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Neonatal outcomes after antenatal influenza immunization during the 2009 H1N1 influenza pandemic: impact on preterm birth, birth weight, and small for gestational age

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Abstract

Neonatal outcomes after antenatal influenza immunization during the 2009 H1N1 influenza pandemic: impact on preterm birth, birth weight, and small for gestational age

By Jennifer L. Richards

Context: Influenza infection during pregnancy is associated with adverse fetal outcomes such as preterm birth and small for gestational age (SGA). Maternal influenza immunization may prevent these adverse infant outcomes during periods of seasonal influenza circulation. There are no published studies on the effect of maternal influenza immunization on adverse infant outcomes during the 2009 influenza A (H1N1) influenza pandemic.

Objective: To evaluate the association between maternal influenza immunization and third trimester preterm birth, low birth weight, and SGA during the 2009 influenza A (H1N1) pandemic.

Design, Setting, Participants: Retrospective cohort study including 3,327 live births within Kaiser Permanente (KP) Georgia and Mid-Atlantic States during the period of 2009 influenza A (H1N1) virus circulation (April 26, 2009 to April 17, 2010). We used KP electronic medical records to identify influenza vaccinations, outcomes, and covariates.

Main outcome measures: Primary outcomes were third trimester preterm birth (27-36 weeks), birth weight, low birth weight (<2500 grams), and small for gestational age.

Results: Infants whose mothers were vaccinated against H1N1 influenza had 36% lower odds of being born preterm than infants of unvaccinated mothers (aOR: 0.64, 95% CI: 0.48-0.85). Infants whose mothers were vaccinated against H1N1 influenza were 55.6 grams (95% CI: 12.4, 98.8) heavier, on average, than infants in the no vaccine group (3364.8 grams versus 3309.2 grams). There was no significant association between maternal H1N1 influenza immunization and low birth weight or SGA.

Conclusions: This is the first study to evaluate the effect of 2009 H1N1 influenza vaccine on preterm birth, birth weight, and SGA. Maternal influenza immunization was associated with reduced odds of third trimester preterm birth during the 2009 influenza A (H1N1) pandemic. Infants of mothers who received 2009 H1N1 influenza vaccine weighed more at birth, on average, than infants born to unvaccinated mothers.

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Contents

Background

Influenza

Influenza is a respiratory illness caused by infection with single-stranded influenza RNA viruses belonging to the orthomyxovirus family. Influenza viruses that infect humans are divided into three groups: A, B, and C. Influenza types A and B are responsible for seasonal influenza epidemics, while influenza type C causes mild infections and does not produce epidemics. Influenza A and B viruses are further subdivided based on their hemagglutinin (HA) and neuraminidase (NA) surface glycoproteins. Influenza A viruses are categorized by both subtype and strain. Subtypes are determined based on HA and NA composition; there are 16 known subtypes of HA and 9 known subtypes of NA among influenza A viruses. Influenza A viruses cause more severe disease in humans. Influenza B viruses are categorized by strain, but not identified by HA/NA composition.[1,2]

Antigenic drift and shift in HA and NA surface antigens can lead to influenza epidemics. Antigen drift occurs through continual minor changes in antigen-coding RNA – primarily point mutations. These minor changes give rise to influenza strains that cause seasonal influenza epidemics. The continual process of antigenic drift necessitates annual review of circulating influenza strains and production of a new seasonal influenza vaccine. In contrast, antigenic shift occurs by the emergence of a novel influenza A subtype that is transmissible person-to-person, able to cause serious disease in humans, and to which there is little population immunity. Novel influenza A strains may emerge due to genetic reassortment of human and animal viruses (e.g., infection of pigs with both avian and human influenza viruses, and subsequent transmission of reassortant virus to humans), or direct animal-to-human transmission (e.g., direct jump of avian influenza virus from birds to humans, or transmission of avian influenza virus to intermediate

host then to humans). The 2009-2010 global H1N1 influenza pandemic resulted from circulation of a novel influenza strain to which most of the population had little to no immunity.[1,2]

Pregnancy Physiology and Adverse Infant Outcomes

Substantial physiologic changes occur in a woman's body during pregnancy; most organ systems undergo adaptations to support the developing fetus. There are several important changes in various body systems that impact susceptibility and response to infections among pregnant women. Physiologic changes that occur during pregnancy include: increased heart rate, stroke volume, oxygen consumption, respiratory rate; and decreased lung capacity, tidal volume, functional residual capacity).[3,4] Physiologic adaptations during pregnancy alter women's ability to tolerate infections, in particular acute respiratory infections such as influenza and pneumonia. Pregnant women are 7-10 times more likely to develop severe disease if infected with influenza, but biologic mechanisms for increased risk are not completely understood.[5]

Various body systems undergo important changes during pregnancy. Anatomically, there is displacement of the diaphragm, heart, and lungs to accommodate the growing fetus. Pregnant women experience substantial increases in total body water, blood and plasma volume (by 40-50% between gestational weeks 6 and 30-34, on average), and red blood cell counts. Cardiac output increases, but maternal blood pressure typically decreases until later in pregnancy due to reduced vascular resistance. However, pregnant women may develop gestational hypertension or preeclampsia. Increases in heart rate and mild dyspnea, or shortness of breath, are common. Lung capacity is affected: inspiratory capacity and tidal volume increase, while functional residual capacity, residual volume, and total lung capacity decrease.[6]

Immune responses are altered in pregnant women. Immune responses are shifted towards anti-inflammatory responses that promote antibody transfer to the fetus, away from inflammatory responses that may contribute to fetal rejection.[7] Humoral and innate immune responses (mediated by T-helper 2 lymphocytes, which induce antibody production) increase, while

cytotoxic or cellular immune response (mediated by natural killer cells, inflammatory macrophages, and T-helper 1 lymphocytes) decreases. Natural killer lymphocytes are reduced by 30 percent. Reduced cellular immunity during pregnancy likely helps to suppress maternal inflammatory response to fetal antigens, but it results in increased susceptibility to intracellular pathogens.[6,7] Pregnant women experience substantial increases in white blood cell (WBC) count over the course of gestation, resulting primarily from increased circulation of segmented neutrophils and granulocytes. Systemic increased WBC may be associated with the increased likelihood among pregnant women to develop systemic inflammatory response or sepsis to infections that would not typically produce a response that severe.[6]

On the other hand, humoral or antibody-mediated immunity is not reduced during pregnancy. Pregnant women maintain their ability to mount an immune response to vaccinations or infections that induce an antibody response. In fact, women may have a higher humoral immune response to influenza vaccine than men.[8] Activated macrophages release cytokines in response to infections. Pro-inflammatory cytokines are associated with maternal infection, preterm labor, and adverse fetal outcomes.[6] Infection and maternal inflammation are considered important risk factors for preterm birth.[9] Functionality of the humoral immune response in pregnant women has important implications for using maternal immunization as a strategy against vaccine-preventable diseases among mothers and infants.

Important adverse outcomes of pregnancy include preterm birth, low birth weight, and being born small for gestational age. Preterm birth is defined as birth at less than 37 weeks completed gestation, and low birth weight is defined as weighing less than 2500 grams at birth, regardless of gestational age.[10,11] Infants may be born at low birth weight because they are born early (preterm birth, <37 weeks gestation) or because of fetal growth restriction in utero. Infants born at less than the tenth percentile of birth weight-for-gestational age (by gender) are considered small for gestational age (SGA).[12]

In the United States, about 12.5% of births are preterm.[12] Risk factors associated with preterm birth include: race, low socioeconomic status, low educational status, high and low maternal age, stress, health behaviors (e.g., smoking), maternal physical characteristics (e.g., body mass index), pregnancy and obstetric history characteristics (e.g., previous preterm birth, current multiple pregnancy), and maternal medical factors (e.g., medical risk factors such as asthma, diabetes, hypertension). Preterm birth is more common among black, African-American, and Afro-Caribbean women than in white women in the United States (16-18% versus 5-9%). Asian and Hispanic women have lower risk of preterm birth.[9,12]

Preterm births may be spontaneous or indicated. About a quarter of preterm births in the United States are medically indicated due to hazardous medical conditions for the mother, fetus, or both (e.g., preeclampsia). Spontaneous preterm births usually occur after preterm labor or preterm rupture of membranes (PROM). Among spontaneous preterm births, those occurring before 32 weeks gestation are more often associated with systemic maternal or fetal infection than those occurring after 32 weeks. Spontaneous preterm births between 32 and 37 weeks are often associated with increases in uterine contraction frequency or uterine volume (e.g., multiple births).[6] Inflammatory response to infections and stimulation of prostaglandin production may also be associated with PROM.[9,12] The impact of common viral infections such as influenza is not well understood, but respiratory infections such as pneumonia have been linked to increased risk of preterm birth and low birth weight.[3,9] Babies born after spontaneous preterm labor or preterm PROM are more likely to be SGA.[6]

Influenza Infection during Pregnancy

Influenza infection causes more severe consequences during pregnancy than in the general population, mostly due to physiologic changes during pregnancy. Epidemiologic evidence suggests that influenza infection during pregnancy is associated with adverse fetal outcomes, such as preterm birth, low birth weight, and small for gestational age. Influenza infection during

pregnancy was identified as a research priority based on findings of higher risk of complications among pregnant women during the 1918 and 1957 influenza pandemics.[13,14] Higher risk of severe disease has also been found among pregnant women infected with 2009 H1N1 influenza, as compared to non-pregnant women of the same age.[5]

Pregnant women were disproportionately affected during the 1918 influenza pandemic in terms of adverse birth outcomes and maternal mortality. About half of women who were infected with influenza or pneumonia during pregnancy had spontaneous abortions or preterm delivery. During the 1918 pandemic, there was a 50% mortality rate among pregnant women. Maternal mortality risk was also elevated during the 1957 pandemic. Influenza was the leading cause of death among pregnant women; it caused about 20% of maternal deaths, with increased risk of mortality in the second and third trimesters as compared to the first trimester. About 25% of all deaths from influenza during the 1957 pandemic among people aged under 50 years were in pregnant women.[13]

Recent studies have evaluated the association of adverse fetal outcomes and infection or hospitalization with seasonal influenza. In a 13-year population-based cohort study in Nova Scotia, McNeil et al. found increased risk of being SGA among infants born to mothers who were hospitalized due to respiratory illness during pregnancy (15.3% versus 9.7%, aRR=1.66, 95% CI: 1.11-2.49). Mean birth weight was significantly lower among infants born to women with respiratory-related hospitalization (3448.5 ± 498.2 versus 3531.3 ± 504.1, p=0.009).[15] In a population-based study of pregnant Hungarian women, Acs et al. found that newborns or fetuses with congenital abnormalities were more likely to have a mother who was infected with influenza during her pregnancy (aPOR=1.3, 95% CI: 1.2-1.4). The authors concluded that the virus was likely not the direct biological cause of congenital abnormalities. Increased prevalence of congenital abnormalities among infected mothers was likely caused by fever associated with influenza illness.[16]

2009 Influenza A (H1N1) Pandemic Influenza during Pregnancy

Risk of complications from influenza infection is further elevated for pregnant women during influenza pandemics. Novel influenza A (H1N1) was first detected in the United States on April 15, 2009, and it circulated until April-May 2010. On June 11, 2009, a worldwide influenza pandemic was declared by the World Health Organization. In the United States, a pandemic influenza vaccine became available in October 2009, after 2009 influenza A (H1N1) had circulated at high levels in many states over the summer months.[17] During the 2009-2010 H1N1 influenza pandemic, pregnant women in the U.S. were disproportionately affected in terms of influenza-associated morbidity and mortality, relative to the general population. A series of surveillance reports and observational studies have shown that pregnant women had higher rates of hospitalization and mortality due to influenza. Further, 2009 influenza A (H1N1) infection in pregnant women may be associated with stillbirth, preterm birth, and lower birth weight.

