pregnancy outcomes was observed during the 1957 pandemic [48]. More recent analyses of population-level birth statistics in the US, Europe, and Japan over time periods spanning the 1918 pandemic also found significantly higher rates of stillbirth during the pandemic year [49–51], thus confirming the findings of smaller observational studies and further illustrating the substantial impact of maternal pandemic influenza infection on birth outcomes at a global level.

During the most recent influenza pandemic in 2009, multiple studies of pregnant women with laboratory-confirmed influenza infection also reported high rates of adverse obstetric and birth outcomes, including preterm birth, low birth weight or small for gestational age infants, as well as need for caesarean delivery [25]. Furthermore, pregnant women who had 2009 H1N1 influenza had an increased risk of these outcomes when compared with women who had non-influenza ARIs [52], women who remained disease free during the pandemic [53] or a pre-pandemic period [54], or a historical cohort [54–56]. Together, these results supported the decision to prioritize pregnant women for influenza vaccination during the 2009 pandemic.

These studies were not without analytic limitations. For example, birth outcome data from appropriate comparison groups were infrequently reported, including data from pregnant women with milder influenza illness, women hospitalized for non-influenza illnesses (during and before the pandemic period), and pregnant women unaffected during the pandemic. Moreover, the overall number of adverse obstetric and birth outcomes in individual studies was small, which hindered precise risk estimates. Finally, some of these analyses may not have accurately distinguished between women who did or did not have influenza during pregnancy (i.e. misclassification bias). Nevertheless, most of these limitations would likely only lead to underestimation of the underlying association between maternal pandemic influenza infection and adverse pregnancy outcomes.

3.2 Seasonal influenza

Although influenza pandemics are unique opportunities to evaluate the impact of novel influenza virus infection on birth outcomes in an immunologically naïve population, analyses of single pandemic influenza seasons are necessarily limited by small sample sizes and relatively infrequent outcomes. Longitudinal cohort studies of pregnancy outcomes over multiple non-pandemic influenza seasons overcome this issue and therefore have greater potential to identify adverse effects of influenza exposure during pregnancy. Multiple large retrospective cohort studies conducted in the US and Canada, utilizing data that spanned multiple influenza seasons and geographic regions, have shown that hospitalizations for respiratory illnesses during pregnancy are longer than hospitalizations for other reasons, particularly if associated with a delivery [35,36]. Furthermore, concomitant respiratory illness and delivery hospitalizations are associated with a higher rate of adverse pregnancy outcomes, including preterm birth, fetal distress, caesarean delivery and intrauterine fetal demise [36], even after adjustment for maternal age, high-risk conditions, hospital and geographic location, and calendar year of influenza season [35,36]. In other analyses, even when maternal respiratory illness/influenza did not precipitate or occur simultaneously with delivery, infants born to mothers who had a respiratory hospitalization or laboratory-confirmed influenza during influenza season were more likely to be small for gestational age with a lower mean birth weight [57,58].

While a majority of studies suggest that influenza disease during pregnancy is associated with certain adverse obstetric or birth outcomes, this has not necessarily been a consistent finding in all such analyses [37,59]. This can be attributed to the known heterogeneity in influenza disease epidemiology (i.e. the impact of influenza should not be expected to be

identical from season to season or between different populations) as well as important differences in methodology and analytic approach between studies. For example, studies have differed with respect to the methods for influenza case ascertainment; in the absence of virologic confirmation of influenza infection, all such studies will be vulnerable to non-differential misclassification bias (e.g. the likelihood of misidentifying women as exposed or unexposed to influenza should be similar between the groups), and this will dilute any observed association between maternal influenza infection and adverse birth outcomes. However, this also means that the significant associations between maternal influenza infection and adverse pregnancy outcomes that have been previously identified are likely to be even stronger.

Studies have also differed in their approach to adjusting for potential confounders, including gestational age at the time of respiratory illness hospitalization, as well as non-health related maternal factors (e.g. demographic characteristics, socioeconomic status, etc.) that have also been previously associated with the seasonality of both births [60] and adverse pregnancy outcomes [61–63]. While failure to account for these variables could result in inaccurate estimates of risk, the studies that have used unique analytic approaches to deal with these potential confounders have reached remarkably similar conclusions. Currie et al. conducted one such analysis by evaluating birth outcomes of siblings that were conceived during different times of the year, thereby using the same woman as her own control for a variety of previously identified confounders [64]. They found that even after controlling for socioeconomic factors that have historically been associated with the seasonality of conceptions and adverse birth outcomes, seasonal differences in both gestation length (a surrogate for preterm delivery) and birth weight remained and were tightly correlated with the level of influenza activity during the month of birth. To illustrate the strength of their findings, when the analysis was restricted to the 2009 pandemic season, the pattern was both more pronounced and shifted to earlier months of conception, which would be expected given the magnitude and timing of the 2009 pandemic relative to other influenza seasons [64].

Perhaps the most important limitation of existing studies of the association between influenza and adverse pregnancy outcomes is the inconsistency in case definitions of these adverse outcomes [65]. Even during the most recent pandemic in 2009 only a small number of studies actually specified the definitions used to classify gestational age dependent outcomes (e.g. spontaneous abortion, stillbirth, etc.), and even then the definitions were not always congruent. Similarly, of the studies that described anthropometric birth outcomes (i.e. based on birth weight), the vast majority reported only mean/median birth weight – these data are only meaningful when analyzed together with the proportion of small for gestational age infants, since preterm birth rates are often quite high in these studies. These discrepancies make it more difficult to pool data from smaller studies to compute statistically meaningful risk estimates. Ultimately, standardized definitions of adverse pregnancy outcomes are needed in order to permit more rigorous assessments of risk due to influenza (and other infections) acquired during pregnancy.

4. Burden of influenza in young infants

Influenza viruses are an important cause of disease in children. In a large meta-analysis, Nair et al. reviewed published and unpublished data from 43 studies and estimated 90 million new cases of influenza (1 million of which were severe acute lower respiratory infections) and between 28,000–115,000 deaths attributable to influenza-associated acute lower respiratory infections globally among children under 5 years of age [66]. Given the substantial contribution of influenza viruses to upper respiratory tract infections (that may also be medically-attended), episodes of croup, bronchiolitis, and acute otitis media [67,68], these figures likely underestimate the true burden of influenza disease in this age group. Importantly, in that meta-analysis, as well as in the vast majority of the studies that have been published subsequent to their literature review, there are substantially fewer burden data specifically for children under 1 year of age, and especially for infants under 6 months of age. Given the decay kinetics of passively transferred maternal antibodies [69], these young infants are the ones that actually stand to benefit from maternal influenza immunization. Unfortunately, epidemiologic studies often exclude this age group in the interest of estimating the effectiveness of childhood influenza immunization [70,71] which is not routinely recommended until at least 6 months of age in most countries. However, burden data for younger infants are also needed in order to assess the impact of maternal influenza immunization.

4.1 Epidemiology of infant influenza in high-income countries

In developed countries, infants under 6 months of age have high rates of healthcare utilization – including outpatient [72] and emergency department visits [73] as well as hospitalizations [74–77] – for ARI or ILI. Although respiratory syncytial virus and rhinoviruses/enteroviruses are the predominant causative pathogens in this age group [67,72], there is also a significant burden of disease attributable to influenza. When compared to other pediatric age groups, infants under 6 months of age have consistently been shown, across populations and influenza seasons, to have the highest rates of influenza-associated hospitalization [74,78–85], with rates second only to individuals older than 65 years of age [86]. In one population-based surveillance study during a single influenza season across three US states, Schrag et al. found that 27% of influenza-associated hospitalizations were among infants under 6 months of age [87]. Infants under 3 months of age likely constitute most of these hospitalizations, with rates three times higher than older age groups [79]. Most of these hospitalizations are among infants without any high-risk medical conditions [88], indicating that their young age was the sole risk factor for hospitalization. In addition, some of these influenza hospitalizations may be complicated by secondary bacterial pneumonia, dehydration, and febrile seizures [89]. Young infants also have higher rates of influenza-associated hospitalizations that require intensive care [87,90] as well as higher influenza-attributable mortality [91] when compared with older children.

Owing to their significantly higher incidence of hospitalization, these young infants place a substantial burden on the healthcare system. For example, in one analysis of hospitalized cases of laboratory-confirmed influenza in children under age 5 identified as part of the New Vaccine Surveillance Network across three influenza seasons in the US, Fairbrother et al.

found that infants under 6 months of age accounted for 45% of total hospital costs and 49% of total inpatient bed days [92]. Similarly, in an analysis at one center, influenza accounted for 3.6% of the total evaluations for suspected serious bacterial infection (SBI) among infants under 3 months of age, and 12% of such evaluations during the winter season [93].

