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Seasonal Influenza Vaccination during Pregnancy and the Risks of Preterm Delivery and Small for Gestational Age Birth

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Abstract

Background—Influenza vaccination is routinely recommended for pregnant women, yet information on perinatal outcomes is sparse.

Methods—We investigated the associations between trivalent (seasonal) influenza vaccination during pregnancy and the risks of preterm delivery (PTD, live birth <37 weeks gestation) and small for gestational age birth (SGA, <10th percentile in weight for sex-specific gestational age) during the influenza seasons 2006–07 through 2009–10. The study population included 1619 mothers of live-born, non-malformed singleton infants interviewed as part of the Slone Epidemiology Center's Birth Defects Study. Associations between influenza vaccination and PTD and SGA were assessed using Cox and logistic regression models, respectively, with propensity scores used to adjust for confounding. Women vaccinated against pandemic H1N1 were excluded from the analysis.

Results—Influenza vaccination during pregnancy showed a near null association with PTD for influenza seasons 2006–07 through 2008–09 compared with unvaccinated women [adjusted hazard ratios (aHR) ranged from 0.79 [95% confidence interval (CI) 0.28, 2.21] in 2007–08 to 1.08 [95% CI: 0.40, 2.95] in 2008–09]. For 2009–10, the risk of PTD was higher in vaccinated women (aHR, 7.81 [95% CI: 2.66, 23.0]). Influenza vaccination was not associated with appreciable risks for SGA for all seasons with sufficient numbers of exposed SGA.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Preterm delivery and maternal characteristics among vaccinated mothers of non-malformed infants participating in the Slone Epidemiology Center's Birth Defect Study by influenza season.

Table S2. Preterm delivery and maternal characteristics among non-vaccinated mothers of non-malformed infants participating in the Slone Epidemiology Center's Birth Defect Study by influenza season.

Table S3. Pregnancy duration and influenza vaccination among mothers of non-malformed infants

Table S4. Association of seasonal influenza vaccination (with or without monovalent pH1N1 vaccination) during pregnancy with the risks of preterm delivery (PTD) and small for gestational age (SGA) among mothers of non-malformed infants.

Table S5. Association of influenza vaccination during pregnancy with the risk of preterm delivery (PTD) among mothers of non-malformed infants, stratified by influenza season and by trimester of pregnancy

Table S6. Association of influenza vaccination during pregnancy with the risk of small for gestational age (SGA) among mothers of non-malformed infants, stratified by influenza season and by trimester of pregnancy.

Conclusion—Though limited by study size, these findings add support to previous observations of little or no increased risk of PTD or SGA associated with seasonal influenza vaccination for three of the four influenza seasons in our study. The increased risk of PTD observed for the 2009–10 influenza season warrants further investigation.

Keywords

infant; small for gestational age; influenza; pregnancy; preterm birth; vaccination

The Centers for Disease Control and Prevention and the American Congress of Obstetricians and Gynecologists recommend seasonal influenza vaccination for all women who will be pregnant during the influenza season in order to reduce their considerably increased risk of influenza-related mortality and morbidity.^{1–3} Nonetheless, vaccination rates among pregnant women in the US remain lower than ideal.^{4,5} Pregnant women may be reluctant to be vaccinated because of concern that the vaccine may harm them or their babies.^{4,6,7} There is limited evidence regarding risks associated with influenza vaccination during pregnancy, partly because pregnant women are typically excluded from clinical trials,^{8,9} leaving a gap in knowledge that can affect vaccine uptake.

Two of the most common adverse pregnancy outcomes are preterm delivery (PTD) and small for gestational age birth (SGA). PTD (live birth before 37 weeks gestation) and SGA (<10th percentile in weight for gestational age) are associated with increased perinatal mortality and both short- and long-term morbidity.^{10–12} Previous studies of seasonal influenza vaccination during pregnancy have found null or protective associations for PTD and SGA,^{13,14} but they have often relied on medical records for exposure assessment, collected limited information on the gestational timing of the vaccination, studied few first trimester exposures, and/or have not evaluated risks by influenza season. The last concern is important since antigens and manufacturing processes vary by season and risks may similarly vary.

We sought to examine the associations between seasonal influenza vaccination [and not pandemic H1N1 (pH1N1) vaccination] during pregnancy and the risks of PTD and SGA among a multiyear retrospective cohort of pregnancies resulting in live-born, non-malformed singleton infants. Exposure to influenza vaccination during pregnancy was obtained by self-report, thereby capturing vaccinations received both inside and outside traditional medical provider settings. Vaccination date was also collected, permitting consideration of the gestational timing of vaccination.