While pregnant women make up 1% of the total U.S. population, 5% of deaths due to 2009 influenza A (H1N1) that were reported to the CDC were in pregnant women. Moreover, during the first two months of the pandemic, 13% of the total deaths were in pregnant women.[18] Over the course of the pandemic, rates of 2009 influenza A (H1N1) infection and hospitalization were higher among pregnant women than among the general population. Among H1N1-infected pregnant women, 32% were hospitalized, compared to 8% hospitalized among those infected in the general population. In the first month of the pandemic, the estimated hospital admission rate for 2009 influenza A (H1N1) infection was significantly higher among pregnant women (0.32 per 100,000, 95% CI: 0.13-0.52) as compared to the general U.S. population (0.076 per 100,000, 95% CI: 0.07-0.09).[19] Surveillance reports indicate that about half of pregnant women who were hospitalized with 2009 influenza A (H1N1) had underlying conditions, such as asthma, obesity, pregestational or gestational diabetes, anemia, and hypertension.[20]

Surveillance by state health departments and local health departments for Chicago, New York City, and the District of Columbia collected reports of 788 pregnant women with 2009

influenza A (H1N1) between April and August 2009. Of these women, 509 were hospitalized, 115 were admitted to intensive care units, and 30 died. More women were infected during their second (42.2%) and third (46.5%) trimesters than during their first trimester (11.3%). Additionally, severe outcomes were most common during the later stages of pregnancy. Among women who died, more were in their second (30.0%) and third (60.0%) trimesters than in their first trimester (10.0%).[20]

Surveillance reports have described the elevated risk of adverse fetal outcomes among women infected with 2009 influenza A (H1N1). A CDC report of 347 severely ill pregnant women infected with 2009 influenza A (H1N1) showed that they were more likely to have preterm and/or low birth weight infants than women in the general population. Further, infants born to women who had been hospitalized for 2009 influenza A (H1N1) infection were more likely to be small for gestational age. Among these women, 75 died and 272 were admitted to intensive care units and survived. High proportions of the 85 infants born during mothers' hospitalization experienced adverse outcomes: 63.6% were born preterm, 4.1% were born SGA, and 69.4% were admitted to the neonatal ICU. Among 54 infants born 5-187 days after mothers' hospital discharge, 20.8% were born preterm, 25.0% were born SGA, and 22.0% were admitted to the neonatal ICU.[21]

Additional studies have found similar results. Among the 788 cases of 2009 influenza A (H1N1) in pregnant women reported by Siston et al., 30.2% of resulting births were preterm.[20] Among pregnant women in the UK, hospitalization with 2009 influenza A (H1N1) infection during pregnancy was associated with increased risk of perinatal mortality (due mostly to increases in stillbirth) and premature birth between September 2009 and January 2010. Hospitalization with 2009 influenza A (H1N1) infection was associated with increased risk of preterm birth both before 37 weeks gestation (aOR = 4.0, 95% CI: 2.7-5.9) and before 32 weeks gestation (aOR=4.9, 95% CI: 2.4-10.0). Women who were hospitalized with 2009 influenza A (H1N1) infection gave birth, on average, 5 gestational days earlier than women in the comparison

group (women who delivered infants between February 2005 and February 2006, who were assumed to be non-infected with 2009 influenza A (H1N1)). Women who gave birth preterm were more likely to be infected during their third trimester of pregnancy. The authors had no data on sex of infants delivered to women in the study cohort, and therefore could not evaluate the effect of maternal influenza immunization on risk of being SGA.[22]

A prospective cohort study of 41 pregnant women with influenza-like illness (ILI) in Rhode Island during the 2009 influenza A (H1N1) pandemic showed a reduction in mean birth weight among mothers infected with 2009 influenza A (H1N1) as compared to those infected with non-H1N1 ILI. The mean birth weight among infants born to women with confirmed 2009 influenza A (H1N1) infection was lower than the mean birth weight of infants born to women with ILI (3186 g versus 3471 g, p=0.04). However, there was no significant effect of 2009 influenza A (H1N1) infection on gestational age at delivery, as compared to non-H1N1 ILI. The average gestational age at delivery was 39.2 weeks among women with confirmed 2009 influenza A (H1N1) infection, compared to 39.6 weeks among women with non-H1N1 ILI. The study did not compare H1N1- or ILI-infected women to women with no respiratory infection.[23]

Influenza Vaccine

Two classes of influenza vaccine are available: trivalent inactivated vaccine (TIV) and live attenuated vaccine. The CDC Advisory Committee on Immunization Practices (ACIP) currently recommends influenza vaccine for all individuals over 6 months old. Influenza vaccine is contraindicated for those with history of allergy to chicken eggs, severe reaction to influenza vaccine, or Guillain-Barré syndrome. Persons in high-risk groups for influenza-related complications include: pregnant women, children under 5 years old, adults over 50 years old, persons with chronic medical conditions, persons who live in nursing homes or long-term care facilities, and persons in close contact with those in high-risk groups (e.g., health care workers, household contacts of infants or elderly persons).[2,24]

Beginning in 2004, the ACIP has recommended immunization with TIV in all three trimesters of pregnancy. Prior to 2004, pregnant women in their second or third trimester were recommended to receive the vaccine..[25] Vaccination with seasonal TIV during pregnancy is believed to be safe and to generate protective levels of antibody against influenza virus. There is no evidence of significant difference in adverse events between pregnant women and the general population. A prospective study of 267 pregnant women in the United Kingdom showed no increased risk of spontaneous abortion, congenital anomalies, preterm delivery, low birth weight, or maternal complications, as compared to background population rates.[26]

Influenza Vaccine Coverage in Pregnant Women

Influenza vaccine coverage among pregnant women in the United States has historically been low. Influenza immunization coverage ranged from approximately 10-20% in pregnant and non-pregnant women between the 2000-2001 and 2008-2009 seasons, with non-pregnant women typically having slightly higher uptake. During the 2009-2010 influenza A (H1N1) pandemic, pregnant women were one of the first priority groups for receiving 2009 H1N1 influenza vaccine. Vaccine coverage increased substantially among pregnant women in 2009-2010 and 2010-2011 from prior years. In 2009-2010, national coverage was 32-51%, and in 2010-2011, national coverage was 44 ± 28-49%.[27] In Georgia and Maryland, respectively, seasonal influenza vaccine coverage among pregnant women with a live birth was 29.9% (95% CI: 5.6%) and 46.1% (95% CI: 4.5%). H1N1 influenza vaccine coverage in the same population in Georgia and Maryland, respectively, was 28.4% (95% CI: 5.6%) and 41.0% (95% CI: 4.5%).[28]

Vaccine uptake practices differ among pregnant women from the general U.S. population. A mail survey of obstetric care providers who are members of the American College of Obstetricians and Gynecologists conducted after the 2009-2010 influenza A (H1N1) pandemic showed that high proportions of providers reported routinely offering 2009-2010 seasonal TIV and 2009 H1N1 influenza vaccine to pregnant patients during the pandemic season. In this

population, 77.6% reported routinely offering seasonal vaccine, and 85.6% reported routinely offering 2009 H1N1 influenza vaccine. Predictors of routinely offering 2009 H1N1 influenza vaccine included: considering primary care and preventive medicine a very important part of practice, observing serious conditions attributed to ILI, personally receiving 2009 H1N1 influenza vaccine, and practicing in multi-specialty group. Reasons reported for not routinely offering influenza vaccine were: inadequate reimbursement, storage limitations, beliefs that vaccine should be administered by another provider.[29]

Evidence Base for Maternal Influenza Immunization

Vaccinating pregnant women against influenza serves two important purposes: (1) protection of the mother against influenza infection, especially when risk of complications is elevated during the second and third trimesters, and (2) protection of infants against influenza infection when they are too young to be vaccinated. Maternal influenza immunization may protect infants through transfer of maternal antibodies across the placenta to the developing fetus, and via breast milk after birth. Maternal antibodies can provide protection before infants are old enough to receive influenza vaccine. No influenza vaccine is licensed for administration in infants under 6 months of age. Child influenza hospitalization rates are highest among infants <6 months old, and influenza causes a majority of infant deaths in the U.S.[30] Alternatives for protecting very young infants include “cocooning”, or vaccination of close contacts (e.g., mothers).

Recent studies have shown a protective effect of maternal influenza immunization against adverse fetal outcomes such as preterm birth, low birth weight, and small for gestational age. In a population-based retrospective cohort study in Georgia, Omer et al. showed that maternal seasonal influenza immunization reduced the likelihood of preterm birth during the putative influenza season (October to May). This effect was strongest during periods of widespread influenza activity (adjusted OR=0.28, 95% CI: 0.11-0.74). Maternal influenza immunization was associated with lower odds of being SGA during periods of widespread influenza activity

(adjusted OR=0.31, 95% CI: 0.13-0.75). This study evaluated the effect of maternal influenza immunization across two influenza seasons, 2004-2005 and 2005-2006, but did not differentiate effects of influenza immunization across different trimesters of pregnancy.[31] Additionally, a recent randomized controlled trial in Bangladesh showed that maternal influenza immunization was associated with higher mean birth weight and reduced risk of being small for gestational age during the period of influenza circulation.[32,33]

A recent study of 69 pregnant women in Milan, Italy demonstrated efficient transplacental transfer of antibody to 2009 influenza A (H1N1) after vaccination during the third trimester of pregnancy. All women had protective antibody titers (1:40) at delivery and at 2 and 5 months post-delivery. At birth and 2 months of age, 95.6% (66/69) infants had protective antibody levels. At 5 months, this proportion declined to 81.2% (56/69).[34] This clinical study demonstrated potential for protection of infants through passive antibody transfer, but there are no studies exploring its impact on influenza disease outcomes.