4.2 Epidemiology of infant influenza in low- and middle-income countries

There are substantially fewer high-quality data on the burden of influenza disease in young infants from developing countries. In their systematic review, Nair et al. identified only 20 studies – reporting data from 13 developing countries – on the epidemiology of influenza virus infections in children under the age of 5, and only five of these studies included data for infants under 1 year of age [66]. Single center studies from these regions provide some information about the burden of influenza disease among infants, but due to heterogeneity in the populations under study, case definitions for influenza-associated illnesses (especially if cases are not laboratory-confirmed), testing and hospitalization patterns, and systems for reporting cases, their results cannot easily be extrapolated to compute country- or region-wide incidence rates. Nonetheless, the available data suggest that the burden of influenza disease in children in many developing countries is likely to be similar to that of developed countries. For example, in a report of sentinel surveillance data of ILI or severe ARI (SARI) from 15 African countries from 2006–2010, children under the age of 5 accounted for 48% of all the ILI and SARI cases (113,164 cases), and 10% of these SARI cases tested positive for influenza [94]. On a country-specific level, investigators in several epidemiologic studies conducted in different regions in Kenya found that infants under age 1 had among the highest rates of influenza-associated SARI [95,96] or medically-attended lower respiratory tract infection [97] of all pediatric age groups, similar to developed countries. In South Africa, both HIV-infected and uninfected infants under 1 year of age were estimated in one analysis to have the highest rates of pneumonia and influenza deaths [98]. In countries with a high burden of tuberculosis (TB), such as South Africa, influenza seasonality in young children may also contribute to the seasonality in hospitalizations for pulmonary TB [99].

A high burden of disease has also been noted in other regions. For example, during the Mother's Gift study in Bangladesh, Zaman et al. reported influenza virus circulation for 10 out of 11 months of observation, with an incidence of laboratory-proven influenza of at least 10% among infants in the first 6 months of life [31]. Madhi et al. reported an influenza attack rate among infants of unvaccinated mothers of 3.6% over two influenza seasons during a clinical trial of maternal influenza immunization in South Africa, and nearly 30% of these infections were due to the influenza strain carried by their mothers [32]. High rates of infant influenza hospitalizations have also been reported from Vietnam [100] and Singapore [101].

In summary, although fewer data on the incidence of influenza disease among young infants have been reported from low- and middle-income countries, wherever high-quality studies have been conducted the overall findings have been remarkably consistent. Taken together with data from high-income countries, these studies provide compelling evidence of the important global burden of influenza in this vulnerable age group.

5. Benefits of maternal influenza immunization

5.1 Pregnant women

There is compelling evidence that maternal influenza immunization is effective for protecting pregnant women against influenza disease. Supportive data come from randomized controlled trials (Table 2) and multiple large retrospective population-based cohort studies. The highest quality evidence comes from two randomized controlled trials in Bangladesh and South Africa. In the Mother's Gift study in Bangladesh, Zaman et al. reported an influenza vaccine effectiveness of 35.8% against episodes of febrile respiratory illness among pregnant women, captured by active community-based surveillance using a protocol-defined case definition. Although they did not have laboratory-confirmation of influenza virus infection, they estimated that 36% of febrile respiratory illnesses up to 6 months postpartum were due to influenza [31]. Similarly, in the clinical trial of maternal influenza immunization in South Africa, a high HIV-prevalence setting, Madhi et al. reported the efficacy of maternal influenza immunization for preventing laboratory-confirmed influenza in HIV-uninfected and HIV-infected pregnant women as 50.4% and 57.7% respectively [32]. Preliminary results from another clinical trial of maternal influenza immunization in Nepal showed that vaccination during pregnancy reduced laboratory-confirmed influenza in mothers by 31%[102]. Notably, these estimates are similar to influenza vaccine effectiveness estimates in other high-risk populations. Another clinical trial of maternal influenza immunization has also been completed in Mali, and the final results of the trials in Nepal and Mali are expected to be similar to those reported from Bangladesh and South Africa. A pooled analysis of the three most recent trials holds the additional promise of demonstrating protective effects against rarer outcomes, such as maternal death due to influenza – this will substantially strengthen the existing evidence base for the benefit of maternal influenza immunization among pregnant women [44].

Clinical trials of maternal influenza immunization have not been feasible in developed countries since routine vaccination of pregnant women has been considered standard practice for decades [3]. Nevertheless, three retrospective studies from the US and Europe have also demonstrated that maternal influenza immunization (against either 2009 pandemic or seasonal influenza) can have a significant protective effect against a variety of clinical outcomes (ARI, ILI, or diagnosis of influenza) associated with laboratory-confirmed influenza infection [103–105]. As an example, one such analysis of two inter-pandemic seasons (2010–2011 and 2011–2012) in a cohort from California and Oregon reported an overall vaccine effectiveness of 44%, consistent with the results of randomized trials [104]. Notably, no studies have explored the protective effect of maternal influenza immunization against cardiopulmonary hospitalization during influenza season – although such a study would be analytically challenging (e.g. need for a large enough sample size, and adequate adjustment for healthcare seeking behavior and provider practice patterns), such an analysis would provide further insight into the broader impact of maternal influenza immunization, since vaccine not only prevents influenza disease, but it may also attenuate it. While some retrospective studies have failed to demonstrate any benefit of maternal influenza immunization, they have had critical limitations. All assessed vaccine effectiveness against a non-specific outcome (i.e. no laboratory confirmation of influenza infection) [106–109],

many utilized passive surveillance for influenza cases which introduces a high likelihood of ascertainment bias [106,109], and some were underpowered to detect a significant difference between the vaccinated and unvaccinated cohorts [107,108].

5.2 Fetal and neonatal outcomes

Obstetric and perinatal outcomes that have been specifically evaluated among vaccine recipients have included rates of spontaneous abortion, stillbirth, fetal death, preterm birth, low birth weight or small for gestational age (SGA) infants, or congenital anomalies. Some of these outcomes may be attributable, in part, to an exaggerated inflammatory milieu at specific stages of fetal development, which may be triggered or exaggerated in the context of influenza virus infection [15]. By averting or attenuating the immune response to influenza virus infection, maternal influenza immunization could therefore confer protection against some of these adverse pregnancy outcomes.

Multiple observational studies have quantified the association between antenatal receipt of influenza vaccine and stillbirth, defined in most studies as pregnancy loss after 20–22 weeks gestation (Table 3). Nearly all of these studies focused on monovalent vaccines against 2009 H1N1 influenza. Important differences in analytical approach and outcome definitions have made comparisons between individual studies difficult, thus precluding assessments of overall effect [110,111]. Many of these studies were undoubtedly underpowered to detect a significant protective effect of maternal influenza immunization against stillbirth given the small number of events. However, in one meta-analysis, Bratton et al. pooled data from seven of these studies, including only those with consistent outcome definitions and sufficient methodologic rigor for minimizing biases common to observational studies, and computed an overall relative risk of 0.73 (95% CI, 0.55–0.96) for stillbirth among women who had received influenza vaccine [112]. Adding credibility to this estimate was the finding that a meta-analysis of the same studies focused instead on spontaneous abortion (defined as pregnancy loss before 20 weeks gestation) as the outcome yielded no significant protective effect [112] – this latter result is expected given that maternal influenza immunization should not have an impact on fetal outcomes that occur earlier in pregnancy (i.e. before vaccination). These results indicate that the main analysis, which found that maternal influenza immunization was associated with a decreased risk of stillbirth, was less likely to be biased by unmeasured differences between the exposed and unexposed groups in their predisposition to an adverse pregnancy outcome, and therefore demonstrated a real protective effect of the vaccine.

More studies have explored the association between both seasonal and 2009 H1N1 pandemic influenza vaccination during pregnancy and preterm birth, defined in all studies as live birth before 37 weeks (Table 4). Given that preterm birth has been linked to a pro-inflammatory milieu, which may be precipitated by influenza virus infection [15], and that multiple observational studies have associated higher preterm birth rates with respiratory hospitalizations during pregnancy [35,36] or periods of influenza circulation [64], a protective effect of maternal immunization is entirely biologically plausible. However, a reduced risk of preterm delivery among pregnant vaccinees has not been consistently observed in all studies. This is likely attributable to both biologic factors, such as differences

in the level of baseline immunity to influenza in the study population, year-to-year variability in viral pathogenicity, or degree of match between vaccine and circulating viral strains, as well as key analytical differences between the studies. For example, whereas virtually all the studies accounted for potential confounding due to co-variates of vaccine receipt (e.g. number of antenatal visits, gestational age at first antenatal visit, other preventive care behaviors, etc.) or preterm delivery (e.g. maternal age, previous preterm delivery, socioeconomic status, etc.), only a small number stratified their analysis by gestational age at vaccination or period of influenza activity. Both of these variables could modify the observed association between maternal immunization and preterm birth. Studies that have accounted for these important variables, and those that have utilized datasets large enough to overcome the overall low rate of preterm birth in developed countries, have more consistently demonstrated a protective effect of maternal immunization against preterm delivery [105,113–117]. These findings suggest that routine maternal influenza immunization has the potential to have an enormous impact on the perinatal morbidity and mortality attributable to prematurity.