Methods

Study population

The Birth Defects Study (BDS), also known as the Pregnancy Health Interview Study, is an ongoing case-control study conducted by the Slone Epidemiology Center at Boston University since 1976.^{15,16} Cases include infants diagnosed with at least one major structural malformation. Controls include live-born infants without any malformations. For the study years included in this analysis (2006–10), malformed infants and controls were

identified from study hospitals serving the areas surrounding Philadelphia and San Diego, as well as Rhode Island, Southern New Hampshire, and (via the New York State Congenital Malformations Registry) parts of New York State. In Massachusetts, cases were identified through its statewide birth defect registry and controls from a population-based random sample of births. This study has been approved by the Institutional Review Boards of Boston University and relevant participating institutions, as appropriate.

Influenza vaccination exposure

Mothers of cases and controls were interviewed by telephone within 6 months of pregnancy completion by a study nurse about demographic, reproductive, medical and behavioural factors, including the dates of their last menstrual period (LMP) and delivery. Beginning in July 2006, mothers were asked if they received any vaccines, 'such as tetanus, pertussis, whooping cough, meningitis, flu shot or any other vaccine' between 2 months before their LMP and the end of the pregnancy. The type and date of vaccination were ascertained, as well as the setting where the vaccine was administered. If the exact date of vaccination was not known, the respondent was asked if it was the beginning, middle, or end of the month and the 5th, 15th, or 25th day of that month was recorded, respectively. Women who were only able to specify a more general range of dates provided the start and end dates of this range. All women who reported receiving an influenza vaccination during pregnancy were asked to provide a release to enable study staff to obtain their vaccine record; approximately 60% of women complied with this request.

Reports of seasonal trivalent influenza vaccination were categorised according to the timing of receipt: anytime during pregnancy (LMP to day before delivery), first trimester (LMP through 14 weeks), second trimester (greater than 15 through 28 weeks), and third trimester (greater than 29 weeks to day before delivery). To maximise the accuracy of gestational timing of exposure, we limited our analyses to women who could be assigned a single trimester of exposure, using the hierarchy of the date from the vaccine provider, then the subject's reported vaccination date, and then the mid-point of the subject's reported exposure date range if that date range spanned only one trimester. Influenza season was determined by vaccination date between August 1 and July 31 of the following year (e.g. a vaccination date of 15 September 2007 or 3 March 2008 was considered a '2007–08' influenza season exposure). To ensure equal opportunity for exposure among non-exposed subjects, we included only non-exposed subjects whose LMP dates fell within the range of LMP dates reported by exposed subjects; the reference group for all analyses was women without reports of any influenza vaccination (which included pH1N1 vaccination for the 2009–10 season) between 2 months before and the end of the pregnancy.

Influenza-like illness (ILI)

In July 2009, assessment of ILI during pregnancy was added to the BDS interview by asking the mother if she had any 'flu or flu-like illness' during pregnancy. If she replied affirmatively, further details were obtained such as start and end date, duration, specific symptoms, test results, and medication used. For this analysis, ILI was defined as any self-report of flu or flu-like illness.

Pregnancy outcomes

Gestational age at delivery and birthweight were obtained by self-report from the mother during the interview. Gestational age was determined by calculating the difference between the LMP and the day of delivery. If the self-reported LMP date differed by more than 7 days from the LMP date calculated from the reported ultrasound-determined due date, then the latter LMP date was used to calculate gestational age. If the self-reported LMP date differed by 7 days or less from the LMP calculated from the due date, we chose to use the self-reported LMP date because it was a date familiar to the mother and raised less confusion during the course of the interview. SGA was based on the sex-specific distribution of birthweights of infants born in the US in 1999–2000.^{17,18}

Study population

Because PTD and SGA are associated with birth defects, we restricted our study to mothers of live-born non-malformed infants (the BDS control group). To estimate seasonal influenza coverage by season and study site, we included women who had opportunity for prenatal exposure to seasonal influenza vaccines during the four seasons for which we had complete information: 2006–07, 2007–08, 2008–09, and 2009–10.

