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Review on the effects of influenza vaccination during pregnancy on preterm births

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Pregnant women are considered to be susceptible to severe influenza illness and are recommended as a priority group to be targeted for influenza vaccination in countries with vaccination programs. Increased rates of poor birth outcomes have also been temporally associated with influenza infection, especially when pandemics strains emerge. Even though the primary purpose for influenza vaccination during pregnancy is to decrease the risk of influenza infection in the women, other potential benefits include protection of their young infants against influenza illness and possibly improving birth outcomes. The 2009 influenza A/H1N1 pandemic highlighted the importance of influenza vaccination during pregnancy, after pregnant women were identified as a group with heightened morbidity and mortality during the pandemic. A few studies conducted before the 2009/10 season and a large number of reports during and after the 2009 pandemic have assessed the association between maternal influenza vaccination and birth outcomes. Although these studies indicate that influenza vaccination is safe for both the mother and the fetus, there are conflicting data on the effect of vaccination in improving preterm birth rates. We reviewed the 2 published randomized control trials and other observational studies that explored the relationship between maternal influenza vaccination and preterm births.

Pregnant Women are at High Risk for Influenza-Related Complications

It has been suggested that pregnant women are at heightened risk for complications of influenza infection compared to healthy non-pregnant woman. Studies on the effects of influenza infections in pregnancy during seasonal epidemics have used rates of excess hospitalizations for acute respiratory illness during influenza season compared to the peri-influenza season as a proxy for influenza associated hospitalisation. The causal relation between hospital admissions and access to care or bias for excess precautionary hospitalizations during pregnancy has yet not been explored in these studies. Neuzil et al. examining data from women enrolled in the Tennessee Medicaid system over 17 influenza seasons (1974–78 and 1981–93) demonstrated that pregnant women were more likely to be hospitalized with an acute cardiopulmonary illness during seasonal influenza epidemics compared with non-pregnant or post-partum women.[1] The highest rate of hospitalization was detected during the third trimester of pregnancy, when pregnant women were 3–4 times more likely than their postpartum counterparts to be hospitalized for a cardiopulmonary illness during influenza season.[1] Also using data from the USA, Cox et al. analyzed data from a representative hospital discharge database during the 1998–2002 influenza seasons and showed that the proportion of hospitalizations among pregnant women with respiratory illness was significantly higher during influenza circulation (3.4 per 1000 hospitalizations of pregnant women) compared with the rest of the year (1.8 per 1000).[2] Furthermore pregnant women with high-risk conditions for which influenza vaccination is recommended by the Advisory Committee on Immunization Practices were >3 times more likely to be hospitalized for respiratory illness during influenza season than women without these conditions.[2] Dodds et al. conducted a 13 year (1990–2002) population-based cohort study involving pregnant women in Nova Scotia, Canada, and compared the rates of hospital admissions and physician visits due to respiratory illness during the influenza season with rates during the influenza season in the year before pregnancy and with rates during non-influenza circulation.[3] The authors reported a rate-ratio of hospital admissions among pregnant women without comorbidities in the third trimester during influenza seasons of 5.1 (95%CI: 3.6 to 7.3) compared with admissions in the year before pregnancy, and of 2.4 (95%CI: 1.7 to 3.4) comparing influenza and non-influenza seasons. Pregnant women with known comorbidities had even higher rate-ratios.[3]

More recently, the emergence of the influenza A/H1N1 pandemic 2009 (A/H1N1pdm09) virus further emphasized the susceptibility of pregnant women to severe influenza illness, at least in the context of emergence of novel strains of the virus. Data collected worldwide during the pandemic strain circulation suggested that pregnant women were disproportionately affected by A/H1N1pdm09 virus infection with regard to severe illness and death compared with the general population. A systematic literature review in 2011 that included reports from 29 countries

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around the world regarding the influenza A/H1N1 pandemic in 2009 found that pregnant women accounted for 6.3% of the hospitalizations, 5.9% of the intensive care unit admissions and 5.7% of deaths that were associated with A/H1N1pdm09 infection; although pregnant women comprise only about 1% of the total population in the USA for example.[4] In pooled data from another systematic review, the average case fatality rate for pregnant women infected with A/H1N1pdm09 was 6.4% (range 0% in Japan to 25% in India) using available data from 10 countries.[5] The highest risk groups for severe complications were described to be women in their second and particularly the third trimesters of pregnancy or pregnant women with underlying medical conditions, although severe illness with intensive care unit admissions and death occurred in all 3 trimesters and among women in whom the only recognized risk factor was pregnancy.[6] In South Africa the second most common underlying condition among the fatal cases related to A/H1N1pdm09 infection was pregnancy (25 of the 45 women of reproductive age who died were pregnant or during the purpuerium period) just after HIV-infection.[7]

Impact of Influenza Disease on Pregnancy Outcomes

Studies using data from the influenza pandemics of the first-half of the 20th century and from the 2009 A/H1N1 pandemic recognized that pregnant women who experienced influenza virus infection during pregnancy had higher risk for pregnancy related complications with increased rates of miscarriages, stillbirths, low birth weight (LBW) and premature deliveries.[8-10] Fewer data are available from inter-pandemic years, although it has been reported that hospitalized pregnant women with respiratory illness during yearly epidemics had higher odds of poor birth outcomes compared with hospitalized pregnant women without respiratory illness.[2,11] The adverse fetal effects of influenza infection during pregnancy could be due to a direct biological effect of maternal viral infection in the fetus, or secondary to influenza illness stimulating an inflammatory response which could include an increase in prostaglandin E and other cytokine and chemokine production that could precipitate labor.[12] On the same note influenza infection normally presents with fever and it has been shown that hyperthermia during pregnancy is associated with an increased risk for certain birth defects and birth adverse outcomes.[13] Congenital transmission of influenza virus from mother to fetus in utero has been reported to be an infrequent phenomenon.[14,15]

