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Impact of Maternal Immunization and Breastfeeding on Influenza-Like Illness and Lower Respiratory Tract Infections in Infants

By

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Master of Public Health

Epidemiology

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Faculty Thesis Advisor

Impact of Maternal Immunization and Breastfeeding on Influenza-Like Illness and Lower Respiratory Tract Infections in Infants

By

Guan Chen

Bachelors of Science

Syracuse University

2011

Faculty Thesis Advisor: Saad Omer, PhD

An abstract of

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Abstract

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By Guan Chen

Background: Influenza is a highly infectious viral disease which creates a substantial burden on high risk populations such as pregnant women and young infants. Maternal immunization is an effective way to increase levels of influenza-specific antibodies in maternal serum and breast milk, providing passive protection to the infant in the months after birth, before the infant's immune system is fully developed or childhood vaccines can be administered.

Objective: The objective of the study was to evaluate the strength of association between the receipt of inactivated influenza vaccine during pregnancy and respiratory outcomes among breastfed infants and non-breastfed infants.

Methods: We conducted an analysis of surveillance data from the Georgia Pregnancy Risk Assessment Monitoring, Georgia Hospital Discharge Data, and Birth Certificate Data on infants born between January 1, 2005 and December 31, 2008. The primary exposure variable was maternal receipt of the influenza vaccine. The outcomes of interest were hospitalizations due to influenza/influenza-like illness (ILI) and pneumonia/lower respiratory tract infections (LRTI) in infants.

Results: A total of 8,393 women were included in the study. Influenza vaccine information was available for 5422 (64.6%) women; of these 916 (16.9%) women received the influenza vaccine during pregnancy. The magnitude of effect of maternal influenza vaccine on ILI was much stronger for breastfed newborns compared to newborns who were not breastfed during the period of at least local, at least regional, and widespread influenza activity. The presence of breastfeeding only influenced the magnitude of effect of maternal influenza vaccine on LRTI during the putative influenza season.

Conclusion: Maternal vaccination and breastfeeding provide infants greater protection than vaccination or breastfeeding alone. Multiple studies have found that full breastfeeding have been shown to confer lower overall illness rates in infants, whereas minimal breastfeeding have not been found to be protective. It is plausible that the association between immunization with the inactivated influenza vaccine during pregnancy and reduced likelihood of ILI or LRTI may be much stronger among exclusive breastfed infants. The results of this study need to be replicated in a larger population to assess the association among infants who were fully breastfed and minimally breastfed.

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Manuscript

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Guan Chen, BS, Saad Omer, PhD, Demilade Adedinsewo, MPH

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Introduction

Influenza is a highly infectious viral disease which creates a substantial burden on health care and society. It is the leading cause of vaccine-preventable deaths in the United States and attributable to more than 200,000 hospitalizations and 36,000 deaths annually.[1] Infection with the influenza virus is associated with increased risks of morbidity and mortality among certain high risk populations such as pregnant woman and young infants.[2] Maternal influenza infection has been associated with increased risk of maternal hospitalization, fetal malformations, low birth weight, and other illnesses.[2, 3] Influenza infection in infants often leads to hospitalization and can predispose the infant to the development of secondary bacterial infections such as acute otitis media and pneumococcal pneumonia.[4,5] Children younger than six months face a substantially higher burden of disease and deaths from influenza infection.[6]

Vaccinating pregnant woman against influenza can prevent substantial number of deaths in both the mother and infant.[2] Pregnant mothers who are immunized against influenza have been shown to provide protection to their infants against respiratory illness. Several studies have demonstrated that neonates are protected from influenza virus infection through transplacentally acquired antibody after influenza infection or vaccination during pregnancy.[7, 8] One study showed that vaccination of pregnant woman with inactivated influenza vaccine had a 63% effectiveness in reducing laboratory-confirmed influenza in their infants up to 6 months of age and 29% in reducing rates of respiratory illness with fever in infants.[9]

Biological and epidemiologic data suggests that breastfeeding is also protective against influenza in young infants. Breast milk is naturally fortified with immunological, nutritive, and bioactive ingredients which protect the infant against influenza.[10] Influenza vaccine antigen-specific IgA has been found in the breast milk of immunized mothers up to 1 year after birth.[11] In the same study, the antibody levels were higher in the breast milk of mothers who received influenza vaccine compared to unvaccinated mothers.

In a recent randomized controlled clinical trial in Bangladesh, researchers discovered that breastfed infants whose mothers received the influenza vaccine during pregnancy had the lowest incidence of respiratory infection with fever.[12] This raises questions on whether additional protection is conferred by breastfeeding through the transfer of antibodies to infants via breast milk. To our knowledge, there are no reported studies which explore the potential impact of both maternal vaccination and breastfeeding on respiratory infections in infants.

The objective of the study was to evaluate the strength of association between the receipt of inactivated influenza vaccine during pregnancy and respiratory outcomes among breastfed and non-breastfed infants.