Maternal influenza immunization may also be associated with improved anthropometric outcomes (e.g. birthweight, likelihood of being small for gestational age, etc.) [113,114,118], however far fewer studies have explored these outcomes and the results have been mixed. These anthropometric outcomes have been among the most inconsistently defined between studies, which has precluded pooled analyses. Importantly, unlike stillbirth or preterm birth, it may not be appropriate to evaluate low birthweight and being small for gestational age as simple dichotomous outcomes. These outcomes likely represent the common endpoint of multiple types of fetal growth restriction, each of which has a unique causal pathway, depending on gestational age, and each of which may have varying prognostic significance, depending on the study population.

5.3 Infants

The earliest evidence for the protective effect of maternally acquired antibodies against influenza infection in infants came from two studies which demonstrated that higher anti-hemagglutinin antibody titers at birth were associated with delayed or shortened influenza illnesses in infants [119,120]. More recent studies of maternal influenza immunization now also provide strong supportive evidence for this protective effect. The highest quality evidence comes from the two clinical trials in Bangladesh and South Africa (Table 2), which reassuringly yielded a protective effect of similar magnitude against respiratory illness due to laboratory-confirmed influenza in infants – Zaman et al. computed a vaccine effectiveness of 63%[31], whereas Madhi et al. found a vaccine efficacy of 48.8% among HIV-unexposed infants [32]. Preliminary data from a third clinical trial in Nepal found that maternal influenza immunization reduced laboratory-confirmed influenza in infants by 30%[102]. Notably, the study in South Africa was not adequately powered to detect a significant protective effect of maternal vaccination against ILI due to laboratory-confirmed influenza in HIV-exposed infants [32] – this may have been due to an HIV-related attenuation of the vaccine-induced immune response in mothers, reduced trans-placental transfer of protective antibodies due to HIV co-infection, or another confounding factor unique to this population. In developed countries, where clinical trials have not been feasible, four retrospective cohort

studies – three in the US and one in the UK – took advantage of significantly larger datasets and also demonstrated a significant protective effect of maternal influenza immunization against infant influenza hospitalization [121–124].

When using less specific outcomes, studies in infants have yielded mixed results, similar to such analyses in pregnant women and other populations. In the clinical trial in South Africa, Madhi et al. found no protective effect of maternal influenza immunization against all-cause respiratory illness or ILI in South African infants [32]. Two retrospective cohort studies in the US also found no protective effect of maternal influenza immunization against hospital admission or outpatient visits for ILI [107] or medically attended ARI [125]. In the absence of virologic confirmation, VE studies will by definition be confounded by co-seasonal non-influenza respiratory illnesses, and will therefore underestimate any protective effect. Similarly, baseline differences in the proportion of infants with high concentrations of maternally-derived antibodies in the study population, as well as differences in infant vaccine schedules between populations, will undoubtedly lead to heterogeneity in assessments of vaccine effect against non-specific outcomes.

Few studies have investigated the impact of maternal influenza immunization on the incidence of complicated or severe influenza disease in infants (i.e. secondary bacterial pneumonia, ICU admission, mechanical ventilation, or death). Forthcoming analysis of the pooled data from the clinical trials in South Africa, Mali, and Nepal has the potential to shed light on these issues [44]. Maternal influenza immunization may also be a promising strategy for preventing a much broader set of outcomes that occur as a result of infant influenza infection. For example, Omer et al. showed that maternal influenza vaccination combined with infant vaccination with pneumococcal conjugate vaccine was superior to either alone for preventing infant febrile respiratory illness, with an estimated vaccine effectiveness of 72.4% during influenza season [126]. Potential mechanisms for this synergistic effect include: limited or delayed acquisition and/or carriage of pneumococci in infants of vaccinated mothers due to protection from influenza infection, or modulation of the infant nasopharyngeal microbiome due to breast milk antibodies, among many others.

Infant influenza infection may be complicated by acute otitis media in 10–50% of cases, and childhood influenza immunization has been associated with a decreased incidence of acute otitis media [127]. Only two studies have evaluated the effect of maternal influenza immunization on the incidence of acute otitis media in this population, and reported conflicting results [107,128]. Influenza infections in infancy often prompt costly evaluations for suspected serious bacterial infections (SBI) [93] that may be preventable, yet the impact of maternal immunization on hospitalizations for SBI has not been explored. Illnesses due to influenza also contribute substantially to excess antibiotic use (among both children and household contacts) as well as school and parental work absenteeism [85,129]. One retrospective study found that postpartum immunization and ‘cocooning’ (immunization of household contacts of newborn infants) was associated with fewer childhood febrile illnesses and antibiotic exposures during influenza season [130]. There have been no similar analyses in households of women who were vaccinated during pregnancy, even though routine maternal immunization is likely to be easier to implement than a cocooning strategy.

Ultimately, these sorts of analyses need to be replicated in other populations in order to capture the full potential impact of routine maternal influenza immunization.

6. Clinical aspects of maternal influenza immunization

6.1 Timing of vaccination

Current US recommendations for influenza immunization during pregnancy do not specify an optimal time for vaccination [131,132]. Yet, the timing of influenza vaccination – in relation to gestational age, anticipated time to delivery, and period of influenza circulation – is likely an important factor in a variety of immunologic and clinical outcomes (Table 5). Most of the studies that have investigated the timing of vaccination as a variable have focused on immunologic endpoints in infants of vaccinated mothers, given the important role of trans-placental antibody transfer in the protection conferred to infants by maternal immunization. Overall the available literature suggests, somewhat intuitively, that a greater interval between vaccination and delivery – up to a certain point – leads to higher cord blood HAI titers and rates of sero-protection at birth (Table 6A). However, only a few studies have analyzed these outcomes stratified by gestational age at the time of vaccination (Table 6B), which is relevant given the profound physiologic changes that occur between the first and second trimester of pregnancy, and their potential impact on both the magnitude and quality of the vaccine-induced antibody response.

In studies where infants have been followed after delivery, the durability (as measured by half-life) of passively-acquired antibodies appears to be similar regardless of the timing of vaccination or initial cord blood antibody titers (Table 7). Taken together, these data indicate that infants with higher titers at birth will also remain sero-protected for longer. Therefore, maximizing the interval between vaccination and delivery is likely to be associated with the most durable, and perhaps also the highest quality, protective antibody response in infants. However, even if optimizing immunologic outcomes in infants were the sole purpose of maternal influenza immunization, the available data are of insufficient quality to define a specific time ‘window’ for vaccination, and this is reflected in current guidelines.

Clinicians offering influenza vaccine to women at different stages of pregnancy must also consider the risk to the mother of influenza virus infection during pregnancy – this includes an assessment of other comorbidities that may elevate the risk of severe influenza disease, as well as gestational age. However, they must also take into account the period of time during which the pregnancy and immediate postpartum period will overlap with the anticipated period of influenza circulation in the community. The latter variable is important not only for estimating the risk for preterm labor/delivery or neonatal infection due to influenza, but also the likelihood of maternal influenza infection in the postpartum period. Few studies have evaluated maternal antibody kinetics in the postpartum period, and these data – largely from trials of 2009 H1N1 influenza vaccine – suggest that the timing of vaccination during pregnancy does not impact rates of sero-protection up to three months after delivery [133]. However, more studies are needed to fully characterize the impact of the timing of influenza vaccination during pregnancy on qualitative aspects of the maternal vaccine-induced immune response, including antibody isotype and subclass switching, affinity maturation, and cellular immunity.

6.2 Influenza vaccine formulations in pregnancy

Although a number of influenza vaccine formulations are now available, in the US only standard dose unadjuvanted inactivated influenza vaccine is recommend for use during pregnancy [134]. Live-attenuated influenza vaccine (LAIV) is not recommended based on purely theoretical concerns for fetal harm or the potential for severe disease due to the attenuated vaccine strain. Notably, multiple observational studies have detected no increased risk of maternal, obstetric, or perinatal adverse events associated with inadvertent LAIV use in pregnant women, for both seasonal and monovalent 2009 H1N1 influenza LAIV preparations [135–139], though the total number of women that received LAIV in these studies was small. However, since LAIV induces lower serum HAI antibody titers than inactivated influenza vaccine [140], these formulations may not be optimal for a maternal influenza immunization strategy whose aim is also to confer protection to infants via transplacental antibody transfer.