Bloom-Feshbach et al. analyzed monthly birth rates in 3 Scandinavian countries and the USA during the time period surrounding the 1918 A/H1N1 pandemic and observed significant reductions in live births after the most intense wave of the 1918 pandemic.[9] The authors postulated that the observed decline in birth rates was due to pandemic influenza infection during the first trimester of pregnancy causing miscarriages in approximately 1 in 10 of the infected women during the peak of the pandemic.[9] Data from 113,331 pregnancies in Norway in 2009 and 2010 showed that pregnant women infected with A/H1N1pdm09 had an almost 2-fold greater risk of fetal death than non-infected pregnant women.[10] Pierce et al. using the UK national cohort of women admitted to hospital with confirmed A/H1N1pdm09 infection in pregnancy, reported a significant increase in perinatal mortality rate (39 [95%CI: 19 to 71] per 1000 total births) among influenza-infected women compared with non-infected women (7 [95%CI: 3 to 13] per 1000); this observation was mainly due to an increase in the rate of stillbirths (27 vs. 6 per 1000 total births; p=0.001).[8] Furthermore, they also reported that influenza-infected women were more likely to deliver prematurely than women not infected by influenza (adjusted odds ratio [aOR], 4.0 [95%CI: 2.7 to 5.9]), with the risk factors for preterm delivery being third trimester influenza infection, admission to intensive care unit and presentation with secondary pneumonia.[8] Likewise data from the USA showed that of the 85 infants born during their mothers' hospitalization for influenza infection 63.6% were born preterm, 4.1% were small for gestational age (SGA), 43.8% had LBW and 69.4% were admitted to the neonatal intensive care unit; rates that are 5 to 15 times higher than the normal USA rates.[16]

In a Canadian cohort study over 13 years, infants born to mothers who were hospitalized for respiratory illness during influenza season were more likely to be SGA (adjusted relative risk, 1.7 [95%CI: 1.1 to 2.5]) and to have a lower mean birth weight than infants whose mothers were hospitalized for reasons other than respiratory illness.[11]

Influenza Vaccination During Pregnancy

Influenza vaccines can provide moderate protection against virologically confirmed influenza infection in healthy adults, and the vaccine effectiveness, ranging from 50%–75% for the seasonal inactivated influenza vaccine, is greatly dependent on how well the vaccine composition matches the circulating strains.[17,18] Similarly vaccination during pregnancy can prevent influenza infection in the women and in addition protects the newborns of vaccinated mothers also from influenza infection during the first 6 months of life.[19,20] Another attractive bonus of maternal immunization would be to protect the fetus from the unintended consequences of infection described above.[21] However, clear evidence that immunization during pregnancy may improve birth outcomes is still lacking and inconsistent observations have been reported.

In this review we identified studies that assessed the impact of influenza vaccination during pregnancy, with any type of influenza vaccine, on the rate of preterm deliveries. We considered both clinical trials and observational studies; passive surveillance studies were not included. We reviewed the published work and propose key information to be included in future reports to help the analysis of pooled data. We focused on the outcome of premature delivery (usually defined as birth at less than 37 completed weeks of gestational age), as it is the birth outcome evaluated in the majority of the reports and due to its importance as a major cause of under-5 mortality.[22] More than 80% of

neonatal deaths occur in LBW babies especially those that are preterm. Furthermore both preterm and term infants who are SGA have an increased risk of disabilities, including stunting and adult onset non-communicable diseases.[23] The figures of neonatal mortality will probably remain the same if more effective interventions are not developed for the prevention of prematurity and SGA births, for which there are currently very few effective interventions. Thus even small decreases in the premature birth rate through direct or indirect methods could have a substantial impact on neonatal and infant mortality.

A pandemic related to influenza A/H1N1pdm09 strain was declared by the World Health Organization (WHO) in mid-2009 and vaccines were developed via an accelerated process targeting this strain.[24] A/H1N1pdm09 containing vaccines were produced by multiple manufacturers using different dosages of antigen, and various formulations; also due to the low stock of available antigens for vaccine production owing to the unprecedented large demand of vaccines the WHO recommended the use of adjuvant A/H1N1 vaccines.[25] In the USA only vaccines without adjuvant were approved, while in some Asian and European countries and Canada monovalent vaccines with different adjuvants were also licensed. Pregnant women were identified as a priority group and intensive efforts were undertaken to increase the coverage of vaccination among this group, despite limited safety data. Later, in 2012, the WHO Strategic Advisory Group for Experts on Immunization recommended pregnant women as the most important risk group for seasonal inactivated influenza vaccination (IIV).[26]

Studies Evaluating the Association of Maternal Influenza Vaccination and Birth Outcomes

To date only 2 randomized-control trials (RCTs) on influenza vaccination during pregnancy have been published, and the rate of prematurity was compared between mothers who received seasonal trivalent IIV and the control group mothers.[20,21] The large majority of the other studies investigating the impact of maternal influenza vaccination during pregnancy on preterm deliveries have been observational. The objective of these observational studies was to evaluate the safety of antenatal vaccination, exploring whether there was an association between vaccination and birth outcomes either prospectively or retrospectively using population-based perinatal databases. We identified 24 observational studies (**Table 1**).[10,27-49]