Methods

This study aims to evaluate the difference in the effect of maternal immunization with influenza vaccine on infant health outcomes among infants born between January 1 2005 and December 31 2008 (the four most recent seasons for which the data were available at the time of analysis) between mothers who breastfeed or did not breastfeed their baby after delivery. The primary exposure variable was maternal receipt of the influenza vaccine (vaccinated vs. unvaccinated against seasonal influenza) during any trimester of pregnancy by mothers of infants born between January 1, 2005 and December 31, 2008. The outcomes of interest in infants were: hospitalizations due to influenza/influenza-like illness (ILI), and hospitalizations due to pneumonia/lower respiratory tract infection (LRTI). Stratification was done by presence of maternal breastfeeding to determine if there was a difference between the groups.

Data Sources and Study Population

We abstracted data on all pregnant women from the Georgia Pregnancy Risk Assessment Monitoring System (PRAMS), a surveillance project managed by the Centers for Disease Control and Prevention (CDC) and state health departments; the Hospital Discharge Data (GDDS), which provides hospital discharge records from the Georgia Hospital Association through the Georgia Department of Public Health; and the Birth Certificate Data, which contains certificates and perinatal information for all births in the state provided by the Georgia Department of Community Health. All data were collected for the time period starting January 1, 2005 through December 31, 2008. All records were linked and the key for linkages was maintained at a secure location at the Georgia

Department of Community Health, Division of Public Health. After the linkage was completed, all personal identifiers were removed from the analysis dataset. All data were from a state representative sample of women with live born infants using a standardized data collection approach developed and managed by the CDC and the state department of health.

The data collection procedure and information contained within each dataset used is described as follows: *PRAMS*-- PRAMS sample is drawn using the state's birth certificate file and includes women who have had a live birth in the state.[13] Some subgroups, particularly those representing small but high-risk populations, are oversampled. Every year, data are collected from the selected women with recent births via mailed questionnaires and telephone. The PRAMS dataset contains information on maternal attitudes and experiences before, during, and shortly after pregnancy, maternal report of influenza vaccine receipt, and newborn birth certificate data including birth date and birth weight data. The PRAMS employs a standardized data collection approach with analysis weights developed by the CDC. *Hospital Discharge Data (GDDS)*-- Georgia Hospital Association provides the Georgia Department of Public Health on an annual basis with an abridged data set of hospital discharge records for the State of Georgia.[14] Each record contains information on admission date, discharge date, length of stay, birth date, race, sex, diagnoses, procedures and other information. In this study, hospital discharge data was linked to PRAMS data for a sample of women who have had a live birth in the state. *Birth Certificate Data*-- Birth certificates for all births in the state are provided to the Georgia Department of Community Health.[15] The certificates contain information on birth weight, gestational age at birth, maternal alcohol and tobacco use

during pregnancy, and other information. The birth certificate number allowed for linkage between all the datasets.

Definition of Influenza Activity Periods

In order to evaluate the impact of the intensity of influenza activity in Georgia on the association between maternal influenza vaccination and respiratory outcomes, we used a modified version of the reported categories of influenza activity in Weekly Influenza Surveillance in Georgia, which assess the spread of influenza within each state for each week based on lab-confirmed and syndromic data.[16] We defined the pre-influenza period as the period between the start of the putative influenza season (October 1) and the beginning of local influenza activity. The pre-influenza period is characterized by the availability of the vaccine and the absence of influenza activity. Stratified analysis was performed for the overall study period, the putative influenza season (1 October–31 May), the pre-influenza period (during the putative influenza season), the period of at least local activity, the period of regional activity, and the period of widespread activity.

Definition of Influenza-Like Illness and Lower Respiratory Tract Infections

A hospital visit was defined as due to influenza/ILI if any of the following ICD-9 diagnosis codes were used at the time of visit: 460, 462, 463, 464.0, 464.10, 464.11, 464.20, 464.21, 464.4, 465.0, 465.8, 465.9, 478.9, 487.1, 487.8, 490, 466, 480.8, 480.9, 481.0, 482.2, 482.3, 482.4, 482.41, 482.49, 484.0, 484.1, 485, 486, 487.0 and 038 (adapted and modified from Erik K. France[17]). A hospital visit was defined as due to pneumonia/LRTI if any of the following ICD-9 diagnosis codes were used at the time of

visit: 466, 480.8, 480.9, 481.0, 482.2, 482.3, 482.4, 482.41, 482.49, 484.0, 484.1, 485, 486, 487.0 and 038. Other covariates include: Infant variables - gestational age, birth weight, sex, birth defect, hospital discharge date, age of infant, principal ICD-9 diagnosis; Maternal variables - education, race, alcohol consumption during pregnancy, marital status, age, education, race, diabetes, hypertension, weight gain, smoking history, month of first prenatal care visit, number of prenatal care visits, hospitalizations during pregnancy, maternal BMI, maternal weight before pregnancy, gestational weeks at 1st prenatal care visit, insurance status, multivitamin use, vitamin in the last three months of pregnancy, and enrollment in the Women, Infants, and Children (WIC) program during pregnancy.