Recent prospective studies in Bangladesh and in an American Navajo and White Mountain Apache population showed that maternal influenza immunization reduces ILI among infants. In a randomized controlled trial of 340 Bangladeshi mother-infant pairs, Zaman et al. showed that maternal influenza immunization reduced rapid-test-confirmed influenza illness by 63% (95% CI: 5-85%) among infants up to 6 months of age.[35] In a nonrandomized prospective study of 1169 American Navajo and White Mountain Apache mother-infant pairs, Eick et al. showed that maternal seasonal influenza vaccination reduced laboratory-confirmed influenza infection by 41% (RR=0.59, 95% CI: 0.37-0.93) among infants up to 6 months of age or end of influenza season. This study also showed that maternal seasonal influenza vaccination reduced the risk of ILI hospitalization among infants by 39% (RR=0.61, 95% CI: 0.45-0.84).[36]

In the United States general population, Benowitz et al. reported that maternal influenza immunization was 91.5% effective at preventing laboratory-confirmed influenza hospitalization in infants under 6 months old. This study compared 113 infants under 12 months of age who were

hospitalized at Yale-New Haven Children's Hospital for laboratory-confirmed influenza between October 2000 and April 2009, with 192 matched controls. Maternal receipt of influenza vaccine was ascertained by interviews with mothers. This study reported the overall effect of maternal influenza immunization across all 9 influenza seasons, and had insufficient power to evaluate variation in effect by influenza season.[37]

However, some studies have shown little effect of maternal influenza immunization on mother and infant influenza-related hospitalizations and infections. In a Kaiser Permanente Northern California study by Black et al. over the 1997-2002 influenza seasons, there was no significant effect of maternal influenza immunization on mother's risk of ILI outpatient visits or ILI in infants born to mothers during the influenza season. The authors suggested that the observed effect may be null due to very low incidence of respiratory illness hospitalization in the overall study population during the years studied. Influenza vaccine coverage averaged 7.5% over the study years.[38] A follow-up study by France et al. expanded the study population to include Kaiser Permanente Colorado, Northern California, Northwest, and Group Health Cooperative, and included 41,129 infants born between 1995 and 2001. This study found no significant effect of maternal influenza immunization against respiratory illness in their infants born during influenza season. Additionally, there was no significant effect of maternal influenza immunization when births were stratified by intensity of influenza activity (peak influenza, RSV-predominant, periseasonal, and summer). As in the Northern California study, the proportion of mothers vaccinated during pregnancy was low, ranging from 0.7% to 20.8% across Kaiser Permanente sites and influenza seasons.[39]

Addressing Confounding in Nonrandomized Influenza Vaccine Effectiveness Studies

Nonrandomized studies of influenza vaccine effectiveness have been critiqued for failure to adequately control for confounding by indication, which can result from differences between vaccinated and unvaccinated individuals due to self-selection into receiving vaccine or not. In

particular, there may be healthy vaccinee bias resulting from greater likelihood of vaccination among individuals with better functional status.[31,40,41]

Several methods have been used to address confounding in observational studies of influenza vaccine effectiveness: (1) selecting confounders based on assessment of association between vaccine and outcome during a period in which there should be no vaccine effect, (2) the difference of differences approach, (3) controlling for a vaccine propensity score as a covariate in models. All three of these methods can be used to adjust for measured confounders, but results may still be affected by residual or unmeasured confounding.

First, confounding may be addressed by selecting a set of covariates that moves the association between vaccine and outcome to the null during a control time period when influenza is not circulating, but influenza vaccine is available (e.g., date of vaccine availability through start date of yearly influenza activity). This approach was adapted by Omer et al. for use in studying vaccine effectiveness against adverse infant outcomes in a population of pregnant women.[31,40,42] The purpose of this approach is to select covariates that control for differences between vaccinated and unvaccinated women during periods of influenza activity, based on their association with outcomes during the selected control time period. Potential covariates are selected if they modify the association between maternal influenza vaccine status and outcome and move the odds ratio towards the null during the control time period. All covariates meeting these criteria are then assessed for inclusion in a final model. Covariates are sequentially dropped (in order of how much they move the odds ratio towards the null) to assess the change in odds ratio (closer or further away from the null). If dropping a potential covariate from the model results in moving the odds ratio away from the null and changing its magnitude by less than 1%, the covariate that resulted in the least change in odds ratio is dropped. If dropping any potential covariate resulted in a change in magnitude more than 1%, the set of covariates at that point in the modeling strategy was considered sufficient to control for confounding.[31] This strategy may be able to account for unmeasured confounding by adjusting odds ratios during a reference period.[43]

Second, the difference of differences approach can be used to assess bias due to underlying differences between vaccinated and unvaccinated groups. This approach, often used in economics, has been used by Fireman et al. for assessing vaccine effectiveness in an elderly population.[44] The purpose of this approach is to estimate the effect of selection bias by comparing outcomes between two groups over two time periods: one group that has received an intervention in the second time period, but not the first, and another group that has not received an intervention in either time period. This removes biases due to differences between the groups that are not due to the intervention (i.e., that exist during the first time period, when no intervention has been applied).[45] In the context of influenza vaccine effectiveness studies, use of the approach assumes that if an influenza vaccine has a protective effect against an outcome, there should be a difference between: the difference in natural log odds of vaccination between those with and without the outcome on days when influenza is circulating, and the difference in natural log odds of vaccination between those with and without the outcome on the same days if influenza were not circulating. Exponentiating this difference in differences of odds gives a ratio of odds ratios, which can be used to calculate "vaccine effectiveness" due to bias.[44]

Third, propensity scores can be used to control for multiple confounding factors that influence probability of vaccination. This method is used to collapse multiple predictors of vaccination status (e.g., age, sex) into a single predictor. Each subject is assigned a single propensity score value based on their combination of component predictors. Propensity scores can be used: (1) as a single predictor in regression modeling, (2) for matching subjects based on propensity score, and (3) to stratify the study population.[46]

Addressing Limitations of Observational Studies of Influenza Vaccine Effectiveness in Managed Care Organization Populations

Managed care organizations are valuable settings for conducting observational studies, due to the availability of detailed medical records on subjects over extended periods of time. For the purposes of the present study, Kaiser Permanente records contain detailed information on

medical visits, diagnoses, procedures, and hospitalizations, as well as birth and infant outcomes. However, there are two important challenges in using MCO populations for studies of influenza vaccine effectiveness: assessment of unmeasured confounders, and sensitivity of influenza vaccination records. While confounding factors may be addressed using the approaches described previously, managed care organization studies may still be impacted by unmeasured confounding.[47]

It has been shown that MCO electronic medical records of influenza immunization status in adult and elderly populations may fail to capture all immunizations. Positive records for influenza vaccine receipt are highly accurate, and the absence of an influenza vaccine record does not necessarily mean that the individual was not vaccinated. Influenza vaccine is available at locations such as workplaces and pharmacies, so many adults may choose to be vaccinated at alternative locations besides their medical provider office. Sy et al. compared Kaiser Permanente Southern California (KPSC) vaccine records for adults 50-79 years old against self-reported vaccine status in a random sample survey. The positive predictive value of having an influenza vaccine recorded was 99.6%, and the negative predictive value of not having an influenza vaccine recorded was 79.5%. Among false negatives, about half had actually received influenza vaccine within the KPSC system, and the other half had received vaccine in another, non-traditional setting.[48] In light of these findings, using MCO records to assess influenza vaccine coverage may be a limitation of the present study.

However, pregnant women are more likely to receive influenza vaccine based on provider recommendation. During the 2009-2010 influenza season, pregnant women in Georgia and Maryland were more likely to be vaccinated against seasonal influenza and 2009 influenza A (H1N1) if offered the vaccine by their medical provider. In Georgia, about half of pregnant women received seasonal TIV and 2009 H1N1 influenza vaccine if offered by their medical provider, compared to less than 5% vaccinated among those not offered the vaccines. Similarly, in Maryland, seasonal TIV and 2009 H1N1 influenza vaccine coverage was significantly higher

(62% and 54%, respectively) among women offered vaccine by their medical providers. Vaccine coverage among those not offered the vaccines by their medical provider was 15% for seasonal TIV and 4% for 2009 H1N1 influenza vaccine.[28] Vaccine coverage among pregnant women enrolled in Kaiser Permanente Georgia and Mid-Atlantic States likely reflects these trends.

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Draft Manuscript

Neonatal outcomes after antenatal influenza immunization during the 2009 H1N1 influenza pandemic: impact on preterm birth, birth weight, and small for gestational age

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Introduction

Influenza infection results in higher morbidity in pregnant women compared to non-pregnant women of similar age.[1-3] Influenza infection during pregnancy is associated with adverse fetal outcomes such as preterm birth and small for gestational age (SGA) birth.[4-9] During the 2009 influenza A (H1N1) pandemic, pregnant women in the United States experienced higher influenza-associated morbidity and mortality relative to the general population.[10,11] Therefore, pregnant women were prioritized to receive 2009 H1N1 influenza vaccine.[12,13]

Maternal influenza immunization may prevent adverse infant outcomes among births during periods of seasonal influenza circulation.[14-16] In a randomized controlled trial in Bangladesh, maternal influenza immunization was associated with higher mean birth weight and reduced risk of being born SGA for births during a period of influenza circulation.[15,16] In a population-based study in the state of Georgia, vaccinated women gave birth to heavier infants and were less likely to have a preterm birth during periods of influenza circulation. Additionally, during periods of widespread influenza activity, vaccinated women were less likely to have infants born SGA.[14]

There are no published studies on the effect of maternal influenza immunization on adverse infant outcomes during the 2009 influenza A (H1N1) pandemic. Our study used a managed care organization population to assess associations between maternal influenza immunization and third trimester preterm birth, low birth weight, and SGA during the pandemic.

Methods

We conducted a retrospective cohort study based on electronic medical records (EMRs) from a managed care organization. The primary exposure was receipt of 2009 H1N1 influenza vaccine during any trimester of pregnancy. Primary outcomes were preterm birth during the third trimester of pregnancy (27-36 weeks gestation), low birth weight (<2500 grams), and SGA.

Using national birth weight percentiles defined by gestational age and gender by Oken et al., we defined SGA as birth weight under 10th percentile for gestational age and gender.[17] The study period was defined by the timing of 2009 influenza A (H1N1) virus circulation: from the collection date in each region of the first positive laboratory test for 2009 influenza A (H1N1), up to the first week when the percentage of influenza specimens that tested positive for 2009 influenza A (H1N1) was <5%. Using this definition, the eligible study period was April 26, 2009 to April 17, 2010 (including births before and after the start of availability of 2009 H1N1 influenza vaccine).