For the risk analyses, we excluded 385 women who reported exposure to the pH1N1 monovalent vaccine in 2009–10 (either alone or in combination with seasonal influenza vaccination) or pH1N1 trivalent vaccine in 2010–11, so that exposure and referent groups were consistent across study years; further, our findings for pH1N1 have been published.¹⁹ Additional exclusions for the risk analyses included: known infant deaths, which were not systematically ascertained ($n = 2$); women with multifetal gestations ($n = 47$); subjects with missing birthweight ($n = 6$); and reports of implausible gestational age (<25 or >42 weeks gestation, $n = 2$). Analyses also excluded women for whom we could either not distinguish seasonal from pH1N1 vaccination in 2009–10 ($n = 7$) or not assign a trimester of exposure based on their date ranges ($n = 78$), but for a sensitivity analysis, these women were included.

Statistical analysis

We considered our study participants to constitute a retrospective cohort of completed pregnancies.^{20,21} Thus, we modelled the hazard of PTD using Cox regression with influenza vaccination as a time-varying exposure; gestational age, in days beginning at LMP, was the timescale.^{22,23} Full-term pregnancies were censored at 37 weeks gestation and women with vaccination later than 37 weeks were excluded ($n = 24$). Models were run separately by trimester of vaccination. Linear regression models were used to evaluate the difference in gestational length (in days) by exposure status. The outcome of SGA was a dichotomous, compound measure that incorporated gestational age; therefore, logistic regression was chosen as the appropriate regression model. These models were also run separately by trimester of vaccination and included influenza vaccinations up until the day before delivery.

Propensity scores were used as covariates in the regression analysis to adjust for confounding and variable selection for the propensity score models was based on c-statistics. Variables included in the propensity score were maternal age at conception, race, education,

family income, marital status, parity, study centre, pre-pregnancy body mass index, family history of birth defects, pregnancy intention, periconceptional folic acid use, alcohol use, smoking, asthma, diabetes, calendar quarter of LMP, infertility treatment, treatment for high blood pressure or toxemia, inter-pregnancy interval, illicit drug use, gestational weight gain, prenatal care initiation in first trimester, history of miscarriage, and employment outside the home. The BDS interview does not identify history of PTD. Inclusion of additional factors and several two-way interaction terms between smoking, asthma, prenatal care initiation, and pregnancy intention did not affect the score's ability to predict exposure (i.e. c-statistic changed <1%). Adjusted analyses were only conducted when the number of exposed cases was four or greater.

For 2009–10, the only influenza season for which we had this information, reports of ILI were tallied by seasonal influenza vaccination exposure status and an odds ratio was calculated. For women vaccinated against seasonal influenza, only reports of ILI occurring after vaccination were included. The association between ILI and preterm birth was calculated as an odds ratio.

All analyses were conducted with SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Overall, 2136 mothers of live-born non-malformed infants were included in estimates of seasonal influenza vaccination coverage for influenza seasons 2006–07 through 2009–10. For our analytical cohort of pregnancy outcomes, the previously mentioned study exclusions were applied (including exclusion of 385 women vaccinated against monovalent or trivalent pH1N1), resulting in 1619 study subjects. The majority of our study participants were white (60%, 964/1619), 25 years or older at time of conception (74%, 1203/1619), and had at least a high school education (89%, 1439/1619; Table 1). When we examined the demographic characteristics of women, by vaccine status, according to season, we observed differences for the 2009–10 season in race, age, study site, and calendar quarter of LMP among vaccinated women (Supporting Information Tables S1–6).

Influenza vaccination

Thirty per cent (637/2136) of women reported seasonal influenza vaccination during pregnancy for the four seasons collectively; for the 2006–07 through 2009–10 seasons, coverage was 18.4% (92/499), 19.6% (140/715), 19.5% (145/743), and 32.7% (261/799), respectively (one woman reported seasonal influenza vaccination for two consecutive seasons while pregnant; Figure 1). Coverage was on average higher in Massachusetts (38%) than other study sites (Philadelphia 25%, San Diego 23%, New York 33%). For our analytic cohort, in which gestational timing of vaccination was assessed, seasonal influenza vaccination was most commonly received during the second trimester of pregnancy (41%, 138/334), followed by the third trimester (34%, 114/334) and first trimester (25%, 82/334); 7% (24/334) of women reported an influenza vaccination after 37 weeks gestation.