Randomized-controlled trials

In a RCT in Bangladesh from 2004 to 2005, where 161 pregnant women in their third trimester were randomized to IIV and 166 to pneumococcal polysaccharide vaccine the risk of preterm births did not differ between the 2 groups during the overall study period and neither the rate of LBW and SGA births.[21] However, when the analysis was restricted to births occurring during the time of influenza virus circulation (58 births in each group) IIV was associated with higher mean birth weights (3,178 grams vs. 2,978 grams; adjusted mean difference =193 g [95%CI: 9 g to 378 g], $p = 0.02$) and 58% (95%CI: 94% to 20%) lower risk of infants being born SGA (25.9% vs. 44.8%, $p = 0.03$). No association was detected between IIV vaccination and prematurity and LBW newborns even just considering the restricted period of influenza circulation.[21]

A randomized placebo-controlled trial in South Africa during the 2011 and 2012 South hemisphere influenza seasons analyzed the outcomes of 1,026 and 1,023 deliveries from women who received either IIV or saline-placebo in the their second or third pregnancy trimesters.[20] In the South African trial 10% of the infants were born at <37 weeks of gestational age, 12.5% were <2500 grams at birth and the median birth weight was 3100 grams, with no differences between infants born to IIV or placebo-recipients. Also an exploratory analysis from that study did not detect any difference in birth weight between infants of IIV compared to placebo-recipients after stratification by births occurring during the influenza season and based on the gender of the infant.[20]

Observational studies

Table 1 summarizes the design of the observational studies described in this review. The association of seasonal influenza vaccine and prematurity has been evaluated in the USA and in Canada in 6 observational studies that used data from years prior the A/H1N1pdm2009 [28,33–35,44,49] and 3 studies that were conducted following the 2009 pandemic season.[37,39,46]

Data on fetal safety of A/H1N1pdm09 monovalent vaccines administered to pregnant women during the 2009/10 pandemic are available from the USA,[30,37] Canada,[43] Argentina,[29] Taiwan [38] and from several European countries.[10,27,31,32,36,40,41,45,48] Unadjuvanted vaccines were used in the North American studies, in France and a study in Taiwan.[30,37,38,40,43,48] The A/H1N1 MF56-adjuvanted formulation was evaluated in Argentina, Italy and the Netherlands.[27,29,42] Four studies in Scandinavia described the birth outcomes after vaccination with an AS03-adjuvanted influenza vaccine.[10,31,36,41] In Germany and Ireland more than one vaccine formulation was commercially available and recommended for use in the pandemic campaigns.[32,45] The emergence of A/H1N1pdm09 in 2009/10 led to concurrent availability of monovalent vaccine and the seasonal influenza vaccines; with four reports from North America evaluating the birth outcomes when both type of vaccines were administered during the same pregnancy.[37,43,46,47]

In the observational studies, as uptake of influenza vaccination could have been biased, adjusting for potential confounders is imperative. It is anticipated that vaccinated women would be different from the non-vaccinated women in several characteristics and that the probability of receiving the vaccine would be associated with these factors. To adjust for group differences and reduce confounding bias in observational studies 2 main approaches were used: propensity scores [31,34,37] and multiple logistic regression analysis.[10,21,27,29,30,33,35,36,39,41-49] In propensity score analyses probability of vaccination is estimated as a function of available variables and then that score is used as a single matching covariate. The propensity score matching allows comparing the risks after vaccination between cohorts that had

Table 1. Summary of observational studies reporting on the association of maternal influenza vaccination and preterm deliveries*

Reference and country	Study date and population	Study design and data collection	Trimester
Van der Maas et al. 2015; Holland[27]	Random sample of pregnant women, eligible for vaccination between Nov-Dec 2009.	Cross-sectional linkage study. Perinatal database. Information on vaccination status was self-reported.	2nd and 3rd. No results by trimester.
Cleary, et al. 2014; Dublin, Ireland[45]	Pregnancies during Dec 2009 to Sep 2010. Singleton deliveries.	Retrospective cohort study using discharge records. Information on vaccination status and type of vaccine was self-reported at delivery.	1st 8%, 2nd 57%, 3rd 35%. No results by trimester.
[a]Nordin, et al. 2014; Seven Vaccine Safety Datalink sites, USA[34]	Pregnancies during 2004–05 through 2008–09 influenza seasons. Live-births with BW ≥500g and GA ≥22 weeks.	Retrospective match cohort study. Perinatal database. Information on vaccination status was obtained from electronic medical registries and medical claims data.	1st 28%, 2nd 43%, 3rd 29%. Results overall and by trimester.
Beau, et al. 2014; France[48]	Deliveries from 21 Oct 2009 to 30 Nov 2010.	Population-based retrospective match cohort study. Perinatal database. Information on vaccination status was obtained from health units databases.	1st 8%, 2nd 52%, 3rd 40%. No results by trimester.
[b]Legge, et al. 2014; Nova Scotia, Canada[39]	Deliveries from 1 Nov 2010 to 31 Mar 2012. Singleton live-births with BW ≥500g and GA ≥20 weeks.	Population-based retrospective cohort study. Perinatal database that also collected self-reported information on vaccination status.	Not reported
Adedinsewo et al. 2013; Georgia, USA[49]	Deliveries from 1 Jan 2005 to 31 Dec 2008. Live-births.	Population-based retrospective cohort study. Information on vaccination status and type of vaccine was self-reported.	Not reported
Chambers et al. 2013; USA and Canada[46]	Pregnancies during Oct 2009 to Apr 2012.	Prospective cohort study. Outcomes and information on vaccination status, type of vaccine and vaccination date collected by telephonic interview and medical records.	1st 32%, 2nd 33%, 3rd 14%. Results overall and by trimester.
Louik at al. 2013; Four regional centers in the USA[37]	Pregnant women during the 2009/10 or 2010/11 season. Singleton live-births.	Retrospective case control study. Within 6 months of delivery, mothers of eligible infants were interviewed by telephone. Information on vaccination status, type of vaccine and vaccination date confirmed by the provider.	1st 36%, 2nd 38% or 3rd26%. Results overall and by trimester.
Ludvigsson et al. 2013; Stockholm County, Sweden[36]	Pregnancies conceived between Feb 2009 to Jan 2010. Singleton live-births.	Population-based retrospective cohort study. Perinatal database. Information on vaccination status was obtained from health units databases.	1st 34%, 2nd 40%, 3rd 36%. No results by trimester.
Cantu et al. 2013; USA[47]	Prenatal visits during 1 Oct to 31 Dec 2009 and 2010. Singleton births.	Retrospective cohort study. Information on vaccination status was obtained from perinatal and clinic vaccination logs.	Not reported
[a]Rubinstein, et al. 2013; 49 public hospitals in Argentina[29]	Deliveries from Sep 2010 to May 2011. Live-births with BW ≥500 g or GA ≥22 weeks.	Cross-sectional study. Data abstraction from medical records and participants survey. Information on vaccination status and vaccination date based on documentation in any official registry.	1st 39%, 2nd 49%, 3rd 10%. No results by trimester. 2nd or 3rd. No results by trimester.