Newer vaccine formulations containing oil-in-water adjuvants, such as MF-59 or AS03, have been licensed for use in many European countries, and more recently in the US as well. Monovalent vaccines against 2009 H1N1 influenza containing either MF-59 or AS03 adjuvant were demonstrated to be safe [141–146] and immunogenic [147–149] during pregnancy. However, efficacy data specific to the use of adjuvanted vaccines in pregnant women are limited [103], and studies directly comparing the immunogenicity, safety [150], and efficacy of adjuvanted and non-adjuvanted vaccines in this population are lacking. Similarly, there have been no studies of high dose inactivated influenza vaccine in pregnant women. Importantly, adjuvanted and higher dose influenza vaccine formulations are associated with improved immunogenicity, even among populations that generally exhibit lower post-vaccination antibody responses [151,152] – in this context, these vaccines may have a uniquely high impact application in maternal influenza immunization programs. Multiple studies have found that pregnant women achieve lower post-vaccination titers than non-pregnant women after influenza vaccination [153,154], especially those that are HIV-infected [155,156]. Moreover, higher HAI titers at the time of delivery likely correlate with more reliable and durable sero-protection in infants (Table 6).

6.3 Safety of maternal influenza immunization

Concern about the safety of vaccines during pregnancy is consistently among the most common reasons cited by pregnant women for non-vaccination [157], and this includes vaccination against influenza [158]. However, more than five decades of observations – from both retrospective studies and prospective randomized controlled trials – have established that influenza vaccination during pregnancy is safe. For example, at the time of the WHO position paper in 2012, a synthesis of the available evidence found no elevated risk of adverse fetal or neonatal outcomes associated with maternal influenza immunization [159]. More recently, three systematic reviews conducted updated analyses of safety studies published since the WHO position paper and detected no increased risk of spontaneous abortion [111], fetal death or stillbirth [110,111], preterm birth [110], or congenital anomalies [111,160] among pregnant women that received influenza vaccine. In fact, as noted previously, some studies have found that maternal influenza immunization was actually associated with a decreased risk of stillbirth [112] or preterm birth [105,113–117].

With regard to maternal safety, three retrospective studies analyzed data from seven sites in the US Vaccine Safety Datalink and found no association between receipt of antenatal influenza vaccine and (1) maternal adverse events in the 42 days after vaccination [161], including among first-trimester vaccinees or those who simultaneously received tetanus, reduced diphtheria, and acellular pertussis vaccine [162], or (2) medically attended adverse obstetric events [163].

6.4 Influenza vaccine coverage and acceptance during pregnancy

Despite the totality of evidence demonstrating both the safety and numerous benefits of maternal influenza immunization, coverage remains suboptimal [158]. In the US, national vaccination coverage estimates among pregnant women increased dramatically from approximately 35% to 50% immediately following the 2009 pandemic season, but have since plateaued [41]. These estimates also mask important disparities in vaccine uptake, with even lower estimates of coverage among younger (under age 30), unmarried, and uninsured women, and among certain minority groups, particularly non-Hispanic black women [164]. Factors that have been consistently linked to non-vaccination include maternal concerns about safety, lack of awareness of maternal or infant disease burden or severity – among both patients and providers – and failure on the part of the obstetric provider to make a strong recommendation for immunization [165–168]. Interventions to improve influenza vaccine uptake in this population that target patients, providers, practices, or all three together, have shown inconsistent benefit [169–172]. These disparate results likely stem from underlying differences between study populations in attitudes toward and barriers to maternal vaccination. Importantly, very few studies on vaccine acceptance have been conducted in developing countries [157], where influenza vaccination coverage rates are even lower. Thus, before maternal influenza immunization can be fully integrated into antenatal care platforms, more rigorously evaluated interventions to reduce vaccine hesitancy among pregnant women are clearly needed.

7. Expert commentary

Routine immunization of pregnant women against influenza has the potential to have a substantial impact on maternal, fetal, and infant morbidity and mortality. There is compelling evidence that pregnant women comprise a disproportionate share of severe illnesses during influenza pandemics. While there is less robust evidence to suggest that seasonal influenza is also more severe among pregnant women than in non-pregnant women, there is nevertheless a substantial burden of seasonal influenza-attributable morbidity on pregnant women and the healthcare system. Moreover, influenza virus infection during pregnancy may precipitate a variety of adverse obstetric and birth outcomes, an effect that is increasingly being appreciated at a population level. Finally, studies from high, middle and low-income countries have demonstrated the extraordinary burden of influenza disease among young infants (<6 months of age).

There is already strong evidence for a protective effect of maternal influenza immunization against laboratory-confirmed infection in both mothers and infants. Supportive data come from two published randomized clinical trials of maternal influenza immunization

conducted in low-income countries, as well as multiple observational studies in high-income countries. Forthcoming data from two additional clinical trials – also conducted in low-income countries – are only expected to add to this evidence base, and pooled analyses of these trials promise to shed light on the full impact of maternal immunization on less frequent outcomes, including severe disease in mothers and infants, as well as adverse pregnancy outcomes.

Despite the strength of the existing evidence, a number of critical knowledge gaps remain. An improved understanding of the influenza vaccine-induced immune response in pregnant women would help guide future immunization strategies and vaccine development – including for other pathogens – in this population. Given that maternal influenza immunization has the potential to impact multiple outcomes that occur over the course of gestation and after delivery, studies evaluating the optimal timing of influenza vaccination and its effect on maternal and neonatal outcomes are also needed. Standardized definitions of birth outcomes in studies of the impact of maternal immunization would permit more rigorous analyses of rare outcomes from both observational studies and clinical trials. Finally, more research is needed, particularly in developing countries, on the determinants of vaccine acceptance among pregnant women, in order to effectively implement maternal influenza immunization into routine practice.

8. Five-year view

In the coming five years we anticipate that the final results of the two completed randomized controlled trials of maternal influenza immunization in Mali and Nepal will become available. These trials were substantially larger than the previously reported trials in Bangladesh and South Africa, and therefore will add to the existing evidence base by providing additional prospective data on the impact of maternal influenza immunization on severe influenza disease in mothers and infants, as well as perinatal outcomes. These data – and results of a pooled analysis – will likely provide further support for routine immunization of pregnant women in both high- and low-income countries. Experience from these trials will also guide surveillance studies, not only for influenza, but a number of vaccine-preventable diseases that may be attractive targets for future maternal vaccines, and will provide important context for future clinical trials.

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Reference annotations

* Of interest

** Of considerable interest

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9. Key issues

- Pregnant women comprise a disproportionate share of severe influenza disease (as measured by influenza hospitalizations and deaths) during pandemics
- There are conflicting data on whether seasonal influenza is more severe (as measured by the need for intensive care unit admission, mechanical ventilation, or death due to influenza) among pregnant women compared with non-pregnant women of child-bearing age, though the burden of influenza-attributable morbidity on the health-care system is still substantial
- Maternal influenza virus infection has been associated with adverse consequences for the developing fetus, including fetal growth restriction, stillbirth and preterm delivery, and the risk for these outcomes is heightened with more severe maternal disease
- Infants too young to be vaccinated have the highest incidence of medically-attended illnesses, emergency department visits, and hospitalizations due to influenza of any pediatric age group, with rates second only to adults over age 65
- There is substantial supportive evidence from two randomized controlled trials and multiple observational studies that maternal influenza immunization prevents maternal and infant influenza disease
- Some observational studies have also demonstrated that maternal influenza immunization is associated with a decreased risk of stillbirth, preterm delivery, and fetal growth restriction, however additional data are needed from prospective studies using standardized birth outcome definitions to assess the consistency and magnitude of this effect
- Forthcoming data from two completed randomized controlled trials of maternal influenza immunization in Mali and Nepal promise to add substantially to the existing evidence base, including the impact of this intervention on rarer outcomes, such as death, severe influenza, and adverse birth outcomes
- More studies are needed to explore the full impact of maternal influenza immunization on maternal and infant outcomes, including infant febrile illnesses that prompt invasive evaluations for suspected serious bacterial infections, episodes of acute otitis media, antibiotic usage (in infants, mothers, and households), and parental work absenteeism
- The impact of the timing of influenza immunization during pregnancy on various immunologic outcomes for both mother and infant,

including antibody transfer, durability, and avidity, has not been fully characterized