Statistical Analysis and Confounder Assessment

We compared the distribution of demographic, pregnancy-related factors and other variables between the two 'exposure' groups (vaccinated vs. unvaccinated). We employed Poisson regression techniques in determining the rate of hospitalizations due to ILI and LRTI among the infants of women surveyed. We calculated an approximate estimate of 'person-time' by subtracting the date of birth from the last date of the year in which the infant was born. We carried out the following adjustments for confounding:

Primary adjustment-- based on the approach of identifying covariates that produced an adjusted incidence density ratio (IDR) of 1 during the pre-influenza period. The rationale for this adjustment and method has been discussed in Jackson et al. and Nelson et al.[18, 19]

Propensity Score adjustment--based on the approach using predicted probabilities from a logistic model which models the probabilities of being in the various levels of the primary predictor as a function of a set of secondary variables which we would like to match on. It employs a method, which provides a single summary number to control for multiple covariates simultaneously, and especially in cases in which the "exposure" is common and the "outcome" is rare. [20, 21] Also, the propensity score algorithm has been proven to generate estimates which are as good or better than standard approaches used in controlling confounding using a pre-defined set of variables.[22] Variables used in the creation of propensity scores included variables that had a bivariate association the 'exposure' and 'outcome' of interest as well as scientifically proven confounders and those with previous literature justifying its inclusion. The rationale for this adjustment and method have been discussed in Bai et al.[23]

Ratio of Ratios adjustment-- this approach has been described frequently and is often used to compare two estimates of the same quantity derived from separate analyses or regression models, such as when comparing the treatment effect in subgroups in a randomized trial sometimes referred to as a test of interaction.[24] This method also applies a formula in the calculation of confidence intervals for the resulting estimate after comparison as described in Altman et al. and Newcombe et al.[24-26] In our study, this approach was used to compare two IDR estimates derived from separate regression models i.e. comparing the effect of vaccination in different influenza activity periods/sub-periods. Each influenza activity period was compared with the pre-influenza activity period or "control period" and estimates and confidence intervals were calculated. Our assumption was that an unmeasured confounder affecting the result estimates in the

"control period" would be inadvertently controlled for in all other influenza activity periods using the ratio of ratios approach, i.e. generating a new incidence density ratio estimate from ratio of the two periods being compared. The change in the beta estimate was calculated as $\theta = \theta_1 - \theta_2$; where θ_2 represents the beta coefficient for the effect estimate obtained in the pre-influenza period. This estimate was then transformed (by calculating its exponent) to produce a 'new estimate' i.e. incidence density ratio estimate after adjusting for the effect in the pre-influenza season. The 95% confidence interval for this 'new estimate' was calculated using the formula $\hat{\theta} - \sqrt{\{(\widehat{\theta_1} - l_1)^2 + (u_2 - \hat{\theta}_2)^2\}}$ and $\hat{\theta} + \sqrt{\{(u_1 - \hat{\theta}_1)^2 + (\hat{\theta}_2 - l_2)^2\}}$ where (l_i, u_i) denotes lower and upper 95% confidence intervals for θ_i, as described by Newcombe and Altman.

We used SAS-callable SUDAAN for statistical analysis. Identified associations were evaluated at the 0.05 significance level. Our data contained an effective sample size of 8,393 live born infants in the state of Georgia born from January 1, 2008 to December 31, 2008.

Results

A total of 8,393 women were included in the study. Influenza vaccine information was available for 5422 (64.6%) women; of these 916 (16.9%) women had received the influenza vaccine during pregnancy.

The odds of having received influenza vaccine during pregnancy were lower for women with maternal medical risk factors (OR=0.73; 95% CI, 0.55-0.96), women with hypertension (OR=0.59; 95% CI, 0.35-0.97), and woman who receive WIC (OR=0.68; 95% CI, 0.54-0.86) (Table 1). Woman with a maternal age less than 19 years (OR=1.70; 95% CI, 1.13-2.55), heath care coverage (OR=1.45; 95% CI, 1.15-1.84), and married (OR=1.30; 95% CI, 1.03-1.65) were more likely to have received the influenza vaccine (Table 1). Gestational age at first prenatal visit was similar for vaccinated women and unvaccinated women (mean: 9.8 weeks vs. 10.8 weeks; p= 0.12), and maternal weight before pregnancy was similar for vaccine recipients and non-recipients (mean: 148.7 lbs versus 152.0 lbs; p= 0.13) (Table 2).

Based on the approach of identifying covariates that produce adjusted IDRs of 1 during the pre-influenza period, the group of covariates in the influenza multivariate models included gestational age for first antenatal visit, maternal age less than 19 years, maternal age more than 35 years, maternal medical risk factors, maternal diabetes, maternal smoking, WIC during pregnancy, married, and black race. The covariates in the pneumonia multivariate models included gestational age for first antenatal visit, maternal age less than 19 years, maternal age more than 35 years, maternal medical risk factors, medical insurance, multivitamin use in pregnancy, maternal smoking, WIC during

pregnancy, married, and black race. In our propensity score analysis, variables which were matched on included gestational age for first antenatal visit, maternal age less than 19 years, maternal age more than 35 years, maternal medical risk factors, maternal diabetes, maternal hypertension, maternal smoking, married, and black race.