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Table 1. Summary of observational studies reporting on the association of maternal influenza vaccination and preterm deliveries* *(Continued)*

Reference and country	Study date and population	Study design and data collection	Trimester
[c]Richards, et al. 2013; Kaiser Permanente Georgia and Mid-Atlantic States, USA[30]	Deliveries from 26 Apr 2009 to 17 Apr 2010. Third trimester live-births.	Population-based retrospective cohort study. Information on vaccination status, type of vaccine and vaccination date from electronic medical records.	
Haberg et al. 2013; Norway[10]	Pregnancies during 2009 to 2010. Singleton births.	Nationwide registry-based retrospective cohort study. Information on vaccination status from the immunization registry.	1st 9%, 2nd 42%, 3rd 49%. No results by trimester.
Launay et al. 2012; Paris, France[40]	Enrolment of pregnant women between 12 and 35 weeks GA from 12 Oct 2009 to 3 Feb 2010.	Prospective cohort study. Information on vaccination status self-reported.	2nd or 3rd. No results by trimester.
[b]Dodds et al. 2012; Nova Scotia, Canada[44]	Deliveries from 1 Apr 2006 to 31 Oct 2009. Singleton births with BW >500g and GA >20 weeks.	Population-based retrospective cohort study. Perinatal electronic database. Information on vaccination status self-reported collected on the same database.	Not reported
[d]Heikkinen et al. 2012; The Netherlands, Italy, and Argentina[42]	Pregnancies during Jan to Aug 2010 in The Netherlands, May to Jun 2010 in Italy, Jul to Aug 2010 in Argentina.	Observational cohort study with active enrolment and retrospective. Information on vaccination status self-reported and if vaccine was reported when possible was confirmed by vaccination records.	1st 4%, 2nd 57%, 3rd 39%. No results by trimester.
Sheffield et al. 2012; Dallas, Texas, USA[28]	Pregnancies during Oct to Mar between 2003 and 2008.	Retrospective cohort study. Perinatal electronic database also containing information on vaccination status.	1st 5%, 2nd or 3rd 95%. No results by trimester.
Kallen et al. 2012; Sweden[41]	Deliveries from Oct 2009 to Dec 2010.	Nationwide registry-based retrospective cohort study. Information on vaccination status from incomplete national health registers and self-reported.	1–19 week of gestation 41%, 20–26 week of gestation 28%, 27–36 week of gestation 31%. Results overall and by trimester.
Pasternak et al. 2012; Denmark[31]	Deliveries from 2 Nov 2009 to 30 Sep 2010. Singleton live-births.	Nationwide registry-based retrospective cohort study. Information on vaccination status and vaccination date was obtained from health units databases.	1st 5%, 2nd or 3rd 95%. Results by trimester.
Oppermann et al. 2012; Germany[32]	Pregnancies during 1 Apr 2009 to 31 Jul 2010.	Prospective observational cohort study. Maternal surveys collecting history of vaccination and pregnancy outcomes; hospital discharge summaries were also reviewed.	Not reported
Fell et al. 2012; Ontario, Canada[43]	Deliveries from 2 Nov 2009 to 30 Apr 2010. Singleton live-births with BW ≥500g and GA ≥20 weeks.	Population-based retrospective cohort study. Perinatal electronic database. Information on vaccination status and type of vaccine self-reported.	Not reported
Lin et al. 2012; Taiwan[38]	Pregnancies during Oct 2009 to Feb 2010.	Retrospective cohort study. Pregnancy outcomes extracted from chart reviews. Information on vaccination status from clinical database.	1st 5%, 2nd 41%, 3rd 53%. No results by trimester.
Omer et al. 2011; Georgia, USA[33]	Deliveries from 1 Jun 2004 to 30 Sep 2006.	Population-based retrospective cohort study. Surveillance data collected from maternal surveys.	Not reported

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Table 1. Summary of observational studies reporting on the association of maternal influenza vaccination and preterm deliveries* *(Continued)*

Reference and country	Study date and population	Study design and data collection	Trimester
		Information on vaccination status self-reported.	
Munoz et al. 2005; Texas, USA[35]	Deliveries from 1 Jul 1998 to 30 Jun 2003. Singletons born to healthy women.	Retrospective match cohort study. Perinatal electronic database. Information on vaccination status from clinical database.	2nd or 3rd. No results by trimester.