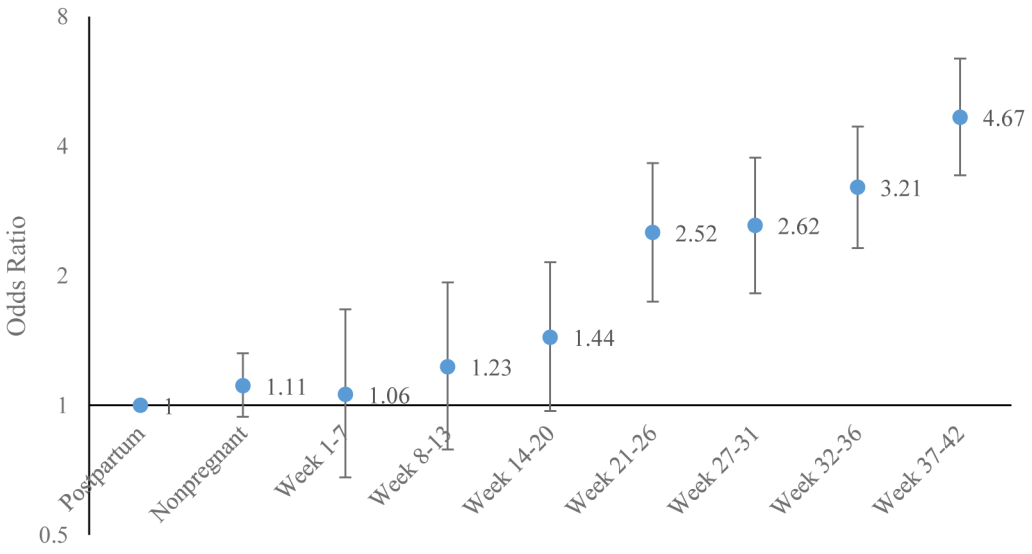

Figure 1.

Odds ratios for any cardiopulmonary event during influenza season among women aged 15–44 years in the Tennessee Medicaid program, by pregnancy status and stage of gestation (by week), 1974–1993. Error bars represent 95% confidence intervals. Figure adapted from data in Table 2 in Neuzil et al [34].

Table 1

Studies evaluating pregnancy as a risk factor for severe disease attributable to seasonal influenza

Author (Year) [Ref]	Years Location	Outcome measure	Analytical considerations					Referent group	Excess morbidity or mortality (rate ratio, 95% CI)		
			Study design	Laboratory confirmation of influenza	Results stratified by influenza year	Results stratified by comorbidity status*	Results stratified by trimester		1st trimester	2nd trimester	3rd trimester
Mullooly (1986) [40]	1975–1979 Oregon, USA	**Medical visits** for acute respiratory disease	Population-based, retrospective cohort	No	**Yes**	No	No	Non-pregnant women	Rate ratios not provided – excess events (p>0.05) noted for the 1976–1978 seasons, with greatest excess during the 1978 influenza epidemic		
Neuzil (1998) [34]	1974–1993 Tennessee, USA	**Hospitalizations** for pneumonia, influenza, and cardiopulmonary diagnoses	Population-based, retrospective cohort	No	No	**Yes**	**Yes**	Post-partum women	1.06 (0.68–1.67) (wk 1–7) 1.23 (0.79–1.93) (wk 8–13)	1.44 (0.97–2.15) (wk 14–20) 2.52 (1.74–3.65) (wk 21–26)	2.62 (1.82–3.76) (wk 27–31) 3.21 (2.32–4.44) (wk 32–36) 4.67 (3.42–6.39) (wk 37–42)
Hartert (2003) [37]	1985–1993 Tennessee, USA	**Hospitalizations** for respiratory illness	Population-based, retrospective cohort	No	No	**Yes**	**Yes**	Pregnant women in the first trimester	Referent	1.50 (1.01–2.23)	2.81 (1.98–3.99)
Dodds (2007) [38]	1990–2002 Nova Scotia, Canada	**Hospitalizations** for respiratory illness	Population-based, retrospective cohort	No	No	**Yes**	**Yes**	Non-pregnant women (same cohort in the year before pregnancy)	1.7 (1.0–2.8)	2.1 (1.3–3.3)	5.1 (3.6–7.3)
Schanzer (2007) [39]	1994–2000 Canada	**Hospitalizations** for respiratory illness	Population-based, retrospective cohort	No	No	**Yes**	No	Non-pregnant women	Rate ratio = 18 for pregnant women compared to non-pregnant women		
Creanga (2011) [24]	1998–2008 10 EIP sites, USA	**Length of stay, mechanical ventilation, ICU admission, pneumonia diagnosis, or death** among influenza hospitalizations	Population-based, retrospective cohort	**Yes**	No	No	No	Non-pregnant women	Rate ratios not provided – non-pregnant women had longer lengths of stay, were more likely to require mechanical ventilation or ICU admission, and have a pneumonia diagnosis at discharge; no significant difference in case fatality rate		
Tempia (2015) [45]	1999–2009 South Africa	**Mortality** (all-cause, or due to pneumonia and influenza)	Ecological	No	No	**Yes*** (HIV status)	No	Non-pregnant women	Results expressed as relative risk (RR), 95% CI RR for all-cause mortality = 2.4 (2.1–2.7); RR for death due to pneumonia and influenza = 2.7 (1.9–3.5)		

*Data for pregnant women without comorbidities shown in table

Abbreviations: CI, confidence interval; wk, week of gestation; EIP, Emerging Infections Program; ICU, intensive care unit

Table 2

Key results of clinical trials of maternal influenza immunization

	Bangladesh [31]	South Africa [32]		Nepal [102][a]
Study characteristics				
Sample size	340	2116 (HIV-uninfected)	194 (HIV-infected)	3693
Gestational age at vaccination	Third trimester	20–36 weeks	20–36 weeks	17–36 weeks
Vaccine effect (all reported as VE unless otherwise stated)				
Maternal outcomes				
Reduction in laboratory-confirmed influenza	N/A	50% (15 to 71)	58% (0.2 to 82)	31% (−11 to 56)
Reduction in influenza-like illness	36% (4 to 57)[b]	4% (−16 to 21)	−0.1% (−64 to 38)	N/A
Infant outcomes				
Reduction in laboratory-confirmed influenza	63% (5 to 85)	49% (12 to 70)	27% (−132 to 77)	30% (5 to 49)
Reduction in influenza-like illness	28% (−5 to 51)[b]	−2% (−10 to 6)	−2% (−26 to 17)	N/A

[a] Preliminary data only

[b] Respiratory illness with fever

Table 3

Key characteristics of published studies on the association between maternal influenza immunization and spontaneous abortion (SAB), stillbirth, or fetal death

Study Year (Author) [Reference]	Country (Region)	Sample size, total (vaccinated)	Vaccine type	Outcome definition	Additional analysis of outcome(s) accounting for				Effect estimate	
					Covariates of vaccine receipt and/or preterm birth	Vaccine match to circulating virus	Gestational age at vaccination	Period(s) of influenza circulation	Unadjusted	Adjusted*
1981 (Deinard) [173]	USA	815 (189)	1976 H1N1	SAB (pregnancy loss at <22 weeks) and stillbirth (pregnancy loss at ≥ 22 weeks)	**Yes**	**Yes**	No	No	Data presented as percentages, not statistically different (p-value not reported)	
2012 (Fell) [117]	Canada (Ontario)	55,570 (23,340)	2009 H1N1	Fetal death (intrauterine death at ≥20 weeks)	**Yes**	**Yes**	No	No	OR = 0.60 (95% CI, 0.44–0.81)	OR = 0.66 (95% CI, 0.47–0.91)
2012 (Heikkinen) [141]	Netherlands, Italy, Argentina	4,508 (2,295)	2009 H1N1	Stillbirth (fetal loss at ≥ 22 weeks)	**Yes**	**Yes**	**Yes**	No	OR = 1.46 (95% CI, 0.24–8.74)	OR = 1.38 (95% CI, 0.22–8.47)
2012 (Kallén) [116]	Sweden	155,526 (18,612)	2009 H1N1	Stillbirth (not defined)	**Yes**	**Yes**	No	No	N/A	OR = 0.77 (95% CI, 0.57–1.03)
2012 (Launay) [174]	France	877 (320)	2009 H1N1	Infant dead before labor and pregnancy loss (not defined)	**Yes**	**Yes**	No	No	Data presented as percentages, not statistically different (p-value not reported)	
2012 (Lin) [175]	Taiwan	396 (198)	2009 H1N1	Stillbirth (not defined)	**Yes**	**Yes**	No	No	Data presented as percentages, not statistically different (p=1)	
2012 (Oppermann) [145]	Germany	1,652 (323)	2009 H1N1	SAB and stillbirth (not defined)	**Yes**	**Yes**	**Yes**	No	N/A	**For SAB: OR = 0.89 (95% CI, 0.36–2.19)**
2012 (Pasternak) [176]	Denmark	54,585 (7,062)	2009 H1N1	SAB (fetal death at <22 weeks) and stillbirth (fetal death at ≥ 22 weeks)	**Yes**	**Yes**	**Yes**	No	For SAB: HR = 1.16 (95% CI, 0.74–1.80)	For SAB: HR = 1.11 (95% CI, 0.71–1.73)