Preterm delivery

In our analytical cohort, 6.6% ($n = 107/1619$) of pregnancies resulted in PTD (Table 2). Gestational age at delivery ranged from 25 to 42 weeks (median, 39). In all seasons collectively, compared with women who reported no influenza vaccination during pregnancy, those who were vaccinated at any time during pregnancy had an adjusted hazard ratio (aHR) of 1.37, with a 95% confidence interval (CI) that included the null. For vaccination during the first, second, and third trimesters, aHRs were 0.66, 1.46, and 1.53, respectively, with all CIs including the null. Findings changed minimally when we included as exposed the 85 women with either unknown influenza vaccination type or with a reported vaccination date range that spanned more than one trimester (data not shown). Stratification by influenza season (Table 3) revealed close to null associations with PTD for the 2006–07 through 2008–09 seasons (aHRs ranged from 0.79 in 2007–08 to 1.08 in 2008–09; all CIs included the null). For the 2009–10 influenza season, the risk of PTD was higher in vaccinated women (aHR = 7.81, [95% CI: 2.66, 23.0]); this risk was greatest for third trimester exposure (aHR = 9.78, [95% CI: 2.64, 36.2]; Supporting Information Tables S1–6). When we restricted the 2009–10 exposed group to the 15 women whose vaccination was confirmed by medical record, the aHR for exposure anytime during pregnancy remained largely unchanged (aHR = 7.32, [95% CI: 1.81, 29.6]). When we included the 154 women vaccinated against both seasonal and pH1N1 influenza that year, we observed an attenuated, but still elevated, risk of PTD (aHR = 3.54, [95% CI: 1.49, 8.41]; Supporting Information Tables S1–6). Overall, the average difference in gestational length of pregnancy between women vaccinated for seasonal influenza alone and those unvaccinated was -0.32 days [95% CI: -1.86 , 1.23] and for 2009–10, it was -6.22 days [95% CI: -10.5 , -1.94] (Supporting Information Tables S1–6).

Because we had no information about prior PTD, we repeated the analysis for 2009–10 stratified by parity. In primiparous women, the crude HR fell to 4.82 [95% CI 1.20, 19.3], but there were too few ($n = 3$) exposed PTD subjects to permit an adjusted analysis; in multiparous women the crude HR increased to 16.7 [95% CI 5.39, 52.0].

SGA

In our analytical cohort, 10.6% (172/1619) of infants were classified as SGA (Table 2). Compared with women reporting no influenza vaccination during pregnancy, those vaccinated at any time during pregnancy had no increased risk for SGA (aOR = 1.03, with a 95% CI that included the null) (Table 2). Women with influenza vaccination during the first, second, and third trimesters had aORs of 0.44, 1.53, and 1.00, respectively; all CIs included the null. Estimates of association with SGA varied for the 2007–08 through the 2009–10 seasons (Table 4); aORs ranged from 0.60 in 2009–10 to 1.40 in 2007–08, with all CIs including the null. AORs for the 2006–07 season could not be estimated because there were too few exposed SGA.

ILI and preterm delivery

For the 2009–10 season, ILI during pregnancy was reported by 3.1% (1/32) women vaccinated against seasonal influenza and 6.4% (22/346) of women not vaccinated (OR = 0.48, [95% CI 0.01, 3.16]). The risk of preterm birth was 4.3% (1/23) among women

reporting ILI and 5.6% (20/355) among women not reporting ILI (OR = 0.76, [95% CI 0.02, 5.24]).

Comment

Among a cohort of pregnancies resulting in singleton, live-born, non-malformed infants, influenza vaccination at any time during pregnancy showed a modest but unstable positive association with PTD. This overall risk was entirely caused by an almost eightfold increased risk in the 2009–10 season, with a CI whose lower bound appreciably excluded the null. For SGA, there was no evidence of an appreciably increased risk overall or for all seasons for which there were sufficient data to estimate risk. Influenza vaccination coverage among pregnant women increased from 2006–07 through 2009–10, which is consistent with national estimates for same period.²⁴

With the exception of our observed risk for PTD in the 2009–10 season, our study's results are in agreement with previous null findings from other studies focused on pre-pH1N1 seasonal influenza vaccination in pregnancy.^{25–29} However, they are not in agreement with recently observed protective associations for these outcomes.^{30,31} Our finding of an almost eightfold increased hazard for PTD associated with the 2009–10 seasonal influenza vaccination has not been previously reported. However, none of these previous studies included an examination of the seasonal trivalent vaccine for the 2009–10 influenza season.