*Preterm birth defined as: birth at <37 weeks gestational age, except stated otherwise.
[a]Preterm birth: birth at 22–<37 weeks gestational age.
[b]Preterm birth: birth at 20–<37 weeks gestational age.
[c]Preterm birth: birth at 27–36 weeks gestational age.
[d]Preterm birth not define.
GA: gestational age; BW: birth weight.

the same likelihood of being vaccinated.[50] Some observational studies documented the time of vaccination in relation to the gestational age and considered vaccination as time-varying exposure.[10,37,46,48] These studies were able to account for the number of women who were exposed to the vaccine during the time they were susceptible to develop a specific outcome, which helps to minimize bias. Nonetheless due to the observational design of most studies they are still vulnerable to confounding and selection bias even after adjusted analyses. Four studies did not report adjusted measures for preterm deliveries and only crude numbers and percentages were shown.[28,32,38,40] An early retrospective study using a database from a large multispecialty clinic in Houston, USA, from 1998 to 2003 compared women who received IIV within 6 months before delivery with non-vaccinated women matched by age at delivery, month of delivery, and type of insurance.[35]

Preterm birth analyses after seasonal influenza vaccination

Table 2 summarizes the different analyses used in the observational studies and illustrates the adjusted effect estimates reported. Six studies evaluated the impact of seasonal IIV not containing the A/H1N1pdm09 strain on preterm birth rates when administered to pregnant women. All studies but one [28] described adjusted odds ratios (aORs) [33,34,44,49] or matched analyses.[35] All the estimated OR were lower than one, however, all the 95% confidence intervals crossed the unit. Sheffield et al. reported that premature delivery rates were significantly decreased in the vaccinated group (5% vs. 6%, $p = 0.004$), however, no adjustment for potential confounders was performed.[28] The largest study involving 7 Vaccine Safety Datalink sites in the USA assessed aOR for preterm birth in propensity score-matched and vaccine exposure time-matched analysis for the 2004–05 through 2008–09 influenza seasons.[34] Using data from almost 60,000 IIV-vaccinated pregnant women, the study revealed a propensity score-matched OR for deliveries <37 weeks gestational age close to 1. In the analyses stratified by trimester, i.e. allowing for equivalent time to potential vaccination, IIV administration was similarly not associated with increased or decreased risk for preterm delivery.[34]

Two studies using data from the Georgia Pregnancy Risk Assessment Monitoring System further stratified their analysis by births occurring during or outside influenza circulation periods.[33,49] These studies by Omer and colleagues, restricting the analyses to infants born during influenza seasons, showed a protective effect on prematurity in mothers who had received influenza vaccination during pregnancy. Consistent 70% and 60% reductions were detected in the 2004 through 2006 influenza seasons [33] and 2005 through 2008 seasons [49] using different models to control for confounding.

Preterm birth analyses after vaccination with A/H1N1pdm09 monovalent vaccines

Observational studies exploring the relationship between maternal influenza immunization with A/H1N1pdm09 monovalent vaccines and preterm births have generated conflicting results, with either null effects or protective effects being reported (**Table 2**).

Six studies[10,27,31,36,42,48] including 3 large studies in Scandinavia found no significant association with A/H1N1pdm09 vaccination during pregnancy and preterm births.[10,31,36] Also in the study by Fell et al., in Canada where 21,363 women reported to have received only an A/H1N1pdm09 monovalent vaccination and 1,977 received both an A/H1N1pdm09 and a seasonal IIV during pregnancy in 2009/10, the prematurity rates did not differ between the vaccinated and the non-vaccinated groups after adjusting for maternal age, education, neighborhood, chronic hypertension, pregnancy-induced hypertension, preeclampsia, history of preterm birth and maternal smoking.[43] In contrast, 4 other studies found that mothers vaccinated with A/H1N1pdm09 had lower odds of preterm births, varying from 0.63 in the USA and 0.86 in Sweden.[29,30,41,45] In the USA Richards et al. restricted their observation period to the timing of pandemic influenza season and limited their analysis to births to mothers who started their third trimester of pregnancy on or after the start of viral circulation. In this way only mothers who had the opportunity for third trimester exposure to the virus were included.[30] They found that vaccinated mothers were 37% less likely to deliver preternaturally compared to non-vaccinated mothers after adjusting for several *a priori* confounders.