Study Year (Author) [Reference]	Country (Region)	Sample size, total (vaccinated)	Vaccine type	Outcome definition	Additional analysis of outcome(s) accounting for				Effect estimate	
					Covariates of vaccine receipt and/or preterm birth	Vaccine match to circulating virus	Gestational age at vaccination	Period(s) of influenza circulation	Unadjusted	Adjusted*
									For stillbirth: HR = 0.43 (95% CI, 0.20–0.92)	For stillbirth: HR = 0.44 (95% CI, 0.20–0.94)
2012 (Sammon) [177]	UK	39,863 (9,161)	2009 H1N1	Fetal death, including early miscarriage (9–12 weeks), late (13–24 weeks), and stillbirth (≥25 weeks)	**Yes**	**Yes**	**Yes**	**Yes**	For late miscarriage: HR = 0.59 (95% CI, 0.45–0.77) For stillbirth: HR = 0.70 (95% CI, 0.47–1.03)	**For late miscarriage: HR = 0.55 (95% CI, 0.40–0.75) For stillbirth: HR = 0.70 (0.38–1.29) (for women vaccinated during influenza season)** ***all estimates assume the investigators' "immunity model'**
2012 (Sheffield) [178]	USA (Texas)	85,783 (8,864)	Seasonal	Stillbirth (not defined)	**Yes**	No	No	No	Data presented as percentages, with reduced rate of stillbirth in vaccinated women (0.3% vs. 0.6%, p=0.006)	
2013 (Cantu) [179]	USA (Alabama)	2,989 (979)	Seasonal & 2009 H1N1	Miscarriage (delivery at <20 weeks) and stillbirth (delivery of non-viable fetus at ≥ 20 weeks)	**Yes**	No	**Yes**	No	Data presented as percentages, not statistically different (RR not reported)	
2013 (Chambers) [180]	USA and Canada	1,032 (841)	Seasonal & 2009 H1N1	SAB (pregnancy loss at <20 weeks) and stillbirth (pregnancy loss at ≥ 20 weeks)	**Yes**	No	**Yes**	No	For SAB: HR = 0.89 (95% CI, 0.34–2.35) For stillbirth: HR = 0.23	For SAB: HR = 0.92 (95% CI, 0.31–2.72) For stillbirth: N/A

Study Year (Author) [Reference]	Country (Region)	Sample size, total (vaccinated)	Vaccine type	Outcome definition	Additional analysis of outcome(s) accounting for				Effect estimate	
					Covariates of vaccine receipt and/or preterm birth	Vaccine match to circulating virus	Gestational age at vaccination	Period(s) of influenza circulation	Unadjusted	Adjusted*
									(95% CI, 0.01–3.93)	
2013 (Haberg) [103]	Norway	113,331 (25,976)	2009 H1N1	Fetal death (pregnancy loss at ≥ 12 weeks)	**Yes**	**Yes**	**Yes**	**Yes**	HR = 0.95 (95% CI, 0.74–1.21)	HR = 0.88 (95% CI, 0.66–1.17)
2013 (Irving) [181]	USA (six Vaccine Safety Datalink sites)	486 (69)	Seasonal	SAB (pregnancy loss at 5–16 weeks)	**Yes**	No	**Yes**	No	OR = 1.10 (95% CI N/A)	OR = 1.23 (95% CI, 0.53–2.89)
2013 (Rubinstein) [142]	Argentina	30,448 (7,293)	2009 H1N1	Fetal mortality (intrauterine death at >22 weeks)	**Yes**	**Yes**	No	No	Data presented as percentages, not statistically different (p=0.08)	
2014 (Beau) [182]	France	4,935 (1,645)	2009 H1N1	All-cause pregnancy loss (not defined)	**Yes**	**Yes**	No	No	HR = 0.59 (95% CI, 0.33–1.04)	**HR = 0.56 (95% CI, 0.31–1.01)**
2014 (Madhi) [32]	South Africa	194 (100)	Seasonal	Stillbirth (fetal death at ≥ 28 weeks)	**Yes**	No	No	No	**Data presented as percentages, not statistically different (p-value not reported)**	
2015 (Baum) [183]	Finland	43,604 (34,241)	2009 H1N1	Stillbirth (fetal death at ≥ 22 weeks)	**Yes**	**Yes**	**Yes**	No	HR = 0.99 (95% CI, 0.63–1.56)	**HR = 1.05 (95% CI, 0.66–1.65)**
2015 (Fabiani) [143]	Italy	5,641 (110)	2009 H1N1	Stillbirth (delivery of dead fetus at ≥ 22 weeks)	**Yes**	**Yes**	No	No	HR = 1.67 (95% CI, 0.53–5.27)	HR = 1.45 (95% CI, 0.46–4.62)
2015 (Ludvigsson) [146]	Sweden	137,886 (41,183)	2009 H1N1	Stillbirth (fetal death at ≥ 22 weeks)	**Yes**	**Yes**	**Yes**	No	HR = 0.83 (95% CI, 0.67–1.02)	HR = 0.83 (95% CI, 0.65–1.04)

*Adjusted for factors indicated in this table. If the effect estimate did not vary by gestational age at vaccination or period of influenza circulation, then the overall adjusted effect estimate is presented

Table 4

Key characteristics of published studies on the association between maternal influenza immunization and preterm birth (defined as live birth before 37 weeks gestation)

Study Year (Author) [Reference]	Country (Region)	Sample size, total (vaccinated)	Vaccine type	Cohort identified by births or pregnancies	Additional analysis of preterm birth accounting for				Effect estimate	
					Covariates of vaccine receipt and/or preterm birth	Vaccine match to circulating virus	Gestational age at vaccination	Period(s) of influenza circulation	Unadjusted	Adjusted*
2004 (Black) [107]	USA (N. California)	49,585 (3,707)	Seasonal	Pregnancies	No	No	No	No	Data presented as percentages, not statistically different (p=0.136)	
2005 (Munoz) [108]	USA (Texas)	892 (218)	Seasonal	Both	No	No	No	No	OR = 0.67 (95% CI, 0.32–1.32)	N/A
2008 (Zaman) [31]	Bangladesh	340 (172)	Seasonal	Pregnancies	No	No	No	No	Data presented as percentages, not statistically different (p=0.54)	
2011 (Omer) [114]	USA (Georgia)	4,168 (578)	Seasonal	Births	**Yes**	No	No	**Yes**	OR = 0.75 (95% CI, 0.54–1.04)	OR = 0.54 (95% CI, 0.32–0.90) (for infants born during putative influenza season)
2012 (Dodds) [184]	Canada (Nova Scotia)	9,647 (1,925)	Seasonal	Births	**Yes**	No	No	No	RR = 0.84 (95% CI, 0.69–1.02)	RR = 0.84 (95% CI, 0.69–1.02)
2012 (Fell) [117]	Canada (Ontario)	55,570 (23,340)	2009 H1N1	Births	**Yes**	**Yes**	No	No	OR = 0.91 (95% CI, 0.85–0.98)	OR = 0.95 (95% CI, 0.88–1.02)
2012 (Heikkinen) [141]	Netherlands, Italy, Argentina	4,508 (2,295)	2009 H1N1	Pregnancies	**Yes**	**Yes**	**Yes**	No	OR = 0.74 (95% CI, 0.55–0.99)	OR = 0.69 (95% CI, 0.51–0.92)