We considered a number of possible explanations for our observed increased risk of PTD in the 2009–10 season. Over half of women vaccinated against influenza that year received the pH1N1 vaccine and were therefore excluded from our analysis, introducing the possibility of significant bias. In a post-hoc analysis, we included women vaccinated against both seasonal and pH1N1 influenza that year and observed an attenuated, but still elevated, risk of PTD. We also found differences in the demographic characteristics of women vaccinated against only seasonal influenza vaccine during the 2009–10 season compared with those vaccinated in previous years. However, our propensity score analysis adjusted for all of these demographic factors. It is also important to note that we did not have information on history of PTD; if such a history were more common among subjects in the 2009–10 season compared with previous seasons, it could confound the association we observed, as history of PTD could both influence the decision to get vaccinated and the risk of PTD in the index pregnancy. However, when we limited the 2009–10 analysis to primiparous women who could not have had a prior PTD, the risk, though attenuated, was still elevated. Unfortunately, numbers were too small (only three exposed PTD) to allow adjustment for other possible confounders. The question of residual confounding by PTD history remains unresolved among the multiparous women. Bias caused by misclassification is also possible, though we previously found that maternal reports of vaccination showed high positive and negative predictive values compared with vaccination records,³² and restricting the analysis to exposures confirmed by medical record had little effect on the overall increased risk. Finally, the elevated risk we observed for PTD in 2009–10 was based on only nine exposed cases overall and five in the third trimester, raising the possibility that our findings may be due to chance, though this seems unlikely based on the lower confidence bound of 2.7.

Strengths of our study include the collection of self-reported influenza vaccination exposure information and our rigorous analytical design. As 24% of influenza vaccinations in our study were provided outside of traditional medical settings (e.g. pharmacies, government flu clinics, schools, workplaces), studies that rely solely on vaccinations recorded in the medical record can result in exposure misclassification, which could bias estimates towards the null.³³ Where available, we were also able to use vaccination records to verify maternal reports and obtain accurate dates. Our comprehensive interview provided data on over 25 maternal risk factors that enabled us to create and evaluate propensity scores for our adjusted analyses. Further, we aligned pregnancies according to LMP, so that the unvaccinated comparison group had the same window of opportunity for influenza vaccination by trimester of pregnancy. In contrast, other studies have selected the unvaccinated comparison group based on the time of delivery, which would be affected by the gestational length of the pregnancy.^{26,34–36}

These considerations notwithstanding, it is noteworthy that the elevated risk for PTD was observed only in the one season (2009–10) when two influenza vaccines were available – the seasonal and pH1N1 strains. With the exception of two studies, other investigations related to that season have focused on pH1N1, without specific consideration of the risks that might be associated with that year's seasonal vaccine. The Vaccines and Medications in Pregnancy Surveillance System, a collaborative effort involving a pregnancy registry cohort (conducted by the Organization of Teratogen Information Specialists) and our case-control BDS, studied the pH1N1 vaccine in pregnancy, including both the 2009–10 season, when the pH1N1 was given as a separate monovalent vaccine, and subsequent years, when it was combined with the seasonal vaccine. The cohort arm identified a threefold increase in PTD risk associated with exposure to the pH1N1 vaccine in the years 2009–12 compared with women not exposed to any vaccine³⁷ (numbers were insufficient to consider risks for 2009–10 seasonal vaccine alone); in analyses of BDS data, for the 2009–10 season, we found a comparable threefold risk associated with exposure to the pH1N1 vaccine, whether or not women were also exposed to that year's seasonal vaccine;¹⁹ a subanalysis confined to the small proportion of women who received the pH1N1 vaccine alone revealed some attenuation in risk. Given that there was likely some misclassification of the two vaccines that year (particularly among women without medical vaccination records available), it is quite possible that the threefold risk observed for pH1N1 was in part explained by the eightfold risk we have now observed in association with that year's seasonal vaccine alone.

Biological explanations for an increased risk of PTD among the women vaccinated with the seasonal vaccine could include a greater susceptibility to pH1N1 infection (conferring an increased risk of PTD) compared with unvaccinated women.³⁸ However, in our study, ILI was not more common in women vaccinated against seasonal influenza in 2009–10 nor was PTD more common in women reporting ILI. Alternative possible explanations could include a novel vaccine antigen exposure, as a new B antigen strain was introduced in the trivalent seasonal vaccine that year;³⁹ further, production practices by vaccine manufacturers may vary by year potentially introducing new antigens.