We first identified all live births during the study period in Kaiser Permanente (KP) Georgia and Mid-Atlantic States (including enrollees in Maryland, northern Virginia, and the District of Columbia). The study population was then restricted to live births to mothers who started their third trimester of pregnancy on or after the start of the study period, to include only mothers who had the opportunity to be exposed to 2009 influenza A (H1N1) virus during their third trimester. We restricted our study population in this way to evaluate the impact of influenza exposure proximate to birth on infant outcomes. Preterm births that occur earlier during pregnancy (e.g., second trimester preterm births) are likely to have different causative factors than those occurring during the third trimester, such as fetal chromosomal abnormalities, fetal and maternal anatomic factors, immunologic factors, and maternal infections such as bacterial vaginosis.[18,19]

We used ICD-9 diagnosis code data on maternal health conditions, pregnancy and birth complications, and maternal demographics from KP EMRs. Underlying conditions were identified by ICD-9 diagnosis codes from 90 days prior to 90 days after last menstrual period (LMP). Gestational diabetes was identified by ICD-9 diagnosis codes between LMP and birth. The final cohort included only mothers who were continuously enrolled in KP for their entire pregnancies (with permitted enrollment gaps of up to 45 days). Influenza A (H1N1) infection was defined as: 1) having a reverse transcription polymerase chain reaction (RT-PCR) test positive for

influenza, or 2) having a medical visit during pregnancy with influenza-related ICD-9 diagnosis code during the period of 2009 influenza A (H1N1) virus circulation.

We used KP EMRs to identify influenza vaccines administered to mothers in our cohort during pregnancy. We defined the type of influenza vaccine administered (e.g., 2009 H1N1 influenza vaccine, seasonal trivalent inactivated vaccine [TIV]) based on HL7 code and administration date (see Supplement 1). For the main analyses, we defined the pregnancy period as between LMP and infant's birth date. We performed sensitivity analyses to evaluate the impact of defining vaccination during the pregnancy period as between LMP and 7 or 14 days prior to infant's birth date (see Supplement 2). We defined three vaccine exposure groups based on vaccines received during pregnancy: 1) 2009 H1N1 influenza vaccine with or without 2009-2010 seasonal trivalent inactivated vaccine (TIV) (H1N1 vaccine); 2) only seasonal TIV (seasonal TIV only); and 3) no influenza vaccine (no vaccine).

We used logistic regression to evaluate the association of maternal influenza vaccine and each of the primary outcomes. We performed a sub-analysis of preterm birth stratified by early versus late timing (27-33 weeks versus 34-36 weeks). We used linear regression to evaluate the differences in mean birth weight among births by exposure group. For each outcome, we stratified by type of influenza vaccine received. We did not stratify our analyses by trimester of vaccination due to limited study power.

There are several methods for adjusting for confounding in nonrandomized observational studies of influenza vaccine effectiveness (VE), primarily to account for differences between vaccinated and unvaccinated individuals (e.g., healthy vaccinee bias).[20] We evaluated the use of a difference-in-differences approach and the approach used by Nelson et al., but concluded that we could use neither approach because there was no valid pre-influenza comparison period, given the timing of virus circulation and vaccine availability.[21,22] We constructed primary adjusted models adjusted for propensity score as a categorical (quintiled) variable. According to an approach described by Arbogast,[23] we used logistic regression to create a propensity score for the

conditional probability of exposure to any 2009-2010 inactivated influenza vaccine based on all measured covariates.[24] We also evaluated the creation of two separate propensity scores indicating likelihood of exposure to 2009 H1N1 influenza vaccine and 2009-2010 seasonal TIV, but there was poor model fit. We constructed secondary adjusted models controlling for *a priori* potential confounders to allow for comparisons with previous studies. *A priori* covariates were: maternal age less than 19 years, maternal age more than 35 years, asthma, gestational diabetes, cardiovascular disease, hypertension during pregnancy, multiple birth, any pregnancy/birth complication, and KP site.

Using our primary adjusted model, we computed three additional measures. We used the following equation to calculate the number needed to be vaccinated (aNNV) to prevent one preterm birth: aNNV = $-\frac{1}{(OR-1)*UER}+\frac{OR}{(OR-1)*(1-UER)}$, where UER = event rate in the unexposed.[25] We used the following expression to calculate the population prevented fraction of preterm birth: $\frac{p_c(1-OR)}{p_c(1-OR)+OR}$, where p_c = proportion of cases vaccinated (we verified that for our data, odds ratios approximated risk ratios for preterm birth).[26] We calculated VE against 2009 influenza A (H1N1) infection using the equation, VE = 1 – adjusted OR. VE was calculated for a secondary analysis cohort that included 40 mothers excluded from the main analyses because they were diagnosed with 2009 influenza A (H1N1) prior to receiving 2009 H1N1 influenza vaccine.

Based on an expected sample of 3,000 and vaccine coverage of 30-50%, our sample size had 80% or higher power to detect odds ratios smaller than 0.66. We used SAS version 9.2 (Cary, NC) for all statistical analyses. Results were considered significant at α=0.05 using two-tailed tests. The study was reviewed and approved by the Kaiser Permanente Institutional Review Boards in both Georgia and Mid-Atlantic States.

Results

There were a total of 4,555 eligible births to 4,446 mothers in KP Georgia and Mid-Atlantic States during the period of 2009 influenza A (H1N1) circulation. The selection process is described in Figure 1. Of these, we excluded the following: 27 second trimester births, 1,160 births to mothers who were already in their third trimester of pregnancy at the start of 2009 influenza A (H1N1) circulation, 1 birth to a mother who was exposed to 14 or fewer days of 2009 influenza A (H1N1) influenza circulation at the start of the study period, and 40 births to mothers who were diagnosed with 2009 influenza A (H1N1) before receiving 2009 H1N1 influenza vaccine. Therefore, our study population included a total of 3,327 third trimester live births to 3,236 mothers between May 25, 2009 and April 17, 2010.

The H1N1 vaccine group included 1125 (33.8%) infants, the seasonal TIV only group included 621 (18.7%) infants, and the no vaccine group included 1581 (47.5%) infants (Table 1, Figure 2). Overall H1N1 influenza vaccine coverage in our cohort was 33.8% (1,125/3,327), and 2009-2010 seasonal TIV coverage was 41.5% (1,380/3,327). Among births on or after October 1, 2009 (the approximate start date of 2009 H1N1 influenza vaccine availability), H1N1 vaccine coverage was 50.1% (1,125/2,247), and 2009-2010 seasonal TIV coverage was 58.0% (1,304/2,247). The odds of having received 2009 H1N1 influenza vaccine were lower for mothers who had pregnancy/birth complications ($p<.01$) and mothers who gave birth within KP Georgia ($p<.01$) (Table 2). VE of 2009 H1N1 influenza vaccine against 2009 influenza A (H1N1) infection during the study period among all mothers in our study cohort was 78.8% (95% confidence interval [CI]: 55.0%, 90.0%).

There were a total of 327 (9.8%) preterm births, including 85 (2.5%) between 27 and 33 weeks gestational age and 242 (7.3%) between 34 and 36 weeks gestational age. A total of 236 (7.4%) infants were born at low birth weight, and 267 (8.4%) were SGA.

In the primary adjusted model, infants in the H1N1 vaccine group had 36% lower odds of being born preterm than infants in the no vaccine group (adjusted odds ratio [aOR]: 0.64, 95% CI:

0.48-0.85) (Table 3). Infants in the H1N1 vaccine group had 47% lower odds of 27-33 weeks preterm birth compared to infants in the no vaccine group (aOR: 0.53, 95% CI: 0.30-0.94), and 33% lower odds of 34-36 weeks preterm birth (aOR: 0.67, 95% CI: 0.49-0.92) (Table 3). For every 25 women vaccinated against 2009 influenza A (H1N1) during pregnancy, 1 preterm birth was prevented. The population prevented fraction of preterm birth prevented by 2009 H1N1 influenza vaccine was 13.3%.

In the primary adjusted model, infants in the H1N1 vaccine group were 55.6 grams (95% CI: 12.4, 98.8) heavier than infants in the no vaccine group (3364.8 grams versus 3309.2 grams) (Table 4). The association between maternal receipt of 2009 H1N1 influenza vaccine and being born at low birth weight during the period of 2009 H1N1 influenza circulation was not significant (aOR: 0.77, 95% CI: 0.56-1.06) (Table 3).

In the primary adjusted model, the association between maternal receipt of 2009 H1N1 influenza vaccine and being born SGA during the period of 2009 H1N1 influenza circulation was not significant (aOR: 1.22, 95% CI: 0.91-1.62) (Table 3). The estimated ORs for the association of H1N1 influenza vaccine were above the null, and the estimated ORs for the association of 2009-2010 seasonal TIV were below the null.

In all but one of our analyses, the unadjusted and secondary adjusted models produced similar results to those obtained using primary adjusted models (Table 3). The ORs were within 10% of primary adjusted ORs, and the significance level of results did not change. The one exception was a change in significance level for the association of maternal receipt of 2009 H1N1 influenza vaccine and low birth weight: the unadjusted OR was within 10% of the primary adjusted OR, but was statistically significant.

Discussion

This is the first study to evaluate the effect of 2009 H1N1 influenza vaccine on preterm birth, birth weight, and SGA. During the 2009 influenza A (H1N1) pandemic, maternal H1N1

influenza immunization was associated with reduced odds of third trimester preterm birth. Also, infants of mothers who received 2009 H1N1 influenza vaccine weighed more at birth, on average, than infants born to unvaccinated mothers. Our VE finding of 79% is similar to reports from other studies of high effectiveness of 2009 H1N1 influenza vaccine against 2009 influenza A (H1N1) infection during the pandemic (i.e., 62%-84%).[27-30]

Our findings should be put into the context of recent findings describing the association between 2009 influenza A (H1N1) infection and risk of adverse infant outcomes. Several studies have shown higher risk among pregnant women infected with 2009 influenza A (H1N1) of having infants born preterm, at lower birth weight, or SGA.[6,8,9] However, unpublished findings by Craig Hansen, PhD (written communication, January 2012) in a study conducted in five Kaiser Permanente regions showed no significant effect of 2009 influenza A (H1N1) infection on these birth outcomes; the lack of association may have been due to high use of antiviral medications within this population. In a study showing adverse impacts of 2009 influenza A (H1N1) infection among pregnant women, the risk of infection and severe outcomes (e.g., hospitalization, admission to intensive care, and death) was higher during the second and third trimesters, as compared to the first trimester.[7] Our focus on third trimester birth reflects our interest in evaluating the hypothesis that influenza virus exposure impacts risk of preterm birth through a biological mechanism proximate to birth, involving inducement of local inflammation and prostaglandin production. Preterm rupture of membranes (PROM) may be induced by local inflammatory response to infection, rather than as a response to the respiratory virus itself.[31] Our finding that maternal H1N1 influenza immunization during pregnancy was associated with lower odds of preterm birth validates the similar recent finding by Omer et al. (2011) during seasonal influenza epidemics in the state of Georgia.[14]

We found that infants of mothers vaccinated against 2009 influenza A (H1N1) weighed more than infants of unvaccinated mothers. This finding is supported by results from earlier studies in Bangladesh, the United States, and Canada that showed similar effects on birth weight

of either influenza vaccination or infection.[14-16] While we found no significant association between maternal influenza immunization and being born at low weight, the statistically significant difference in mean birth weight between vaccinated and unvaccinated mothers is important biologically and for informing immunization policy prioritizing pregnant women. Further research is needed to elucidate pathogenesis of influenza infection in pregnant women and its impacts on fetal growth.