The study by Kallen et al. using the Swedish national medical birth register to describe birth outcomes for all births during 2009 and 2010 found a protective effect of vaccination against

Table 2. Product used and adjusted risk measures in observational studies reporting on the association of maternal influenza vaccination and preterm deliveries

Reference	Product	Analyses	Results
Nordin, et al. 2014 [34]	Seasonal not containing A/H1N1pdm09	OR calculated by conditional logistic regression. Vaccinated women were matched with unvaccinated by propensity score (1:1).	aOR: 0.97 (0.93 to 1.02), aOR: 0.99 (0.91 to 1.08) 1st trimester, aOR: 0.96 (0.90 to 1.03) 2nd trimester, aOR: 0.98 (0.87 to 1.09) 3rd trimester
Adedinsewo, et al. 2013 [49]	Seasonal not containing A/H1N1pdm09	OR adjusted for covariates identified during the control period.	aOR: 0.83 (0.60 to 1.17)
Dodds, et al. 2012 [44]	Seasonal not containing A/H1N1pdm	OR calculated by logistic regression with adjustment for potential confounders.	aOR: 0.84 (0.69 to 1.02)
Omer, et al. 2011[33]	Seasonal not containing A/H1N1pdm09	OR calculated by logistic regression with adjustment for potential confounders. Stratification by influenza circulation.	aOR: 0.83 (0.55 to 1.26) overall period, aOR: 0.27 (0.08 to 0.86) period with widespread influenza activity
Munoz, et al. 2005[35]	Seasonal not containing A/H1N1pdm09	Vaccinated women matched with unvaccinated (1:3.5) for maternal age at delivery, month of delivery, and type of insurance.	OR: 0.67 (0.32 to 1.32)
Legge, et al. 2014 [39]	Seasonal containing A/H1N1pdm09	OR calculated by logistic regression adjusted for potential confounding variables found to be associated with vaccination in a backward stepwise regression model.	aOR: 0.75 (0.60 to 0.94)
Chambers, et al. 2013 [46]	A/H1N1pdm09 with (28%) or without seasonal (2009/10) or seasonal containing A/H1N1pdm09 (2010/12)	HR calculated by Cox regression with vaccination as a time-varying exposure adjusted for potential confounding variables.	aHR: 3.28 (1.25 to 8.63) overall anytime in pregnancy, aHR: 3.32 (1.20 to 9.18) 2009/10 season anytime in pregnancy, aHR: 2.25 (0.88 to 5.75) 20010–12 seasons anytime in pregnancy
Louik, at al. 2013 [37]	A/H1N1pdm09 with or without seasonal (Oct 2009-Jul 2010) or seasonal containing A/H1N1pdm09 (Aug 2010–Jul 2011)	HR calculated by Cox regression with vaccination as a time-varying exposure. Vaccinated women were matched with unvaccinated by propensity score.	aHR: 1.03 (0.50 to 2.10) overall anytime in pregnancy, aHR: 2.82 (1.16 to 6.86) 2009/10 season overall anytime in pregnancy, aHR: 2.17 (0.65 to 7.20) 2009/10 season monovalent anytime in pregnancy, aHR: 0.22 (0.06 to 0.83) 20010/11 season anytime in pregnancy
Cantu, et al. 2013 [47]	A/H1N1pdm09 with or without seasonal (2009/10) or seasonal containing A/H1N1pdm09 (2010/12)	RR adjusted for potential confounders by multivariable logistic regression.	aRR: 1.2 (0.9 to 1.6)
Richards, et al. 2013 [30]	A/H1N1pdm09 with or without seasonal	OR calculated by logistic regression adjusted for potential confounding variables.	aOR: 0.63 (0.47 to 0.84)
Fell, et al. 2012[43]	A/H1N1pdm09 with (8.5%) or without seasonal	RR calculated by logistic regression with adjustment for potential confounders.	aOR: 0.95 (0.88 to 1.02)
Cleary, et al. 2014 [45]	A/H1N1pdm09	OR calculated by logistic regression adjusted for potential confounding variables.	aOR: 0.72 (0.58 to 0.89)
Beau, et al. 2014 [48]	A/H1N1pdm09 (93% unadjuvanted vaccine, Panzema)	HR calculated by Cox regression with vaccination as time-varying exposure. Adjusted measures using conditional forward stepwise regression. Vaccinated women were matched with unvaccinated (1:2).	aOR: 0.82 (0.64 to 1.06)

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Table 2. Product used and adjusted risk measures in observational studies reporting on the association of maternal influenza vaccination and preterm deliveries *(Continued)*

Reference	Product	Analyses	Results
Ludvigsson, et al. 2013 [36]	AS03-A/H1N1pdm09 (Pandemix)	OR calculated by logistic regression with adjustment for potential confounders.	aOR: 0.99 (0.89 to 1.10)
Haberg et al. 2013 [10]	AS03-A/H1N1pdm09 (Pandemix)	HR calculated using gestational age as the time metric variable and adjusted for potential confounders.	aHR: 1.0 (0.93 to 1.09)
Kallen, et al. 2012[41]	AS03-A/H1N1pdm09 (Pandemix)	OR adjusted by the Mantel–Haenszel method for potential confounders.	aOR: 0.86 (0.77 to 0.96), aOR: 0.95 (0.85 to 1.08) 1–19 week of gestation, aOR: 1.09 (0.94 to 1.26) 20–26 week of gestation, aOR: 0.81 (0.69 to 0.96) 27–36 week of gestation
Pasternak, et al. 2012[31]	AS03-A/H1N1pdm09 (Pandemrix)	OR calculated by logistic regression. Vaccinated women were matched with unvaccinated by propensity score (1:1).	aOR: 1.32 (0.76 to 2.31) 1st trimester, aOR: 1.0 (0.84 to 1.17) 2nd and 3rd trimesters
Van der Maas, et al. 2015 [27]	2-doses MF59-A(H1N1)pdm (Focetria)	ORs calculated by logistic regression adjusted for potential confounding variables.	aOR: 0.98 (0.59 to 1.62)
Rubinstein, et al. 2013 [29]	MF59-A/H1N1pdm09 (Focetria)	OR calculated by logistic regression adjusted for potential confounders.	aOR: 0.79 (0.69 to 0.90)
Heikkinen, et al. 2012 [42]	MF59-A/H1N1pdm09 (Focetria)	OR calculated by logistic regression with stepwise approach for potential confounders and proportional hazard models that adjust for differential follow-up time.	aOR: 0.75 (0.55 to 1.01), adjusted proportional hazard: 0.69 (0.51 to 0.92)

aOR: adjusted odds ratio; aHR: adjusted hazard ratio; aRR: adjusted risk ratio.