Pregnant women are now considered to be among the highest priority groups to receive influenza vaccination,^{3,26,40} as maternal vaccination has been shown to benefit both the

pregnant woman and her offspring. Continuing research on influenza vaccination and perinatal outcomes is critical to provide additional information on the safety of influenza vaccination during pregnancy. This is particularly important as the vaccines are not identical from year to year, with variations in both the antigen strains selected and production practices.

In conclusion, with the exception of PTD associated with the 2009–10 seasonal vaccine, our study found no meaningful increases in PTD or SGA risks associated with seasonal trivalent influenza vaccination during pregnancy over the years of our study. These findings provide some reassurance to providers and pregnant women regarding seasonal influenza vaccine safety. The finding for PTD risk during the season when there was a separate pandemic vaccine warrants further consideration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Prevalence of seasonal influenza vaccination by study site and influenza season among mothers of non-malformed infants participating in the Slone Epidemiology Center's Birth Defects Study, 2006–10. Seasonal coverage was estimated among 2136 women during the following influenza seasons: 2006–07 ($n = 499$), 2007–08 ($n = 715$), 2008–09 ($n = 743$), and 2009–10 ($n = 799$). Individual season numbers do not sum to total because of non-mutually exclusive influenza season exposure.

Table 1

Maternal characteristics, influenza vaccination during pregnancy, preterm delivery (PTD), and small for gestational age (SGA) among mothers of non-malformed infants

	All		Influenza vaccination ^a		PTD		SGA	
	n	%	n	%	n	%	n	%
All	1619	100	334	20.6	107	6.6	172	10.6
Maternal race								
White	964	59.5	242	25.1	40	4.1	60	6.2
Black	170	10.5	17	10.0	15	8.8	33	19.4
Hispanic or Latina	329	20.3	55	16.7	39	11.9	53	16.1
Other	151	9.3	20	13.2	13	8.6	26	17.2
Missing	5	0.3	0	0.0	0	0.0	0	0.0
Maternal age (years)								
<20	120	7.4	13	10.8	7	5.8	18	15.0
20–24	290	17.9	38	13.1	21	7.2	42	14.5
25–29	440	27.2	98	22.3	28	6.4	44	10.0
30–34	485	30.0	125	25.8	29	6.0	39	8.0
35	278	17.2	59	21.2	21	7.6	29	10.4
Missing	6	0.4	1	16.7	1	16.7	0	0.0
Maternal educational attainment								
Less than grammar	42	2.6	6	14.3	3	7.1	9	21.4
Grammar school	138	8.5	19	13.8	14	10.1	25	18.1
High school	650	40.1	98	15.1	48	7.4	75	11.5
College	787	48.6	211	26.8	42	5.3	63	8.0
Missing	2	0.1	0	0	0	0.0	0	0.0
Body mass index (kg/m ²)								
<18.5	61	3.8	12	19.7	7	11.5	9	14.8
18.5–<25	935	57.8	204	21.8	53	5.7	103	11.0
25–<30	330	20.4	69	20.9	24	7.3	27	8.2
30	235	14.5	40	17.0	19	8.1	25	10.6
Missing	58	3.6	9	15.5	4	6.9	8	13.8

	All		Influenza vaccination ^a		PTD		SGA	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Study centre								
Boston	484	29.9	131	27.1	37	7.6	51	10.5
New York	240	14.8	56	23.3	13	5.4	13	5.4
Philadelphia	521	32.2	94	18.0	35	6.7	61	11.7
San Diego	374	23.1	53	14.2	22	5.9	47	12.6
Calendar quarter of LMP								
January–March	455	28.1	97	21.3	32	7.0	47	10.3
April–June	437	27.0	120	27.5	35	8.0	46	10.5
July–September	380	23.5	87	22.9	22	5.8	37	9.7
October–December	347	21.4	30	8.6	18	5.2	42	12.1
By flu season ^b								
2006–07	439	100.0	74	16.8	33	7.6 ^c	42	9.6 ^d
2007–08	589	100.0	107	18.2	43	7.4 ^c	62	10.5 ^d
2008–09	537	100.0	112	20.9	29	5.5 ^c	66	12.3 ^d
2009–10	387	100.0	41	10.6	21	5.6 ^c	37	9.6 ^d

^aThis represents the per cent vaccinated for seasonal influenza within our analytic cohort, not the prevalence of seasonal influenza vaccination among all women surveyed during study years (see Figure 1).