There was no association between maternal H1N1 influenza immunization and infants being small for gestational age. Previous findings by Omer et al. showed a protective effect of maternal seasonal influenza immunization against infants' risk of being born SGA during periods of widespread influenza activity.[14] In this study, we were unable to stratify our analysis by intensity of influenza activity due to limited study power and because influenza activity during the pandemic did not follow the typical escalation and waning pattern of seasonal epidemics. Further, most "widespread" influenza activity weeks during the 2009-2010 influenza season occurred during summer 2009 prior to the availability of 2009 H1N1 influenza vaccine, limiting our ability to evaluate the vaccine's effect on risk for SGA during widespread activity.[32]

Our study has several strengths and limitations. We used vaccine records directly from mother's KP EMRs, and therefore did not rely on maternal self-report of vaccination status. Mothers may have been misclassified if vaccinated at alternative locations, such as pharmacies or workplaces, but we believe it likely that any misclassification of vaccine exposure was non-differential. Recent data published by the CDC on influenza vaccine uptake among pregnant women during the 2009-2010 influenza season showed that pregnant women were significantly more likely to be vaccinated at the recommendation of their medical provider.[33] Further, vaccine coverage in our study population was higher than 2009-2010 state vaccine coverage estimates for Georgia and Maryland.[33] Moreover, underestimation of coverage was likely to result in conservative estimates of the protective effect of 2009 H1N1 influenza vaccine due to non-differential misclassification of vaccine exposure.

We conducted sensitivity analyses to evaluate the effect of two assumptions about vaccine exposure in our cohort: (1) we assigned vaccine type based on HL7 code and administration date (described in Supplement 1), and (2) we defined vaccination during pregnancy as between LMP and infant's date of birth (described in Supplement 2). Our reported findings are more conservative than we would have obtained if these assumptions had not been made.

Additionally, we were unable to control for mother's race – a known confounder associated with likelihood of influenza vaccination, preterm birth, and other adverse infant outcomes – because data on this variable was only available for 22.8% (759/3,327) births. We chose to control for confounding by indication between vaccinated and unvaccinated pregnant women using a propensity score approach, but there remains a possibility that there are important unmeasured confounders.

Future studies evaluating the effect of maternal influenza immunization during both seasonal and pandemic seasons are essential to explore additional questions, including differences in effect by maternal nutritional status and trimester of vaccination, and investigating the effect of maternal influenza immunization on influenza incidence among infants.

Our findings demonstrate the importance of vaccinating pregnant women during influenza pandemics, in part for the purpose of protecting their infants from adverse birth outcomes. Previous findings of reduced likelihood of preterm birth during periods of influenza circulation among vaccinated women were repeated in this study. Further, our data suggest that every 25 maternal H1N1 influenza immunizations prevented one preterm birth. This low figure has important implications for cost-effectiveness estimates of maternal influenza immunization during pandemics, given the substantial medical and societal costs of preterm birth. This study not only reinforces previous findings about maternal influenza immunization during seasonal epidemics, but validates vaccine policy choices during the 2009 influenza A (H1N1) pandemic when pregnant women were a priority group for receiving pandemic vaccine. This study provides

an evidence base for continuing to prioritize pregnant women to receive vaccine in future pandemics.

Acknowledgement

Jennifer L. Richards had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Tables and Figures

Figure 1. Definition of primary analysis cohort.

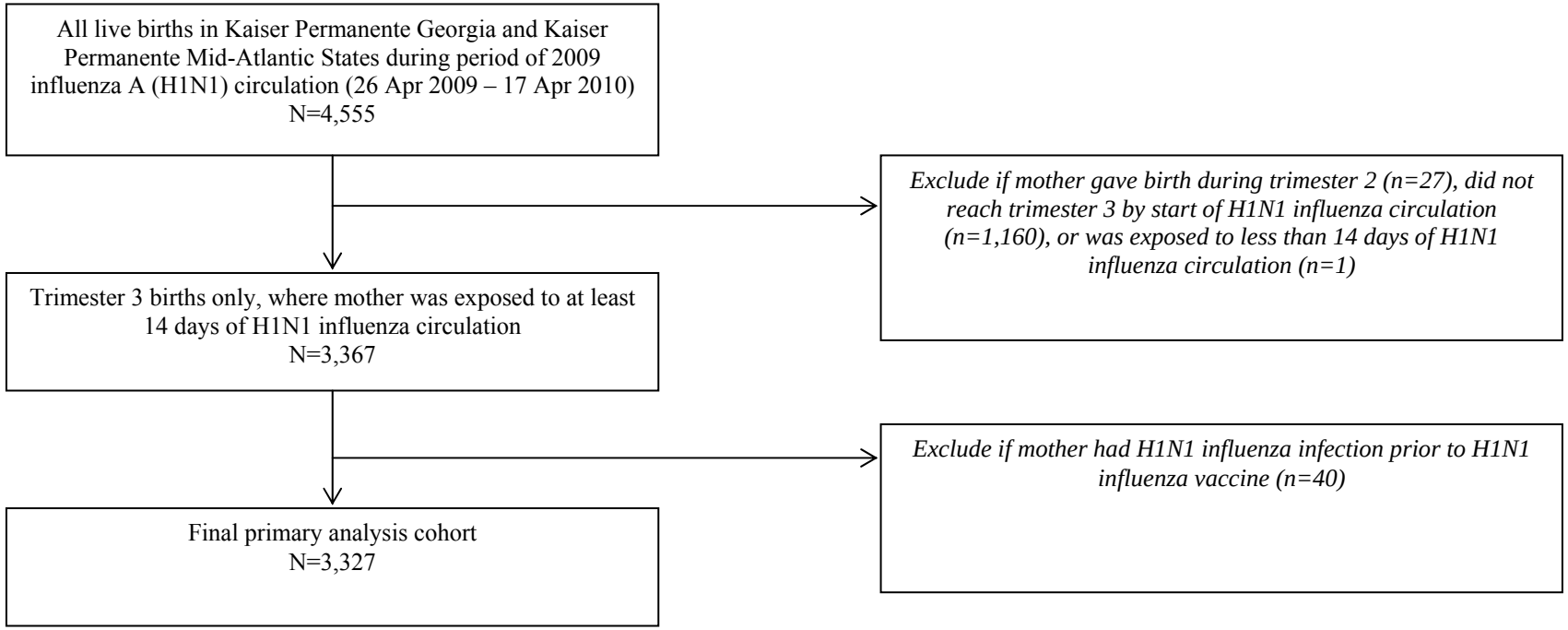
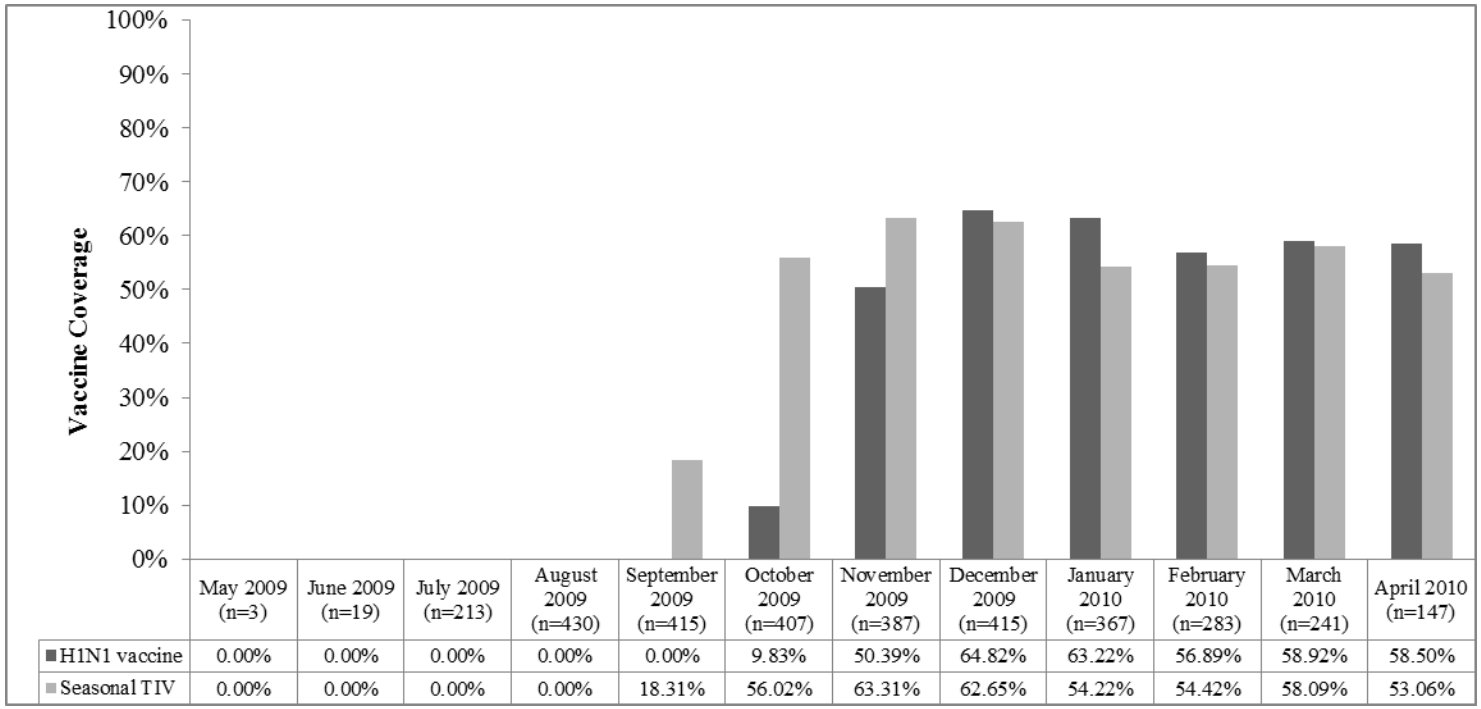


Figure 2. Influenza vaccine coverage among mothers of infants born during period of 2009 influenza A (H1N1) circulation, by infant's birth month.



	May 2009 (n=3)	June 2009 (n=19)	July 2009 (n=213)	August 2009 (n=430)	September 2009 (n=415)	October 2009 (n=407)	November 2009 (n=387)	December 2009 (n=415)	January 2010 (n=367)	February 2010 (n=283)	March 2010 (n=241)	April 2010 (n=147)
H1N1 vaccine	0.00%	0.00%	0.00%	0.00%	0.00%	9.83%	50.39%	64.82%	63.22%	56.89%	58.92%	58.50%
Seasonal TIV	0.00%	0.00%	0.00%	0.00%	18.31%	56.02%	63.31%	62.65%	54.22%	54.42%	58.09%	53.06%

Table 1. Influenza vaccine exposure among mothers of infants born during period of 2009 influenza A (H1N1) circulation, overall and by Kaiser Permanente site.