The adjusted and unadjusted IDRs were not significant for the association between receipt of maternal influenza vaccine and incidence rate of ILI for any of the influenza activity period or for the analysis without consideration of influenza activity. During the putative influenza season (1 October–31 May), infants whose mothers were vaccinated against influenza during pregnancy had a higher incidence rate of ILI than infants of unvaccinated mothers (adjusted IDR=0.91; 95% CI, 0.60-1.38) (Table 3). The magnitude of effect of maternal influenza vaccine on ILI increased during the period when there was at least local influenza activity in any part of the state (adjusted IDR=0.80; 95% CI, 0.50-1.29), at least regional activity (adjusted IDR=0.84; 95% CI, 0.52-1.35) and widespread influenza activity (adjusted IDR=0.87; 95% CI, 0.52-1.47) (Table 3).

In the unadjusted, primary adjusted, and propensity score models, the magnitude of effect of maternal influenza vaccine on influenza-like illness was much stronger for breastfed newborns compared to newborns who were not breastfed during the period of at least local influenza activity (adjusted IDR=0.66; 95% CI, 0.35-1.25 [breastfed] vs. IDR=1.02; 95% CI, 0.56- 1.86 [not breastfed]), at least regional influenza activity (adjusted IDR=0.71; 95% CI, 0.37-1.34 [breastfed] vs. IDR=0.91; 95% CI, 0.49- 1.69 [not breastfed]), and widespread influenza activity (adjusted IDR=0.70; 95% CI, 0.34-

1.45 [breastfed] vs. IDR=0.83; 95% CI, 0.44-1.58 [not breastfed]) (Table 4). There was not a significant difference in the strength of association between breastfed infants and infants who were not breastfed.

The IDRs were also not significant for the association between receipt of maternal influenza vaccine and incidence rate of LRTI. During the putative influenza season infants whose mothers were vaccinated against influenza during pregnancy had a higher incidence rate of LRTI than infants of unvaccinated mothers (adjusted IDR=0.80; 95% CI, 0.46-1.39) (Table 5). The magnitude of effect of maternal influenza vaccine on LTRI increased during the period when there was at least local influenza activity (adjusted IDR=0.63; 95% CI, 0.35-1.12), at least regional activity (adjusted IDR=0.64; 95% CI, 0.36-1.14) and widespread influenza activity (adjusted IDR=0.79; 95% CI, 0.43-1.48) (Table 5).

For the putative influenza season, the magnitude of effect of maternal influenza vaccine on LTRI was greater in breastfed infants (adjusted IDR=0.62; 95% CI, 0.30-1.27) compared to infants who were not breastfed (adjusted IDR=1.00; 95% CI, 0.49-2.02) (Table 6). There was not a significant difference in the strength of association between breastfed infants and infants who were not breastfed. Presence of breastfeeding did not influence the magnitude of effect of maternal influenza vaccine on LRTI for any of other the influenza activity period or for the analysis without consideration of influenza activity.

Discussion

Our findings were not significant for the association between receipt of maternal influenza vaccine and respiratory outcomes among breastfed and non-breastfed infants for any of the influenza activity period or for the analysis without consideration of influenza activity.

However, this study does demonstrate that there is a stronger association between immunization with the inactivated influenza vaccine during pregnancy and reduced likelihood of ILI among breastfed infants compared to infants who were not breastfed. The magnitude of association during local, regional, and widespread influenza activity periods (measured by the values of IDRs) were higher among breastfed infants than infants who were not breastfed. Although the IDRs were not statistically significant between breastfed and non-breastfed groups, there was a consensus among the unadjusted, primary adjusted, and propensity score models which showed an overall increase of effect in the point estimates among breastfed infants.

The presence of breastfeeding only influenced the magnitude of effect of maternal influenza vaccine on LRTI during the putative influenza season. However, our study failed to demonstrate an effect of breastfeeding on the association between maternal immunization with the influenza vaccine and LRTI during local, regional, and widespread influenza activity period and for the analysis without consideration of influenza activity. There were conflicting results among the different models. The lack of an observed effect could have been due to small or difficult to measure effect size and challenges related to the study population.

Our study supports the ACIP recommendation for routine vaccination of woman who will be pregnant during influenza season and the American Academy of Pediatrics recommendation to breastfeed infants.[27, 28] More efforts need to be made to encourage countries to increase influenza immunization rates in pregnant women, a high risk population with a substantial burden of influenza-related morbidly and mortality, and increase the presence of breastfeeding to provide greater protection against infant respiratory illness.