premature birth after adjusting for multiple maternal characteristics (aOR 0.86 [95%CI: 0.77 to 0.96]).[41] However, in a subanalysis restricted to women with known vaccination week compared with non-vaccinated women who were still pregnant in that week, the OR was no longer significant, and when data was stratified according to timing of vaccination a protective effect on the risk of preterm birth was only detected when vaccination was made after week 26 of gestational age. On the contrary, another study from Sweden using historical cohort data from Stockholm County during the same time period estimated a non-significant aOR despite adjusting for similar confounders and found similar risk estimates in the first and the second/third trimester, suggesting that timing of vaccination had no effect on preterm deliveries.[36] Of note the 2 studies reported dissimilar vaccination rates with 63% of women pregnant in Stockholm County being registered as vaccinated in a web-based vaccination registry and less than 12% identified as vaccinated nationally.[36,41]

Heikkinen et al. conducted a mixed prospective and retrospective cohort study that evaluated the safety of MF-59 adjuvanted A/H1N1pdm09 vaccine among 2,295 vaccinated and 2,213 non-vaccinated pregnant women.[42] In this study a significant reduction in prematurity was seen in the vaccinated cohort in an analysis using proportional hazard models with gestational age as the time factor, whereas, when aOR was estimated using logistic regression models a similar however non-significant association between vaccination and preterm births was detected.[42]

Preterm birth analyses after vaccination with seasonal IIV formulations containing pandemic strain

Four studies in North America during and following the A/H1N1 2009 pandemic assessed whether preterm birth rates differed between mothers who received seasonal influenza vaccine containing the pandemic strain and non-vaccinated women [37,39,46,47] (**Table 2**).

Utilizing two distinct study designs, a prospective cohort and a case control, using data from the Vaccines and Medications in Pregnancy Surveillance System, Louik et al. and Chambers et al. performed time-varying exposure analyses on the risk of prematurity after vaccination.[37,46] In the case control study using propensity scores, Louik et al. evaluated the safety of pandemic A/H1N1 influenza vaccine in pregnancy during 2 consecutive influenza seasons, 2009/10 and 2010/11 (monovalent A/H1N1pdm09 vaccine in 2009/10 or seasonal IIV A/H1N1pdm09-containing vaccine in 2010/11). When the 2 seasons were analyzed separately, the authors detected reduced risk of preterm delivery in the 2010/11 season with the seasonal IIV, but an elevated risk for monovalent A/H1N1pdm09 vaccination in the 2009/10 season when more

than 80% of women also reported exposure to the 2009/10 seasonal IIV. This was particularly evident in those vaccinated during the first trimester, with an adjusted Hazard Ratio (aHR) of 4.8 (95%CI: 1.5 to 16.1) compared to aHR of 2.8 (95%CI: 1.2 to 6.9) with vaccination any time in pregnancy.[37] In the prospective cohort study, Chambers et al. detected an elevated risk of premature birth in vaccinated women with point estimates above 2 for the 2009–2012 seasons combined following vaccination at any time in pregnancy, albeit, with wide confidence intervals (aHR 3.28 [95%CI: 1.25 to 8.63]). Stratification by year revealed a heightened risk particularly during the 2009/10 season (aHR 3.32 [95%CI: 1.20 to 9.18]). This observation might be due to high risk pregnant women being more likely of have been selected to receive vaccine during the pandemic, what may have biased the observation toward a null effect, and in fact could explain the increase detected.

Using a population-based perinatal database in the province of Nova Scotia, Canada, Legge et al. examine birth outcomes from vaccinated and non-vaccinated women who gave birth between November 2010 and March 2012. Using logistic regression analysis adjusted for potential confounding variables they found a 25% reduction on preterm births among infants whose mothers received the seasonal influenza vaccine during pregnancy.[39]

Limitations of the Observational Studies

Most of the studies reviewed were retrospective analyses of cohorts varying in size and not randomized controlled trials. The limitations of the studies included in this review are largely inherent to the nature of observational studies. The wide discrepancies observed in the effect of antenatal vaccination on preterm deliveries may be due to differences in study design, and covariates analyzed, not taking in consideration the gestational age at vaccination and the actual timing of influenza season.