	Overall (n=3,327)		KP Georgia (n=1,004)		KP Mid-Atlantic States (n=2,323)	
	n	(%)	n	(%)	n	(%)
Type of vaccine received during pregnancy, all categories						
2009 H1N1 influenza vaccine plus 2009-2010 seasonal TIV	759	(22.8)	191	(19.0)	568	(24.5)
Only 2009 H1N1 influenza vaccine	366	(11.0)	95	(9.5)	271	(11.7)
Only 2009-2010 seasonal TIV	611	(18.4)	117	(11.7)	494	(21.3)
Both 2009-2010 seasonal TIV and 2008-2009 seasonal TIV	10	(0.3)	4	(0.4)	6	(0.3)
Only 2008-2009 seasonal TIV	61	(1.8)	31	(3.1)	30	(1.3)
No vaccine	1520	(45.7)	566	(56.4)	954	(41.1)
Type of vaccine during pregnancy, primary analysis categories						
H1N1 vaccine	1125	(33.8)	286	(28.5)	839	(36.1)
Seasonal TIV only	621	(18.7)	121	(12.1)	500	(21.5)
Any 2009-2010 inactivated influenza vaccine	1746	(52.5)	407	(40.5)	1339	(57.6)
No vaccine	1581	(47.5)	597	(59.5)	984	(42.4)

Table 2. Receipt of influenza vaccine during pregnancy categorized by maternal characteristics and type of vaccine received.

	No. (%) of Subjects					Unadjusted logistic regression modeling					
Characteristics	**All (N=3327)**	**H1N1 vaccine (n=1125)**	**Seasonal TIV only (n=621)**	**Any 2009-2010 inactivated influenza vaccine (n=1746)**	**No vaccine (n=1581)**	**H1N1 vaccine, OR (95% CI)**	**p-value**	**Seasonal TIV only, OR (95% CI)**	**p-value**	**Any 2009-2010 inactivated influenza vaccine, OR (95% CI)**	**p-value**
Maternal age less than 19 y	40 (1.2)	12 (1.1)	5 (0.8)	17 (1.0)	23 (1.5)	0.73 (0.36-1.47)	0.38	0.55 (0.21-1.45)	0.23	0.67 (0.36-1.25)	0.21
Maternal age more than 35 y	752 (22.6)	262 (23.3)	137 (22.1)	399 (22.9)	353 (22.3)	1.06 (0.88-1.27)	0.55	0.99 (0.79-1.23)	0.89	1.03 (0.88-1.21)	0.72
Asthma	120 (4.0)	44 (3.9)	25 (4.0)	69 (4.0)	51 (3.2)	1.20 (0.80-1.81)	0.38	1.31 (0.81-2.14)	0.27	1.24 (0.86-1.79)	0.25
Maternal diabetes	476 (15.7)	169 (15.0)	81 (13.0)	250 (14.3)	226 (14.3)	1.04 (0.84-1.29)	0.72	0.94 (0.72-1.24)	0.67	1.01 (0.83-1.22)	0.95
Multiple birth	181 (5.4)	60 (5.3)	30 (4.8)	90 (5.2)	91 (5.8)	0.92 (0.66-1.29)	0.64	0.83 (0.54-1.27)	0.39	0.89 (0.66-1.20)	0.44
Cardiovascular disease	183 (6.0)	55 (4.9)	46 (7.4)	101 (5.8)	82 (5.2)	0.92 (0.65-1.31)	0.66	1.53 (1.05-2.23)	0.03	1.13 (0.84-1.52)	0.43
Hypertension during pregnancy	507 (15.2)	162 (14.4)	109 (17.6)	271 (15.5)	236 (14.9)	0.96 (0.77-1.19)	0.70	1.21 (0.95-1.56)	0.13	1.05 (0.87-1.27)	0.63
Any pregnancy complication[a]	1921 (57.7)	602 (53.5)	362 (58.3)	964 (55.2)	957 (60.5)	0.75 (0.64-0.88)	<.01	0.91 (0.76-1.10)	0.33	0.80 (0.70-0.92)	<.01

[a]Any pregnancy complication includes the following: fetal abnormality affecting maternal management; fetal or placental problems affecting maternal management; polyhydramnios; oligohydramnios, PROM, amniotis; antepartum hemorrhage, abruptio pacentae, and placenta previa; and antepartum complications.

Table 3. ORs for association of maternal influenza immunization with infant outcomes, among infants born during period of 2009 influenza A (H1N1) virus circulation.

	H1N1 vaccine		Seasonal TIV only		Any 2009-2010 inactivated influenza vaccine	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Primary adjusted models[a]						
Preterm birth (27-36 weeks)	0.64 (0.48-0.85)[b]	<.01	0.64 (0.45-0.92)	0.01	0.64 (0.50-0.82)	<.01
Birth at 27-33 weeks	0.53 (0.30-0.94)	0.03	0.63 (0.32-1.25)	0.18	0.57 (0.35-0.92)	0.02
Birth at 34-36 weeks	0.67 (0.49-0.92)	0.01	0.65 (0.43-0.97)	0.04	0.66 (0.50-0.88)	<.01
Low birth weight (<2500 grams)	0.77 (0.56-1.06)	0.11	0.65 (0.43-0.99)	0.04	0.73 (0.55-0.97)	0.03
Small for gestational age	1.22 (0.91-1.62)	0.18	0.89 (0.61-1.30)	0.54	1.10 (0.84-1.43)	0.48
Secondary adjusted models[c]						
Preterm birth (27-36 weeks)	0.63 (0.47-0.84)[a]	<.01	0.62 (0.43-0.90)	0.01	0.62 (0.48-0.81)	<.01
Birth at 27-33 weeks	0.52 (0.29-0.94)	0.03	0.64 (0.32-1.28)	0.21	0.56 (0.34-0.93)	0.02
Birth at 34-36 weeks	0.66 (0.48-0.91)	0.01	0.61 (0.41-0.93)	0.02	0.64 (0.48-0.86)	<.01
Low birth weight (<2500 grams)	0.78 (0.56-1.10)	0.16	0.64 (0.41-1.00)	<0.05	0.73 (0.54-0.99)	0.05
Small for gestational age	1.25 (0.93-1.67)	0.14	0.89 (0.61-1.31)	0.56	1.12 (0.86-1.47)	0.41
Unadjusted models						
Preterm birth (27-36 weeks)	0.60 (0.46-0.79)	<.01	0.64 (0.46-0.88)	0.01	0.62 (0.49-0.78)	<.01
Birth at 27-33 weeks	0.49 (0.29-0.83)	0.01	0.66 (0.36-1.19)	0.17	0.55 (0.35-0.85)	0.01
Birth at 34-36 weeks	0.65 (0.48-0.87)	<.01	0.63 (0.43-0.92)	0.02	0.64 (0.49-0.83)	<.01
Low birth weight (<2500 grams)	0.71 (0.52-0.96)	0.03	0.66 (0.45-0.97)	0.03	0.69 (0.53-0.91)	0.01
Small for gestational age	1.15 (0.87-1.52)	0.31	0.91 (0.64-1.30)	0.59	1.06 (0.83-1.37)	0.63

NOTES: Reference group for all models is group that was not exposed to any 2009-2010 inactivated influenza vaccine. [a]Primary adjusted models control for propensity score (categorized into quintiles) created as the likelihood of receipt of any 2009-2010 inactivated influenza vaccine, based on all measured a priori confounders.[b]Interpretation: During the period of 2009-2010 H1N1 influenza circulation, the adjusted odds of third trimester preterm birth were 36% lower among infants of mothers who received 2009 influenza A(H1N1) vaccine, as compared to infants of unvaccinated mothers.[c] Secondary adjusted models control for a priori confounders: maternal age <19 years, maternal age >35 years, maternal asthma, gestational diabetes, maternal CVD, hypertension during pregnancy, any pregnancy/birth complication, multiple birth, and KP site.

Table 4. Comparison of birth weight among infants born during period of 2009 influenza A (H1N1) virus circulation, by mother's influenza vaccine status.

	Primary adjusted models[a]		Secondary adjusted models[b]		Unadjusted models	
Type of influenza vaccine received by mother during pregnancy	**Birth weight (grams), mean (95% CI)**	**Increase in birth weight (grams), compared to reference group, mean (95% CI)**	**Birth weight (grams), mean (95% CI)**	**Increase in birth weight (grams), compared to reference group, mean (95% CI)**	**Birth weight (grams), mean (95% CI)**	**Increase in birth weight (grams), compared to reference group, mean (95% CI)**
Comparison of type of inactivated influenza vaccine received, versus no vaccine						
H1N1 vaccine	3364.8 (3322.7, 3406.8)	55.6 (12.4, 98.8)	3432.1 (3389.7, 3474.5)	45.6 (2.5, 88.7)	3308.5 (3275.5, 3341.5)	63.2 (20.0, 106.3)
Seasonal TIV only	3376.6 (3326.3, 3427.0)	67.5 (15.3, 119.6)	3453.7 (3401.2, 3506.2)	67.2 (14.3, 120.1)	3320.3 (3276.4, 3364.1)	74.9 (23.0, 126.6)
No vaccine	3309.2 (3268.7, 3349.7)	Reference	3386.5 (3344.4, 3428.6)	Reference	3245.3 (3217.6, 3273.1)	Reference
Comparison of any 2009-2010 inactivated influenza vaccine received, versus no vaccine						
Any 2009-2010 inactivated influenza vaccine	3369.2 (3332.3, 3406.0)	59.8 (21.3, 98.4)	3439.5 (3401.5, 3477.5)	53.1 (14.4, 91.7)	3312.7 (3286.4, 3339.1)	67.4 (29.1, 105.7)
No vaccine	3309.3 (3268.9, 3349.8)	Reference	3386.5 (3344.4, 3428.5)	Reference	3245.3 (3217.6, 3273.1)	Reference

NOTES: Reference group for all models is group that was not exposed to any 2009-2010 inactivated influenza vaccine. [a]Primary adjusted models control for propensity score (categorized into quintiles) created as the likelihood of receipt of any 2009-2010 inactivated influenza vaccine, based on all measured a priori confounders. [b]Secondary adjusted models control for a priori confounders: maternal age <19 years, maternal age >35 years, maternal asthma, maternal diabetes, maternal CVD, hypertension during pregnancy, any pregnancy/birth complication, multiple birth, and KP site.