Maternal immunization with the influenza vaccine has significant effectiveness in protecting infants against influenza.[7, 9] Several studies have demonstrated that the neonates are protected from influenza virus infection through transplacentally acquired antibody after influenza infection or vaccination during pregnancy.[8, 29] Maternal antibodies acquired through vaccination which cross the placenta via active transport from the mother to the fetus have been shown to provide infants protection during the first few months of life, when their immune system is not yet fully developed and functioning.[7, 8] Protection against influenza virus infection is correlated with levels of mucosal immunoglobulin A in the respiratory tract and serum immunoglobulin.[10] Such critical protection includes virus-specific immune responses with immunoglobulin production, cellular immune responses, and specific anti-viral cytokines. There has also been evidence that breast milk contains influenza specific antibodies, acquired through maternal influenza vaccination, which provides infants protection from respiratory infection.[11]

Maternal immunization is an effective way to increase levels of influenza-specific antibodies in maternal serum and breast milk, providing passive protection to the infant in the months after birth, before the infant's immune system is fully developed and before many childhood vaccines can be administered. There has been epidemiological evidence that maternal vaccination and the presence breastfeeding provide greater protection than just vaccination or breastfeeding alone. In a recent maternal vaccine trial in Dhaka, Bangladesh, researchers discovered that there was a significant, independent reductions of respiratory infection with fever in infants who were exclusively breastfed (nearly 40% reduction compared with not exclusively breastfed) and infants of mothers who received the influenza vaccine (28% reduction compared with pneumococcal vaccine).[12] Exclusively breastfed infants whose mothers received influenza vaccine while pregnant had the lowest incidence of respiratory infection with fever.

Strengths and limitations

There were numerous strengths to our study. Since this was a population-based study with a sampling strategy designed to produce representative estimates, the distribution of influenza vaccination in pregnancy would be similar to that of the general population, hence adding to the generalizability of our findings. In order to address confounding, we used the pre-influenza period (i.e., the season where vaccine was available but there was minimal circulation of influenza virus) as the ‘‘control’’ period. The use of the pre-influenza period for selecting confounders from a broad set of covariates is an approach suggested by Nelson et al. and Jackson et al. which takes advantage of the seasonality of influenza circulation.[24, 25] The associations observed in our study were robust in adjustment for confounders identified using this approach thus

supporting the validity of our findings. The use of propensity score is an effective strategy from alternative designs and an optimal method for analyzing causal questions with large datasets.[22] Propensity score matching are robust to choice-based sampling and usually outperforms other matching techniques because it balances on many covariates simultaneously, which can potentially approximate the balance achieved through randomization.

This study has few limitations. Although we assessed and adjusted for many covariates, like any observational study, there is a possibility of residual confounding and selection bias. Moreover, data on influenza and pneumonia infection during pregnancy were not included in the PRAMS dataset. Although the primary explanation of the effects of influenza immunization in pregnancy on respiratory infection is through prevention of infection, having laboratory confirmed influenza and pneumonia infection data would have provided additional support for our findings. Another issue was that the information regarding maternal influenza immunization was based on recall and could be susceptible to information bias. However, the vaccination rates in our study were similar to the rates computed by other authors for Georgia, and to the United States national level coverage estimated by the National Health Interview Survey.[30, 31] The PRAMS dataset did not contain information regarding the precise trimester of vaccination. Therefore, the effect of vaccination in a specific trimester could not be evaluated.

The study also lacked a sufficient sample size to evaluate the effect of maternal vaccination on exclusive breastfed infant. Multiple studies have found that fully breastfed infants have been shown to have lower overall illness rates, whereas minimal

breastfeeding has not been found to be protective.[32] Full breastfeeding for more than 6 months provides greater protection against respiratory tract infection that does full breastfeeding for only 4 to less than 6 months.[33] It is plausible that the association between immunization with the inactivated influenza vaccine during pregnancy and reduced likelihood of ILI may be much stronger among exclusive breastfed infants. We may also observe an effect of exclusive breastfeeding on the association between maternal immunization with the influenza vaccine and LRTI. The results of this study, nevertheless, need to be replicated in a larger population to assess the association between maternal vaccination and respiratory illness among infants who are exclusively breastfed for more than 6 months, infants who were minimally breastfed, and infants who were not breastfed.

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Table 1. Receipt of influenza vaccine during pregnancy categorized by maternal characteristics.