Study Year (Author) [Reference]	Country (Region)	Sample size, total (vaccinated)	Vaccine type	Cohort identified by births or pregnancies	Additional analysis of preterm birth accounting for				Effect estimate	
					Covariates of vaccine receipt and/or preterm birth	Vaccine match to circulating virus	Gestational age at vaccination	Period(s) of influenza circulation	Unadjusted	Adjusted*
2012 (Kallén) [116]	Sweden	155,526 (18,612)	2009 H1N1	Pregnancies	**Yes**	**Yes**	**Yes**	No	N/A	OR = 0.81 (95% CI, 0.69–0.96) (for women vaccinated after 26 weeks gestation)
2012 (Launay) [174]	France	877 (320)	2009 H1N1	Pregnancies	**Yes**	**Yes**	No	No	Data presented as percentages, not statistically different (p=0.80)	
2012 (Lin) [175]	Taiwan	396 (198)	2009 H1N1	Pregnancies	**Yes**	**Yes**	No	No	Data presented as percentages, not statistically different (p-value not reported)	
2012 (Oppermann) [145]	Germany	1,652 (323)	2009 H1N1	Pregnancies	**Yes**	**Yes**	**Yes**	No	Data presented as percentages, not statistically different (p-value not reported)	
2012 (Pasternak) [144]	Denmark	51,050 (6,545)	2009 H1N1	Births	**Yes**	**Yes**	**Yes**	No	OR = 1.00 (95% CI, 0.89–1.13) (for women vaccinated in the second and third trimesters)	OR = 1.00 (95% CI, 0.84–1.17)
2012 (Richards) [105]	USA (Georgia, Maryland, Virginia, District of Columbia)	2,706 (1,125)	2009 H1N1	Births	**Yes**	**Yes**	**Yes**	**Yes**	OR = 0.60 (95% CI, 0.46–0.79)	OR = 0.63 (95% CI, 0.47–0.84)
2012 (Sheffield) [178]	USA (Texas)	85,783 (8,864)	Seasonal	Both	**Yes**	No	No	No	Data presented as percentages, with reduced rate of preterm birth in vaccinated women (5% vs. 6%, p=0.004)	

Study Year (Author) [Reference]	Country (Region)	Sample size, total (vaccinated)	Vaccine type	Cohort identified by births or pregnancies	Additional analysis of preterm birth accounting for				Effect estimate	
					Covariates of vaccine receipt and/or preterm birth	Vaccine match to circulating virus	Gestational age at vaccination	Period(s) of influenza circulation	Unadjusted	Adjusted*
2012 (Steinhoff) [118]	Bangladesh	116 (58)	Seasonal	Pregnancies	**Yes**	No	No	**Yes**	OR = 0.72 (95% CI, 0.30–1.70)	OR = 0.32 (95% CI, 0.05–2.29)
2013 (Adedinsewo) [113]	USA (Georgia)	5,422 (916)	Seasonal	Births	**Yes**	No	No	**Yes**	OR = 1.04 (95% CI, 0.48–2.28)	OR = 0.44 (95% CI, 0.21–0.91) (for infants born during widespread influenza circulation)
2013 (Cantu) [179]	USA (Alabama)	2,989 (979)	Seasonal & 2009 H1N1	Pregnancies	**Yes**	No	**Yes**	No	RR = 1.20 (95% CI, 1.06–1.40)	RR = 1.20 (95% CI, 0.90–1.60)
2013 (Chambers) [180]	USA and Canada	893 (736)	Seasonal & 2009 H1N1	Pregnancies	**Yes**	No	**Yes**	No	HR = 2.93 (95% CI, 1.27–6.76)	HR = 3.28 (95% CI, 1.25–8.63) (for women vaccinated in any trimester)
2013 (Haberg) [103]	Norway	113,331 (25,976)	2009 H1N1	Births	**Yes**	**Yes**	**Yes**	**Yes**	N/A	OR = 1.00 (95% CI, 0.93–1.09)
2013 (Louik) [185]	USA (Massachusetts, Philadelphia, San Diego, New York)	951 (378)	Seasonal & 2009 H1N1	Births	**Yes**	No	**Yes**	No	HR = 1.50 (95% CI, 0.83–2.70)	HR = 1.03 (95% CI, 0.50–2.10)
2013 (Ludvigsson) [186]	Sweden	21,087 (7,790)	2009 H1N1	Births	**Yes**	**Yes**	**Yes**	No	OR = 0.97 (95% CI, 0.86–1.08)	OR = 0.99 (95% CI, 0.89–1.10)
2013 (Rubinstein) [142]	Argentina	30,448 (7,293)	2009 H1N1	Both	**Yes**	**Yes**	No	No	OR = 0.73 (95% CI, 0.65–0.83)	OR = 0.79 (95% CI, 0.69–0.90)

Study Year (Author) [Reference]	Country (Region)	Sample size, total (vaccinated)	Vaccine type	Cohort identified by births or pregnancies	Additional analysis of preterm birth accounting for				Effect estimate	
					Covariates of vaccine receipt and/or preterm birth	Vaccine match to circulating virus	Gestational age at vaccination	Period(s) of influenza circulation	Unadjusted	Adjusted*
2014 (Ahrens) [109]	USA (Pennsylvania, California, Rhode Island, New Hampshire, New York, Massachusetts)	1,619 (334)	Seasonal	Births	**Yes**	No	**Yes**	No	OR = 1.30 (95% CI, 0.83–2.05)	OR = 1.37 (95% CI, 0.84–2.23)
2014 (Beau) [182]	France	4,935 (1,645)	2009 H1N1	Pregnancies	**Yes**	**Yes**	No	No	HR = 1.02 (95% CI, 0.80–1.30)	HR = 0.82 (95% CI, 0.64–1.06)
2014 (Cleary) [187]	Ireland	6,894 (2,996)	2009 H1N1	Both	**Yes**	**Yes**	No	No	OR = 0.71 (95% CI, 0.58–0.88)	OR = 0.72 (95% CI, 0.58–0.89)
2014 (Legge) [115]	Canada (Nova Scotia)	11,293 (1,856)	Seasonal	Births	**Yes**	No	No	No	OR = 0.75 (95% CI, 0.60–0.93)	OR = 0.75 (95% CI, 0.60–0.94)
2014 (Madhi) [32]	South Africa	194 (100)	Seasonal	Pregnancies	**Yes**	No	No	No	Data presented as percentages, not statistically different (p-value not reported)	
2014 (Nordin) [188]	USA (seven Vaccine Safety Datalink sites)	115,108 (57,554)	Seasonal	Pregnancies	**Yes**	No	**Yes**	No	N/A	OR = 0.97 (95% CI, 0.93–1.02)
2015 (Baum) [183]	Finland	43,604 (34,241)	2009 H1N1	Pregnancies	**Yes**	**Yes**	**Yes**	No	HR = 1.01 (95% CI, 0.90–1.14)	HR = 1.00 (95% CI, 0.89–1.12)
2015 (Fabiani) [143]	Italy	5,641 (110)	2009 H1N1	Pregnancies	**Yes**	**Yes**	No	No	HR = 1.13 (95% CI, 0.94–1.37)	HR = 1.15 (95% CI, 0.95–1.39)
2015 (van der Maas) [189]	Netherlands	1,627 (1,104)	2009 H1N1	Both	**Yes**	**Yes**	No	No	OR = 0.95 (95% CI, 0.59–1.54)	**OR = 0.98 (95% CI, 0.59–1.62)**

*Adjusted for factors indicated in this table. If the effect estimate did not vary by gestational age at vaccination or period of influenza circulation, then the overall adjusted effect estimate is presented

Table 5

Immunologic outcomes shown to be (or potentially) impacted by the timing of maternal influenza immunization during pregnancy

Outcome	Observed effect(s)	References
Mother		
Immunoglobulin subclass response	No data	No data
Avidity of vaccine-induced antibodies *	Earlier vaccination associated with increased avidity *	[190]
Durability of antibody response post-partum	Timing of vaccination during pregnancy does not affect the durability of antibodies post-partum, but HIV-infected women have less durable sero-protective titers	[133,148,156,191]
Breast milk antibody response (quantity and quality)	Maternal influenza immunization is associated with increased breast milk anti-influenza IgA titers – effect of timing of vaccination on quantity, specificity, and function of these antibodies remains uncertain	[192]
Infant		
Efficiency of trans-placental antibody transfer (i.e. infant:maternal ratio)	Greater interval between vaccination and delivery associated with enhanced transplacental transfer	[32,69,156,193]
Peak cord blood antibody titers or sero-protection rate	Greater interval between vaccination and delivery associated with increased cord blood antibody titers and rates and durability of sero-protection in infants in some studies	[32,122,147,156,194,195]
Avidity of maternally-derived antibodies *	Earlier vaccination associated with increased avidity *	[190]
Durability (i.e. half-life) of maternally-derived antibodies	Timing of vaccination during pregnancy does not affect the half-life of maternally-derived antibodies	[69,148,156,193]

* Data for pertussis only

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Table 6

Studies of trans-placental transfer of influenza antibodies among infants of vaccinated mothers, based on (A) timing of vaccination relative to delivery and (B) gestational age at the time of vaccination. Both the absolute time interval between vaccination and delivery as well as the gestational age at the time of vaccination are factors in the efficiency of trans-placental antibody transfer.