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Supplementary Materials

Supplement 1: Classification of Influenza Vaccines Administered to Study Mothers

A total of 2,576 influenza vaccine doses were administered during pregnancy to mothers in our cohort. Influenza vaccine data for pregnant women enrolled in KP Mid-Atlantic States included vaccines coded as HL7 126 (novel influenza H1N1-09, preservative free inactivated vaccine) over the period 2007-2010. We assumed that all vaccines coded as HL7 126 prior to October 1, 2009 were recorded using an incorrect HL7 code. A total of 757 (29.4%) doses were coded as HL7 126 prior to October 1, 2009; 721 (28.0%) doses were coded as HL7 126 on or after October 1, 2009. To account for potential miscoding of vaccines, we applied an algorithm with the following assumptions to assign vaccine type: 1) If mothers received one influenza vaccine during the 2009-2010 influenza season and it was not coded as HL7 128, we assumed that it was 2009-2010 seasonal TIV if administered prior to October 1, 2009, and that it was 2009 H1N1 influenza vaccine if administered on or after October 1, 2009; 2) If mothers received two influenza vaccines after October 1, 2009 and neither was coded as HL7 128, we assumed that the first vaccine received was 2009-2010 seasonal TIV and the second was 2009 H1N1 influenza vaccine.

We performed a sensitivity analysis to assess the impact of changing the algorithm we used to identify vaccine types based on the timing of availability of 2009 H1N1 influenza vaccine during the 2009-2010 influenza season. We modified our algorithm to assume that all single inactivated influenza vaccines given after October 1, 2009 that were not coded as HL7 128 were 2009-2010 seasonal TIV. This change effectively recoded all vaccines that were recoded as 2009 H1N1 influenza vaccine in the primary analysis back to 2009-2010 seasonal TIV. The true distribution of 2009-2010 seasonal TIV versus 2009 H1N1 influenza vaccines, among those vaccines with questionable coding, likely fell somewhere in the middle of these two algorithm assumptions. Results obtained using the sensitivity analysis algorithm were qualitatively similar

to those obtained in our primary analysis. Odds ratios for the association of maternal influenza immunization with preterm birth, low birth weight, and SGA were within the confidence intervals obtained in our primary analysis. Comparisons of specific results are presented in Supplementary Table 1.

Supplementary Table 1. Sensitivity analyses of ORs for association of maternal influenza immunization with infant outcomes, among infants born during period of 2009 influenza A (H1N1) virus circulation, using alternative vaccine definition algorithm.

	H1N1 vaccine		Seasonal TIV only		Any 2009-2010 inactivated influenza vaccine	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Primary adjusted models[a]						
Preterm birth (27-36 weeks)	0.63 (0.47-0.84)[b]	<.01	0.68 (0.48-0.97)	0.03	0.65 (0.51-0.83)	<.01
Birth at 27-33 weeks	0.54 (0.30-0.97)	0.04	0.72 (0.37-1.39)	0.32	0.60 (0.37-0.98)	0.04
Birth at 34-36 weeks	0.66 (0.48-0.91)	0.01	0.67 (0.45-1.00)	0.05	0.67 (0.50-0.88)	<.01
Low birth weight (<2500 grams)	0.80 (0.58-1.10)	0.17	0.72 (0.48-1.08)	0.11	0.77 (0.58-1.02)	0.07
Small for gestational age	1.25 (0.94-1.67)	0.13	0.89 (0.60-1.30)	0.54	1.12 (0.86-1.46)	0.40
Secondary adjusted models[c]						
Preterm birth (27-36 weeks)	0.61 (0.45-0.82)	<.01	0.68 (0.47-0.98)	0.04	0.64 (0.49-0.82)	<.01
Birth at 27-33 weeks	0.51 (0.28-0.93)	0.03	0.75 (0.38-1.47)	0.39	0.59 (0.36-0.97)	0.04
Birth at 34-36 weeks	0.64 (0.46-0.89)	<.01	0.66 (0.44-1.00)	<0.05	0.65 (0.49-0.87)	<.01
Low birth weight (<2500 grams)	0.80 (0.56-1.12)	0.19	0.73 (0.47-1.13)	0.16	0.77 (0.57-1.05)	0.10
Small for gestational age	1.28 (0.96-1.71)	0.10	0.90 (0.61-1.33)	0.59	1.14 (0.87-1.49)	0.33
Unadjusted models						
Preterm birth (27-36 weeks)	0.60 (0.45-0.78)	<.01	0.66 (0.48-0.91)	0.01	0.62 (0.49-0.78)	<.01
Birth at 27-33 weeks	0.48 (0.28-0.83)	<.01	0.68 (0.37-1.23)	0.20	0.55 (0.35-0.86)	<.01
Birth at 34-36 weeks	0.64 (0.47-0.87)	<.01	0.65 (0.45-0.95)	0.03	0.64 (0.49-0.84)	<.01
Low birth weight (<2500 grams)	0.72 (0.53-0.98)	0.04	0.69 (0.47-1.00)	<0.05	0.71 (0.54-0.93)	0.01
Small for gestational age	1.19 (0.91-1.57)	0.21	0.92 (0.64-1.31)	0.64	1.09 (0.85-1.40)	0.49

NOTES: Reference group for all models is group that was not exposed to any 2009-2010 inactivated influenza vaccine. [a]Primary adjusted models control for propensity score (categorized into quintiles) created as the likelihood of receipt of any 2009-2010 inactivated influenza vaccine, based on all measured a priori confounders.[b]Interpretation: During the period of 2009-2010 H1N1 influenza circulation, the adjusted odds of third trimester preterm birth were 37% lower among infants of mothers who received 2009 influenza A(H1N1) vaccine, as compared to infants of unvaccinated mothers.[c]Secondary adjusted models control for a priori confounders: maternal age <19 years, maternal age >35 years, maternal asthma, maternal diabetes, maternal CVD, hypertension during pregnancy, any pregnancy/birth complication, multiple birth, and KP site.

Supplement 2: Definition of Pregnancy Period for Classification of Vaccine Exposure

In our primary analysis, we defined influenza vaccination during pregnancy as being between LMP and infant's birth date. We performed sensitivity analyses to assess the impact of applying a restriction that defined mother's exposure to inactivated influenza vaccine as being between estimated LMP and at least 7 or 14 days prior to the infant's birth date. Results obtained after applying this restriction were qualitatively similar to those obtained in our primary analysis. ORs remained significant and within original CIs. Comparisons of specific results are presented in Supplementary Tables 2 and 3.

Supplementary Table 2. Sensitivity analyses of ORs for association of maternal influenza immunization with infant outcomes, among infants born during period of 2009 influenza A (H1N1) virus circulation, defining influenza vaccination during pregnancy as being vaccinated between LMP and at least 7 days prior to birth.

	H1N1 vaccine		Seasonal TIV only		Any 2009-2010 inactivated influenza vaccine	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Primary adjusted models[a]						
Preterm birth (27-36 weeks)	0.58 (0.42-0.80)[b]	<.01	0.71 (0.53-0.95)	0.02	0.65 (0.51-0.83)	<.01
Birth at 27-33 weeks	0.47 (0.24-0.91)	0.03	0.66 (0.37-1.17)	0.15	0.56 (0.35-0.92)	0.02
Birth at 34-36 weeks	0.62 (0.43-0.89)	<.01	0.73 (0.52-1.02)	0.06	0.68 (0.51-0.89)	<.01
Low birth weight (<2500 grams)	0.67 (0.46-0.97)	0.03	0.81 (0.58-1.13)	0.22	0.74 (0.56-0.99)	0.04
Small for gestational age	1.17 (0.86-1.61)	0.32	1.05 (0.76-1.44)	0.78	1.11 (0.85-1.44)	0.45
Secondary adjusted models[c]						
Preterm birth (27-36 weeks)	0.57 (0.41-0.80)	<.01	0.69 (0.51-0.93)	0.02	0.63 (0.49-0.82)	<.01
Birth at 27-33 weeks	0.46 (0.23-0.91)	0.03	0.66 (0.36-1.19)	0.17	0.56 (0.34-0.92)	0.02
Birth at 34-36 weeks	0.61 (0.42-0.89)	<.01	0.70 (0.49-0.98)	0.04	0.66 (0.49-0.87)	<.01
Low birth weight (<2500 grams)	0.69 (0.47-1.03)	0.07	0.80 (0.56-1.14)	0.22	0.75 (0.55-1.02)	0.06
Small for gestational age	1.22 (0.88-1.67)	0.23	1.05 (0.76-1.45)	0.76	1.13 (0.86-1.48)	0.37
Unadjusted models						
Preterm birth (27-36 weeks)	0.57 (0.42-0.77)	<.01	0.67 (0.51-0.89)	<.01	0.62 (0.49-0.78)	<.01
Birth at 27-33 weeks	0.45 (0.24-0.83)	0.01	0.63 (0.38-1.07)	0.09	0.55 (0.35-0.85)	<.01
Birth at 34-36 weeks	0.61 (0.43-0.86)	<.01	0.69 (0.50-0.94)	0.02	0.65 (0.50-0.85)	<.01
Low birth weight (<2500 grams)	0.63 (0.44-0.89)	<.01	0.77 (0.56-1.06)	0.10	0.70 (0.54-0.92)	<.01
Small for gestational age	1.11 (0.82-1.51)	0.51	1.04 (0.77-1.40)	0.80	1.07 (0.84-1.38)	0.58

NOTES: Reference group for all models is group that was not exposed to any 2009-2010 inactivated influenza vaccine. [a]Primary adjusted models control for propensity score (categorized into quintiles) created as the likelihood of receipt of any 2009-2010 inactivated influenza vaccine, based on all measured a priori confounders.[b]Interpretation: During the period of 2009-2010 H1N1 influenza circulation, the adjusted odds of third trimester preterm birth were 42% lower among infants of mothers who received 2009 influenza A(H1N1) vaccine, as compared to infants of unvaccinated mothers.[c]Secondary adjusted models control for a priori confounders: maternal age <19 years, maternal age >35 years, maternal asthma, maternal diabetes, maternal CVD, hypertension during pregnancy, any pregnancy/birth complication, multiple birth, and KP site.

Supplementary Table 3. Sensitivity analyses of ORs for association of maternal influenza immunization with infant outcomes, among infants born during period of 2009-2010 H1N1 influenza circulation, defining influenza vaccination during pregnancy as being vaccinated between LMP and at least 14 days prior to birth.