Characteristics	Maternal Demographic Category (Yes)		Maternal Demographic Category (No)		p-value	OR (95% CI) [a]
	Vaccinated [b] [n (%)]	Total [c] [n (%)]	Vaccinated [b] [n (%)]	Total [c] [n (%)]	Wald Chi 2	
Maternal age less than 19 y	98 (27.3)	432 (7.6)	818 (18.1)	4990 (92.4)	0.025	1.70 (1.13, 2.55)
Maternal age more than 35 y	98 (21.6)	536 (9.6)	818 (18.5)	4886 (90.4)	0.318	1.21 (0.85, 1.74)
Multiple births	74 (19.7)	422 (1.9)	841 (18.8)	4992 (98.2)	0.832	1.06 (0.62, 1.80)
Labor/delivery complications [e]	302 (20.0)	1753 (31.6)	384 (16.6)	2494 (68.4)	0.108	1.26 (0.96, 1.66)
Maternal medical risk factors [d]	253 (15.3)	1696 (24.4)	640 (19.9)	3601 (75.6)	0.017	0.73 (0.55, 0.96)
Birth defect	24 (16.3)	118 (1.0)	838 (19.0)	5003 (99.0)	0.564	0.84 (0.44, 1.57)
Maternal Diabetes	24 (16.7)	131 (2.1)	869 (18.8)	5166 (98.0)	0.712	0.87 (0.39, 1.91)
Maternal Hypertension	57 (12.1)	404 (3.4)	836 (19.0)	4893 (96.6)	0.022	0.59 (0.35, 0.97)
Mother insured	507 (21.6)	2644 (50.8)	408 (15.9)	2768 (49.2)	0.002	1.45 (1.15, 1.84)
Multivitamin use in pregnancy	821 (19.5)	4721 (88.0)	87 (14.1)	656 (12.0)	0.032	1.48 (0.99, 2.21)
Smoking during pregnancy	47 (13.5)	381 (5.9)	863 (19.1)	5011 (94.1)	0.097	0.66 (0.38, 1.15)
Alcohol use during pregnancy	9 (47.0)	32 (0.6)	671 (17.5)	4184 (99.4)	0.116	4.19 (1.38, 12.74)
WIC in pregnancy	456 (16.0)	3002 (52.5)	449 (21.9)	2332 (47.5)	0.001	0.68 (0.54, 0.86)
Black Race	401 (16.5)	2563 (30.1)	515 (19.8)	2857 (70.0)	0.073	0.80 (0.63, 1.03)
Education less than 12th grade	167 (21.0)	889 (19.5)	679 (18.1)	4184 (80.5)	0.248	1.21 (0.89, 1.65)
Mother married	498 (20.5)	2854 (57.6)	414 (16.5)	2546 (42.4)	0.027	1.30 (1.03, 1.65)
Maternal Breastfeeding	261 (15.2)	1611 (29.7)	617 (20.5)	3531 (70.3)	0.005	0.69 (0.53, 0.91)

All percentages calculated with analytical weights.

[a] Ratio of the odds of having received influenza vaccine by mothers in each binary (yes/no) category of a covariate, e.g., the odds of having received an influenza vaccine were 30% higher among married women than among unmarried women.

[b] Number and proportion of mothers in each of the binary (yes/no) category of a covariate who received the influenza vaccine, e.g. 16.5% of unmarried mothers had received the influenza vaccine compared to 20.5% of married women.

[c] Total (and weighted percent) of respondents with ''Yes'' or ''No'' in a maternal/demographic characteristic category (out of all respondents).

[d] Medical risk factors include acute or chronic lung disease; anemia; cardiac disease; diabetes; eclampsia; genital herpes; hemoglobinopathy; hydraminos/oligohydraminos; chronic hypertension; pregnancy-induced hypertension, incompetent cervix; previous infant >4,000g; previous preterm, SGA, or low birth weight delivery; renal disease; Rh sensitization; rubella; syphilis; and uterine bleeding.

[e] Labor/delivery complications include abruptio placenta, anesthetic complications, breech presentation, cephalo-pelvic disproportion, cord prolapse, dysfunctional labor, excessive bleeding, febrile (100uF/38uC), fetal distress, moderate to heavy meconium staining, placenta previa, labor <3 h, premature rupture of membranes >12 h, labor >20 h, and seizures during labor.

Table 2. Receipt of influenza vaccine during pregnancy by infant and maternal characteristics.

Variable		Maternal Receipt of Influenza Vaccine				
	Overall Mean (SD) n=5422	Vaccinated Mean (SD)	n=916	Not vaccinated Mean (SD)	n=4506	p-value
Maternal age	26.9 (0.14)	27.3 (0.35)	916	26.8 (0.15)	4506	0.171
Maternal BMI	25.8 (0.15)	25.2 (0.34)	851	25.9 (0.16)	4242	0.073
Maternal Weight before pregnancy (lbs)	151.4 (0.88)	148.7 (1.93)	884	152.0 (0.98)	4379	0.132
Gestational age at first prenatal care visit (wks)	10.6 (0.30)	9.8 (0.56)	885	10.8 (0.34)	4353	0.115
Birth weight (gram)	3241.9 (10.18)	3253.2 (23.58)	905	3239.3 (11.54)	4438	0.603
Gestational age (wks)	38.4 (0.04)	38.4 (0.12)	908	38.4 (0.03)	4466	0.967
Gestational age (days)	271.8 (0.49)	272.6 (0.64)	830	271.6 (0.58)	4113	0.298
Breastfeeding duration (wks)	56.6 (0.85)	55.7 (2.03)	873	56.8 (0.93)	4199	0.631

All means and standard errors calculated with analytical weights.

Table 3. Association between Maternal influenza vaccination and rate of Influenza like illnesses in their infants (2005 – 2008).