Several maternal characteristics were almost consistently found to be significantly associated with receipt of influenza vaccine like higher socioeconomic strata, working outside the home, early antenatal booking, parity, private insurance, older age and were included as possible confounders in the adjusted analyses.[29,37,41,45,48] In some studies a higher prevalence of underlying risk factors was detected among vaccinated women, which is not surprising as vaccination was primarily recommended in women with comorbidities. There are also numerous confounding characteristics that may increase the risk of preterm births and poor birth outcomes in general including maternal age, smoking, alcohol or drug use, previous history of preterm birth, socio-economic status and chronic diseases. Major confounders like prior preterm deliveries, inter-pregnancy interval, medical and obstetric histories, gestational diabetes, folic acid use for example were rarely recoded and used in the adjusted models. The overall assessment of potential confounding variables was inconsistent between the different studies. Using multiple strategies to control for potential confounding, including propensity matching, alignment of vaccinated and non-vaccinated women by their pregnancy start date and restricting comparisons to women with equivalent time to be vaccinated bias is reduced, however, the analyses were unable to control for unmeasured confounders or eliminate potential selection and information biases that may have influenced the estimates even after adjustments. In some studies the results were essentially unchanged after adjusting for various maternal characteristics associated with vaccine uptake, which suggests that these variables were not actual confounders of the association between vaccine receipt and birth outcomes in those studies.[29,30,39,45]

In most studies data on whether women were immunized were obtained from medical record based registries and women vaccinated at alternative sites might have been misclassified in these cohorts, also the partial completeness of these records was stressed in some studies.[34,36,41,48] Other studies relied on maternal self-reported vaccination status with [37] or without further confirmation from providers records.[27,39,45] In these cases it was not possible to confirm that women who did not report exposure did not actually receive the vaccine, with a risk of false-negative controls, driving any risk estimate toward the null.

A few studies collected information regarding the time in pregnancy when vaccination took place, which is important as depending on the stage in pregnancy exposure to vaccines may have differential consequences and allows for exclusion of outcomes soon after.[10,29,31,34,36,37,41,42,45,46,48] However, only 4 studies report on the effect of vaccination on prematurity stratified by trimester of pregnancy,[34,37,41,46] with one study suggesting a nonspecific protective effect of influenza vaccination on the rate of preterm births in women vaccinated during the third trimester.[41]

The association of vaccine effect with the presence of influenza in the community is an important question to consider, as the most plausible direct biological mechanism of the vaccine effect on birth outcomes is likely through protection of maternal infection. The highest estimates of protection of maternal vaccination against preterm deliveries were calculated during the widespread influenza activity period in the USA.[30,33,49] Nonetheless, the 40% to 70% reduction in risk of preterm deliveries during the period of viral circulation in these observational studies appears very large, taking in consideration that the efficacy of maternal vaccination is probably only 50% and that influenza infection is not associated with preterm birth rates to that level of magnitude. The A/H1N1pdm09 studies were conducted late in the pandemic season hence exposure to the virus was probably marginal, consequently, any positive effect of maternal vaccination on birth outcomes would be nonspecific and probably not attributable to the prevention of infection. The RCT in Bangladesh, however, found no effect of influenza vaccination during pregnancy on birth outcomes during the overall study period but a protective effect during influenza circulation, not supporting the theory that maternal vaccination provides a nonspecific protective effect on birth outcomes.[21]

The data from the studies where adjuvanted influenza vaccines were evaluated are encouraging, and taken together these studies partially alleviate concerns about safety of adjuvanted pandemic influenza vaccines during pregnancy. However, more studies are

needed examining other types of vaccine adjuvants. In the countries that used MF59-adjuvanted A/H1N1pdm09 2-dose vaccination was recommended to pregnant women, but no stratification of birth outcomes was presented accordingly to women who received both doses is provided.[42,48]

Conclusion

Reports during seasonal influenza epidemics, previous pandemics and the most recent influenza A/H1N1pdm2009 pandemic, have suggested that pregnancy predisposes otherwise healthy women to increased risk for serious complications from influenza infection. The causes of preterm birth are multifaceted, but infection during pregnancy has been identified as a risk factor with the suggested association being mediated in part by inflammatory responses.[51] The indication for influenza-induced premature births and other adverse pregnancy outcomes such as stillbirths, LBW and SGA, provides evidence of the importance for prevention of infection during pregnancy, especially since improved birth outcomes are critical for achieving reductions in neonatal mortality. The period during fetal development is also a crucial window that can have life-long consequences, thus identifying prenatal strategies that may improve neonatal outcomes is of major importance. Maternal immunization, including influenza vaccination may be one of these effective interventions. However the current evidences do not provide totally compelling evidence that this is achievable through the current influenza vaccines.

The results from the RCT in Bangladesh although showing a substantial effect on birth weight in a *post-hoc* sub-analysis had a small sample size [19] and these results were not corroborated by a larger RCT in South Africa.[20] Also, the utility of pneumococcal polysaccharide vaccine in the Bangladesh study, cannot exclude maternal pneumococcal vaccination having contributed to the adverse birth outcome rather than a benefit of IIV vaccination. Well designed, high-quality, observational studies add valuable information regarding the effect of public-health interventions or exposures on birth outcomes, but observational studies are more prone to bias from confounding than RCTs, and thus the strength of the evidence is lower than that from RCTs. During the 2009 pandemic the high vaccination rates in pregnancy and the thorough surveillance of the vaccinated pregnant women resulted in a unique opportunity to investigate the association of maternal immunization with obstetric outcomes using observational designs, however the description of different studies is very heterogeneous.

In summary no strong association of maternal influenza vaccination with an increased risk of preterm birth was detected. Actually studies generally reported either no association or modest decreased risks especially during the 2009/10 pandemic season. Nevertheless, any obvious protective effect of vaccination observed during the pandemic does not necessary translate to the same effect in seasonal epidemics, where lower morbidity is usually detected, vaccines formulations with different antigen quantity are used and poorer match between the circulating virus and the vaccine formulation is more likely to occur. When pooled analyses are attempted stratification by the type of vaccine should be shown. Hence, future studies with improved statistical designs including prospective follow-up studies using virological end points with adjustments for seasonality, time in pregnancy of vaccination and other biases are needed to confirm these data.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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