	H1N1 vaccine		Seasonal TIV only		Any 2009-2010 inactivated influenza vaccine	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Primary adjusted models[a]						
Preterm birth (27-36 weeks)	0.62 (0.47-0.83)[b]	<.01	0.63 (0.44-0.91)	0.01	0.63 (0.49-0.81)	<.01
Birth at 27-33 weeks	0.57 (0.32-1.02)	0.06	0.68 (0.35-1.35)	0.27	0.61 (0.37-0.99)	<.05
Birth at 34-36 weeks	0.64 (0.46-0.89)	<.01	0.62 (0.41-0.93)	0.02	0.63 (0.48-0.84)	<.01
Low birth weight (<2500 grams)	0.81 (0.59-1.13)	0.21	0.69 (0.46-1.05)	0.08	0.77 (0.58-1.03)	0.07
Small for gestational age	1.24 (0.93-1.66)	0.14	0.93 (0.64-1.36)	0.71	1.37 (0.87-1.47)	0.37
Secondary adjusted models[c]						
Preterm birth (27-36 weeks)	0.60 (0.45-0.81)	<.01	0.63 (0.43-0.91)	0.01	0.61 (0.47-0.79)	<.01
Birth at 27-33 weeks	0.54 (0.30-0.99)	0.04	0.72 (0.36-1.44)	0.35	0.60 (0.36-0.99)	<.05
Birth at 34-36 weeks	0.62 (0.45-0.87)	<.01	0.60 (0.39-0.92)	0.02	0.61 (0.46-0.82)	<.01
Low birth weight (<2500 grams)	0.81 (0.57-1.15)	0.24	0.71 (0.46-1.10)	0.13	0.77 (0.57-1.05)	0.10
Small for gestational age	1.27 (0.95-1.71)	0.11	0.94 (0.64-1.39)	0.77	1.15 (0.88-1.50)	0.31
Unadjusted models						
Preterm birth (27-36 weeks)	0.60 (0.45-0.79)	<.01	0.63 (0.45-0.88)	<.01	0.61 (0.48-0.77)	<.01
Birth at 27-33 weeks	0.53 (0.31-0.90)	0.02	0.66 (0.36-1.22)	0.18	0.58 (0.36-0.90)	0.02
Birth at 34-36 weeks	0.62 (0.46-0.85)	<.01	0.62 (0.42-0.91)	0.02	0.62 (0.48-0.81)	<.01
Low birth weight (<2500 grams)	0.75 (0.55-1.02)	0.07	0.69 (0.47-1.02)	0.06	0.73 (0.56-0.95)	0.02
Small for gestational age	1.18 (0.89-1.56)	0.25	0.96 (0.68-1.37)	0.83	1.10 (0.85-1.41)	0.47

NOTES: Reference group for all models is group that was not exposed to any 2009-2010 inactivated influenza vaccine. [a]Primary adjusted models control for propensity score (categorized into quintiles) created as the likelihood of receipt of any 2009-2010 inactivated influenza vaccine, based on all measured a priori confounders.[b]Interpretation: During the period of 2009-2010 H1N1 influenza circulation, the adjusted odds of third trimester preterm birth were 38% lower among infants of mothers who received 2009 influenza A(H1N1) vaccine, as compared to infants of unvaccinated mothers.[c]Secondary adjusted models control for a priori confounders: maternal age <19 years, maternal age >35 years, maternal asthma, maternal diabetes, maternal CVD, hypertension during pregnancy, multiple birth, and KP site.

Public Health Implications

Maternal influenza immunization has substantial public health implications. This study validates previous findings that maternal influenza immunization may be one important strategy of reducing risk of adverse infant outcomes among pregnant women who are exposed to seasonal and pandemic influenza. The protective effect of maternal influenza immunization against preterm birth has now been reported in three study populations, in both developed and developing countries, including a randomized controlled trial. This study moves our understanding of maternal influenza immunization forward by assessing effects during pandemic influenza. There remain important questions to be addressed by future studies.

Long-Term Implications of Adverse Infant Outcomes

Being born preterm, at low birth weight, or small for gestational age have important implications for growth and development. About 12 percent of all infants born in the United States are born premature (before 37 weeks gestation); the largest number of preterm births occur between 32 and 36 weeks gestation.[1,2] Between 1990 and 2002, preterm births increased by approximately 7 percent; the increase was substantially due to increases in preterm births at 32-36 weeks. Preterm births in the U.S. were associated with at least $26.2 billion in societal costs in 2005.[2]

While there have been significant advances in medical care for and survival of infants born preterm, these infants remain at higher risk of adverse health outcomes as compared to infants born at 37-41 weeks gestation.[2] Infants born preterm are biologically immature; they may have underdeveloped organ systems and require medical intervention.[2] Infants who are born premature may be at higher risk of mortality, morbidity, and developmental problems, including the following: breathing problems due to underdevelopment of the lungs; health problems of the

respiratory, gastrointestinal, immunologic, and nervous systems; poorer growth and physical development; and motor, cognitive, sensory, and learning problems.[1,2] While infants born earlier than 32 weeks have the most severe outcomes, premature infants born closer to term are at higher risk of mortality and neurodevelopmental disabilities compared to infants born at term, including delays in achieving infant milestones and difficulty with fine motor skills and learning.[2-4]

How This Study Adds to Maternal Influenza Immunization Research

This study validates prior findings of a protective effect of maternal influenza immunization against preterm birth and lower birth weight during periods of seasonal influenza circulation. Our findings demonstrated that the protective effect of maternal influenza immunization is present during an influenza pandemic, in addition to during seasonal influenza epidemics. Further, prior studies noted that findings would need to be replicated in additional populations in order to evaluate the differential impact of maternal influenza immunization by population. This study replicated prior findings in a managed care organization population – representing the insured general public – in both Georgia and the Mid-Atlantic region of the United States.

This is the first epidemiologic study to evaluate the effect of 2009 H1N1 influenza vaccine on adverse infant outcomes. Several studies and surveillance reports from the pandemic have reported higher rates of adverse infant outcomes among pregnant women infected with H1N1 influenza, as compared to non-infected pregnant women.[5-10] Combined with these findings, our study helps to demonstrate that maternal pandemic influenza immunization has substantial potential impacts on adverse infant outcomes through prevention of influenza infection. Vaccinating pregnant women against H1N1 influenza infection has the potential to prevent against the increased risk of adverse infant outcomes caused by H1N1 influenza infection.

Maternal Immunization as Feasible Strategy for Addressing Risk of Adverse Infant Outcomes

Causes and etiologies of adverse infant outcomes such as preterm birth are numerous and complex. Current evidence, including this study, indicates that maternal influenza immunization is one feasible means of addressing some fraction of preterm birth and lower birth weight outcomes.

Findings from this and other studies demonstrating the protective effect of maternal influenza immunization can be used to inform influenza vaccine policy, and to encourage pregnant women to be vaccinated. Pregnant women are among the highest priority groups to receive influenza vaccine during seasonal epidemics and pandemics. Historically, vaccine coverage has been low among pregnant women (10-20%), but it has increased substantially since the 2009 influenza A (H1N1) pandemic. During the pandemic, national influenza vaccine coverage among pregnant women was 32-51%; coverage remained at that level (44 ± 28-49%) in the 2010-2011 influenza season.[11] During the 2009 influenza A (H1N1) pandemic, pregnant women were more likely to receive influenza vaccine if recommended by their medical providers. Evidence of the protective effect of maternal influenza immunization against adverse infant outcomes may encourage more obstetric care providers to recommend the vaccine, and more pregnant women to receive the vaccine. This evidence can be used to inform future national recommendations for influenza vaccination, including continuing to prioritize pregnant women during pandemics.

Future Research and Data Needs

Findings from this study should be used to inform further exploration and confirmation of the association between maternal influenza immunization and infant outcomes in epidemiologic studies. Additionally, further studies are needed in two important areas: (1) to evaluate the effect of maternal influenza immunization on influenza infection among infants, and (2) to elucidate the

pathogenesis of influenza infection in pregnant women, and biological mechanisms through which influenza infection and immunization cause or mediate, respectively, adverse infant outcomes.

Future epidemiologic studies of maternal influenza immunization should focus on both seasonal and pandemic influenza. Studies of pandemic influenza immunization should evaluate differential effects by race, trimester of vaccination, maternal nutritional status, and intensity of influenza activity. Importantly, this study has highlighted the need for improved during future pandemics (i.e., cognizance of the importance of accurate and complete data on vaccine administration, influenza infection, and maternal and infant outcomes for future studies of maternal influenza immunization). Studies of seasonal influenza immunization should also evaluate differential effects by race, trimester of vaccination, and maternal nutritional status, but should also be extended to larger populations over several influenza seasons in order to confirm previous findings. Additionally, future studies should evaluate the effects of maternal influenza infection and immunization on adverse infant outcomes within the same study population.

Future epidemiologic studies should also evaluate the effect of maternal influenza immunization on influenza infection among infants. We were unable to evaluate the effect of immunization on respiratory illness (e.g., influenza-like illness, laboratory-confirmed influenza) in infants after birth because we only had data on infants up to 30 days after birth. One primary reason for influenza vaccination of pregnant women is to protect infants against influenza infection when they are too young to be vaccinated. Maternal influenza immunization may protect infants through antibody transfer across the placenta or via breast milk, or through a cocooning effect produced by vaccinating the mother (who is often their closest contact). Recent studies have demonstrated reduction in influenza-associated illnesses among vaccinated mothers in Bangladesh, American Navajos and White Mountain Apaches, and Connecticut.[12-14] Two additional studies showed no significant effect of maternal influenza immunization on influenza-like illness in infants[15] or respiratory illness in infants.[16] These studies may not have had

sufficient power to show an effect due to overall low incidence of primary outcomes in the study populations. Further studies should be conducted in different populations and across multiple influenza seasons to assess the effect of maternal influenza immunization. If data can be obtained on infant outcomes during the 2009 H1N1 influenza A (H1N1) pandemic, it would also be useful to evaluate the effect of maternal influenza immunization on influenza illness among infants during the pandemic. This effect is especially of interest because of the higher morbidity and mortality experienced during pandemics due to limited population immunity.

Beyond observational epidemiologic studies, future studies are needed to elucidate the pathogenesis of influenza infection in pregnant women, and biological mechanisms through which influenza infection and immunization cause or mediate, respectively, adverse infant outcomes. Such studies will help to inform current understanding of biological mechanisms underlying influenza infection during pregnancy.

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Kaiser Permanente Georgia Institutional Review Board Approval

KAISER PERMANENTE

NOTIFICATION OF APPROVAL

January 10, 2012

To: Saad Omer

CC: Dzifa Adjaye-Gbewonyo

Study ID: GA-11SOmer-01

Modification ID: MR6_GA-11SOmer-01

Study Title: Vaccine Safety Datalink

The study modification was reviewed and approved by the Kaiser Permanente Georgia Institutional Review Board (KPGA IRB) expedited review procedures on January 10, 2012.

Study document reviewed:

- Study Proposal for "Infant Outcomes Associated with Influenza Immunization and Influenza Infection During Pregnancy: A Retrospective Cohort Study" (VSD sub-study)

The IRB determined that the sub-study involves no more than minimal risk to the participants. The IRB waived the requirement to obtain informed consent for this sub-study and the IRB waived the requirement for written Privacy Rule authorization for this sub-study.

Please use this notification of approval should the funding agency require documentation of IRB approval. Our Federalwide Assurance number is FWA 00002344 – IRB 00000406.

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