Analysis period	Unadjusted model	Primary adjusted [a]	Propensity score [b]
	OR (95% CI) [c]	OR (95% CI) [c]	OR (95% CI) [c]
All Seasons/ periods	0.96 (0.63, 1.48)	1.10 (0.74, 1.62)	0.97 (0.66, 1.42)
Putative influenza period	0.82 (0.52, 1.28)	0.91 (0.60, 1.38)	0.83 (0.55, 1.24)
Pre-influenza period	1.00 (0.60, 1.67)	1.00 (0.63, 1.60)	1.00 (0.64, 1.57)
Period of at least local influenza activity	0.73 (0.43, 1.24)	0.80 (0.50, 1.29)	0.72 (0.43, 1.19)
Period of at least regional influenza activity	0.74 (0.43, 1.28)	0.84 (0.52, 1.35)	0.76 (0.45, 1.27)
Period of widespread influenza activity	0.88 (0.46, 1.68)	0.87 (0.52, 1.47)	0.85 (0.45, 1.61)

[a] The primary adjusted models were based on the approach of identifying covariates that produced adjusted IDRs closest to 1 during the pre-influenza period and included the following covariates: gestational age for first antenatal visit, maternal age less than 19 years, maternal age more than 35 years, maternal medical risk factors, maternal diabetes, maternal smoking, WIC during pregnancy, married, and black race.

[b] Propensity scores were calculated using the following covariates: gestational age for first antenatal visit, maternal age less than 19 years, maternal age more than 35 years, maternal medical risk factors, maternal diabetes, maternal hypertension, maternal smoking, married, and black race.

[c] Ratio of the incidence rate of prematurity in newborns of mothers who received influenza vaccine during pregnancy compared to mothers who did not receive the vaccine by intensity of influenza activity, e.g., in the analysis of all seasons/periods, the (unadjusted) incidence rate of prematurity were 25% lower among the infants of mothers who received the influenza vaccine during pregnancy than among infants whose mothers who did not receive the vaccine.

Table 4. Association between Maternal influenza vaccination and rate of Influenza like illnesses in their infants by presence of breastfeeding (2005 – 2008).

	Breastfed Infants			Non-Breastfed Infants		
Analysis period	**Unadjusted**	**Primary adjusted**	**Propensity score**	**Unadjusted**	**Primary adjusted**	**Propensity score**
	OR (95% CI) [c]	**OR (95% CI) [c]**	**OR (95% CI) [c]**	**OR (95% CI) [c]**	**OR (95% CI) [c]**	**OR (95% CI) [c]**
All Seasons/ periods	1.07 (0.57, 1.99)	0.97 (0.55, 1.69)	1.11 (0.63, 1.98)	0.99 (0.55, 1.80)	1.32 (0.79, 2.19)	0.91 (0.52, 1.61)
Putative influenza period	0.71 (0.36, 1.41)	0.65 (0.35, 1.22)	0.71 (0.38, 1.33)	1.08 (0.58, 1.99)	1.41 (0.83, 2.41)	1.04 (0.58, 1.86)
Pre-influenza period	1.00 (0.47, 2.15)	1.00 (0.51, 1.98)	1.00 (0.50, 2.01)	1.00 (0.49, 2.04)	1.00 (0.55, 1.83)	1.00 (0.52, 1.94)
Period of at least local influenza activity	0.74 (0.37, 1.48)	0.66 (0.35, 1.25)	0.74 (0.39, 1.41)	0.93 (0.40, 2.17)	1.02 (0.56, 1.86)	0.83 (0.35, 1.94)
Period of at least regional influenza activity	0.76 (0.38, 1.54)	0.71 (0.37, 1.34)	0.81 (0.42, 1.54)	0.92 (0.38, 2.23)	0.91 (0.49, 1.69)	0.83 (0.34, 2.00)
Period of widespread influenza activity	0.83 (0.36, 1.89)	0.70 (0.34, 1.45)	0.82 (0.39, 1.71)	1.15 (0.42, 3.19)	0.83 (0.44, 1.58)	0.99 (0.34, 2.84)

[a] The primary adjusted models were based on the approach of identifying covariates that produced adjusted IDRs closest to 1 during the pre-influenza period and included the following covariates: gestational age for first antenatal visit, maternal age less than 19 years, maternal age more than 35 years, maternal medical risk factors, maternal diabetes, maternal smoking, WIC during pregnancy, married, and black race.

[b] Propensity scores were calculated using the following covariates: gestational age for first antenatal visit, maternal age less than 19 years, maternal age more than 35 years, maternal medical risk factors, maternal diabetes, maternal hypertension, maternal smoking, married, and black race.

[c] Ratio of the incidence rate of prematurity in newborns of mothers who received influenza vaccine during pregnancy compared to mothers who did not receive the vaccine by intensity of influenza activity, e.g., in the analysis of all seasons/periods, the (unadjusted) incidence rate of prematurity were 25% lower among the infants of mothers who received the influenza vaccine during pregnancy than among infants whose mothers who did not receive the vaccine.

Table 5. Association between Maternal influenza vaccination and rate of Lower Respiratory Tract Infection in their infants (2005 – 2008).