A: Trans-placental transfer of influenza antibodies based on *timing of maternal vaccination relative to delivery*. With greater intervals between vaccination and delivery, there are higher rates of sero-protection (HAI titer ≥ 1:40) in cord blood, and in some studies, higher ratios of cord blood to maternal HAI titers

Study characteristic	Author (Year) Location [Reference]	Sample size (N) (number that received influenza vaccine)	Influenza vaccine antigens	Interval between vaccination and delivery (days)	Ratio of infant to mother GMT at birth	Cord blood/ infant sero-protection rate (%)	Comment
Unadjuvanted vaccines	Madhi (2014) & Nunes (2015) South Africa [32,156]	142 (HIV-uninfected cohort)	A/California/H1N1	81.1 (SD 31.7)	0.9	89.7%	Data on infant to mother GMT ratio or cord blood sero-protection rate were not reported stratified by timing of maternal vaccination
			A/Victoria/H3N2		0.82	82.1%	
			B/Brisbane		0.96	94.9%	
	Zaman (2008) & Steinhoff (2010) Bangladesh [31,193]	172	A/New Caledonia/H1N1	54 (range 0–89)	1.1	Not reported	
			A/Fujian/H3N2		1.0		
			B/Hong Kong		0.8		
	Englund (1993) USA [69]	13	A/Taiwan/H1N1	35.5 (range 12–62)	0.97	Not reported	
			A/Sichuan/H3N2		0.99		
			B/Victoria		0.94		
	Blanchard-Rohner (2013) Switzerland [194]	101	A/California/H1N1	<15	Not reported	67%	Increased cord blood sero-protection rate associated with increasing interval between vaccination and delivery
				15–30		79%	
				31–90		91%	
				91–120		91%	
				>121		87%	
			A/Perth/H3N2	<15	Not reported	33%	
				15–30		86%	
				31–90		94%	
				91–120		91%	
				>121		88%	
			B/Brisbane	<15	Not reported	50%	
				15–30		93%	

A: Trans-placental transfer of influenza antibodies based on *timing of maternal vaccination relative to delivery*. With greater intervals between vaccination and delivery, there are higher rates of sero-protection (HAI titer ≥ 1:40) in cord blood, and in some studies, higher ratios of cord blood to maternal HAI titers

Study characteristic	Author (Year) Location [Reference]	Sample size (N) (number that received influenza vaccine)	Influenza vaccine antigens	Interval between vaccination and delivery (days)	Ratio of infant to mother GMT at birth	Cord blood/ infant sero-protection rate (%)	Comment
				31–90		88%	
				91–120		91%	
				>121		86%	
	Lin (2013) Taiwan [195]	42	A/California/H1N1	<21	<1	100% (n=1)	Ratio of infant to maternal GMT only >1 associated with vaccination >5 weeks before delivery
				22–35	<1	80% (n=5)	
				>35	>1	87% (n=38)	
			A/Perth/H3N2	<21	<1	100% (n=1)	
				22–35	<1	100% (n=5)	
				>35	>1	63% (n=38)	
			B/Brisbane	<21	<1	100% (n=1)	
				22–35	<1	60% (n=5)	
				>35	>1	45% (n=38)	
Adjuvanted vaccines	Helmig (2015) Denmark [196]	19	A/California/H1N1 (AS03 adjuvanted)	20–43	0.90	89.5%	Despite adjuvanting, a shorter interval between vaccination and delivery is associated with lower rates of sero-protective HAI titers in cord blood
	Puleston (2010) UK [147]	77	A/California/H1N1 (AS03 adjuvanted)	<10	Not reported	50%	
				>10		79%	
HIV-exposed infants	Madhi (2014) & Nunes (2015) South Africa [32,156]	70	A/California/H1N1	76.5 (SD 31.7)	0.66	60.7%	A smaller proportion of HIV-exposed infants are sero-protected at birth, despite similar intervals between vaccination and delivery, and similar ratios of infant to mother GMT – this is likely attributable to lower peak post-vaccination GMTs in immunized mothers
			A/Victoria/H3N2		0.92	42.9%	
			B/Brisbane		0.96	78.6%	
	Abzug (2013) USA [191]	127	A/California/H1N1 (two doses)	66 (range 9–155)	1	65%	

B: Trans-placental transfer of influenza antibodies based on *gestational age at the time of vaccination*. The efficiency of trans-placental antibody transfer appears to be similar in women vaccinated in the second trimester as compared with those vaccinated in the third trimester

Study characteristic	Author (Year) Location [Reference]	Sample size (N) (i.e. number that received influenza vaccine)	Influenza vaccine antigens	Gestational age at vaccination (weeks)	Ratio of infant to mother GMT at birth	Cord blood/ infant sero-protection rate (%)(i.e. HAI titer ≥1:40)	Comment
Unadjuvanted vaccines	Eick (2011) USA [122]	123	A/New Caledonia/H1N1	14–27	Not reported	61%	No significant difference in cord blood sero-protection rate between women vaccinated in the second trimester compared to women vaccinated in the third trimester
				28–42		69.6%	
		60	A/Panama/H3N2	14–27	Not reported	80%	
				28–42		77.6%	
		60	A/Wyoming/H3N2	14–27	Not reported	65%	
				28–42		69.4%	
		63	A/Wisconsin/H3N2	14–27	Not reported	14.3%	
				28–42		22%	
		63	B/Sichuan	14–27	Not reported	58.3%	
				28–42		67.5%	
		92	B/Hong Kong	14–27	Not reported	30.4%	
				28–42		42.5%	
		63	B/Shanghai	14–27	Not reported	66.7%	
				28–42		70.7%	
		31	B/Brisbane	14–27	Not reported	71%	
				28–42		73%	
	Yamaguchi (2009) Japan [197]	125	A/Solomon/H1N1 A/Hiroshima/H3N2 B/Malaysia	14–27	(161.1%)	Not reported	Data on infant to mother GMT ratio or cord blood sero-protection rate were not reported stratified by timing of maternal vaccination
				28–42	(127.4%)		
	Chao (2013) Taiwan [198]	41	A/California/2009 (10 women received MF59 adjuvanted vaccine)	All trimesters	Not reported	75.6%	
	Jackson (2011) USA [199]	120	A/California/2009 (two doses)	27–34	1.81 (for 25μg) 2.96 (for 49μg)	Not reported	
	Tsatsaris (2011) France [133]	107	A/California/2009	22–34	Not reported	95%	
Adjuvanted vaccines	Zuccotti (2011) Italy [148]	75	A/California/2009 (MF59 adjuvanted)	Third trimester	0.55	95.6%	

Table 7

Studies of postpartum kinetics of trans-placentally acquired influenza antibodies in infants of vaccinated mothers. The half-life of maternally-derived influenza antibodies is unaffected by the timing of vaccination

Author (Year) Location [Reference]	Sample size (N) (i.e. number that received influenza vaccine)	Interval between vaccination and delivery (days)	Influenza vaccine antigens	Infant:mother ratio	Half-life of infant influenza antibodies (days)	Comment
Englund (1993) USA [69]	13	35.5 (range 12–62)	A/Taiwan/H1N1 A/Sichuan/H3N2 B/Victoria	0.99 0.97 0.94	42 (±20) 40 (±16) 50 (±20)	
Zaman (2008) & Steinhoff (2010) Bangladesh [31,193]	172	54 (range 0–89)	A/New Caledonia/H1N1 A/Fujian/H3N2 B/Hong Kong	1.1 1.0 0.8	42–50 (95% CI 37–56) (for all subtypes)	At 20–26 weeks after delivery infant vaccinees still had higher GMTs than controls for influenza A subtypes (but not influenza B)
Madhi (2014) & Nunes (2015) South Africa [32,156]	142 (HIV-uninfected)	81.1 (SD 31.7)	A/California/H1N1 A/Victoria/H3N2 B/Brisbane	0.9 0.82 0.96	46.1 (95% CI 41.9–50.3)* 44.4 (95% CI 40.4–48.3)* 43.9 (95% CI 40.0–47.8)*	Higher infant GMT associated with a greater interval between vaccination and delivery
	70 (HIV-infected)	76.5 (SD 31.7)	A/California/H1N1 A/Victoria/H3N2 B/Brisbane	0.66 0.92 0.96	56.4 (95% CI 50.8–62.1)* 65.1 (95% CI 57.7–72.5)* 63.7 (95% CI 56.2–71.1)*	HIV-exposed infants had lower initial titers compared to HIV-unexposed infants
Zuccotti (2010) Italy [148]	75	Not specified (all third trimester)	A/California/H1N1 (MF59 adjuvanted)	0.55	83.4 (95% CI 63.8–107.9)	At 5 months after delivery 81.2% of infants still had HAI titer ≥1:40

*Adjusted for initial hemagglutinin inhibitor titer