Analysis period	Unadjusted model	Primary adjusted	Propensity score
	OR (95% CI) [c]	OR (95% CI) [c]	OR (95% CI) [c]
All Seasons/ periods	0.80 (0.42, 1.54)	0.92 (0.55, 1.54)	0.86 (0.50, 1.49)
Putative influenza period	0.70 (0.36, 1.38)	0.80 (0.46, 1.39)	0.73 (0.41, 1.30)
Pre-influenza period	1.00 (0.47, 2.13)	1.00 (0.56, 1.79)	1.00 (0.53, 1.88)
Period of at least local influenza activity	0.57 (0.28, 1.18)	0.63 (0.35, 1.12)	0.59 (0.31, 1.12)
Period of at least regional influenza activity	0.60 (0.29, 1.23)	0.64 (0.36, 1.14)	0.61 (0.32, 1.17)
Period of widespread influenza activity	1.01 (0.46, 2.21)	0.79 (0.43, 1.48)	0.91 (0.44, 1.89)

[a] The primary adjusted models were based on the approach of identifying covariates that produced adjusted IDRs closest to 1 during the pre-influenza period and included the following covariates: gestational age for first antenatal visit, maternal age less than 19 years, maternal age more than 35 years, maternal medical risk factors, medical insurance, multivitamin use in pregnancy, maternal smoking, WIC during pregnancy, married, and black race.

[b] Propensity scores were calculated using the following covariates: gestational age for first antenatal visit, maternal age less than 19 years, maternal age more than 35 years, maternal medical risk factors, maternal diabetes, maternal hypertension, maternal smoking, married, and black race.

[c] Ratio of the incidence rate of prematurity in newborns of mothers who received influenza vaccine during pregnancy compared to mothers who did not receive the vaccine by intensity of influenza activity, e.g., in the analysis of all seasons/periods, the (unadjusted) incidence rate of prematurity were 25% lower among the infants of mothers who received the influenza vaccine during pregnancy than among infants whose mothers who did not receive the vaccine.

Table 6. Association between Maternal influenza vaccination and rate of Lower Respiratory Tract Infection in their infants by presence of breastfeeding (2005 – 2008).

	Breastfed Infants			Non-Breastfed Infants		
Analysis period	**Unadjusted**	**Primary adjusted**	**Propensity score**	**Unadjusted**	**Primary adjusted**	**Propensity score**
	OR (95% CI) [c]	**OR (95% CI) [c]**	**OR (95% CI) [c]**	**OR (95% CI) [c]**	**OR (95% CI) [c]**	**OR (95% CI) [c]**
All Seasons/ periods	0.86 (0.37, 1.97)	0.79 (0.41, 1.55)	0.92 (0.46, 1.82)	0.77 (0.29, 2.00)	0.92 (0.48, 1.76)	0.72 (0.26, 1.98)
Putative influenza period	0.62 (0.25, 1.50)	0.62 (0.30, 1.27)	0.67 (0.32, 1.39)	0.95 (0.35, 2.55)	1.00 (0.49, 2.02)	0.84 (0.30, 2.37)
Pre-influenza period	1.00 (0.38, 2.63)	1.00 (0.47, 2.12)	1.00 (0.45, 2.24)	1.00 (0.31, 3.23)	1.00 (0.54, 1.84)	1.00 (0.29, 3.42)
Period of at least local influenza activity	0.57 (0.23, 1.40)	0.59 (0.29, 1.23)	0.62 (0.29, 1.32)	0.64 (0.18, 2.26)	0.35 (0.18, 0.68)	0.51 (0.13, 1.94)
Period of at least regional influenza activity	0.59 (0.24, 1.45)	0.61 (0.30, 1.27)	0.64 (0.30, 1.36)	0.67 (0.19, 2.38)	0.35 (0.18, 0.68)	0.54 (0.14, 2.03)
Period of widespread influenza activity	1.12 (0.42, 3.01)	0.81 (0.36, 1.82)	0.95 (0.41, 2.19)	0.97 (0.26, 3.60)	0.33 (0.16, 0.69)	0.74 (0.18, 3.03)

[a] The primary adjusted models were based on the approach of identifying covariates that produced adjusted IDRs closest to 1 during the pre-influenza period and included the following covariates: gestational age for first antenatal visit, maternal age less than 19 years, maternal age more than 35 years, maternal medical risk factors, medical insurance, multivitamin use in pregnancy, maternal smoking, WIC during pregnancy, married, and black race.

[b] Propensity scores were calculated using the following covariates: gestational age for first antenatal visit, maternal age less than 19 years, maternal age more than 35 years, maternal medical risk factors, maternal diabetes, maternal hypertension, maternal smoking, married, and black race.

[c] Ratio of the incidence rate of prematurity in newborns of mothers who received influenza vaccine during pregnancy compared to mothers who did not receive the vaccine by intensity of influenza activity, e.g., in the analysis of all seasons/periods, the (unadjusted) incidence rate of prematurity were 25% lower among the infants of mothers who received the influenza vaccine during pregnancy than among infants whose mothers who did not receive the vaccine.