^bNote 'by flu season' columns do not sum to totals because 333 women were included as unexposed in two influenza seasons: (80 in 2006–07 and 2007–08, 132 in 2007–08 and 2008–09, and 121 in 2008–09 and 2009–10; these included 15 PTD, 31 SGA, 4 PTD and SGA, and 283 normal births).

^cThis represents the per cent PTD within our analytic cohort, not the risk of PTD among all women surveyed during study years. The overall risks of PTD by influenza season were 7.8% (39/499) in 2006–07, 7.7% (55/715) in 2007–08, 7.0% (52/743) in 2008–09, and 5.6% (45/799) in 2009–10.

^dThis represents the per cent SGA within our analytic cohort, not the prevalence of SGA among all women surveyed during study years. The overall risks of SGA by influenza season were 10.8% (54/499) in 2006–07, 11.3% (81/715) in 2007–08, 12.0% (89/743) in 2008–09, and 9.3% (74/799) in 2009–10.

PTD, preterm delivery; SGA, small for gestational age according to reference birthweight percentiles; kg, kilogram; m, metre; LMP, last menstrual period.

Association of influenza vaccination during pregnancy with the risks of preterm delivery (PTD) and small for gestational age (SGA) among mothers of non-malformed infants

Table 2

Influenza vaccination timing ^a	All		PTD ^b		Unadjusted		Adjusted ^c	
	n	%	n	%	HR	[95% CI]	HR	[95% CI]
All	1595	100.0	107	6.7				
None	1285	80.6	83	6.5				
Anytime during pregnancy	310	19.4	24	7.7	1.30	[0.83, 2.05]	1.37	[0.84, 2.23]
First trimester	82	5.1	4	4.9	0.74	[0.27, 2.02]	0.66	[0.22, 1.97]
Second trimester	138	8.7	13	9.4	1.49	[0.83, 2.67]	1.46	[0.75, 2.84]
Third trimester	90	5.6	7	7.8	1.55	[0.71, 3.36]	1.53	[0.66, 3.56]
	All		SGA ^d		Unadjusted		Adjusted	
	n	%	n	%	OR	[95% CI]	OR	[95% CI]
All	1619	100.0	172	10.6				
None	1285	79.4	142	11.1				
Anytime during pregnancy	334	20.6	30	9.0	0.79	[0.53, 1.20]	1.03	[0.66, 1.62]
First trimester	82	5.1	4	4.9	0.41	[0.11, 1.13]	0.44	[0.15, 1.29]
Second trimester	138	8.5	16	11.6	1.06	[0.61, 1.83]	1.53	[0.81, 2.88]
Third trimester	114	7.0	10	8.8	0.77	[0.40, 1.52]	1.00	[0.48, 2.09]

^aRepresents the unvaccinated and the vaccinated against seasonal influenza only; 385 vaccinated against pandemic H1N1 were excluded from the analysis (including 20 PTD and 32 SGA).

^bThis represents the per cent preterm birth within our analytic cohort, not the risk of PTD among all women surveyed during study years (7.2 %; 153/2136).

^cAdjusted for propensity score.

^dThis represents the per cent SGA within our analytic cohort, not the prevalence of SGA among all women surveyed during study years (10.6 %; 232/2136).

PTD, preterm delivery; HR, hazard ratio; CI, confidence interval; OR, odds ratio; SGA, small for gestational age according to reference birthweight percentiles.

Association of influenza vaccination during pregnancy with the risk of preterm delivery (PTD) among mothers of non-malformed infants, stratified by influenza season

Table 3

Influenza vaccination timing	All		PTD		Unadjusted		Adjusted ^a	
	<i>n</i>	%	<i>n</i>	%	HR	[95% CI]	HR	[95% CI]
2006–07 Season								
All	436	100.0	33	7.6				
None	365	83.7	29	7.9				
Anytime during pregnancy	71	16.3	4	5.6	0.79	[0.28, 2.26]	1.03	[0.32, 3.33]
2007–08 Season								
All	585	100.0	43	7.4				
None	482	82.4	38	7.9				
Anytime during pregnancy	103	17.6	5	4.9	0.64	[0.25, 1.63]	0.79	[0.28, 2.21]
2008–09 Season								
All	529	100.0	29	5.5				
None	425	80.3	23	5.4				
Anytime during pregnancy	104	19.7	6	5.8	1.12	[0.46, 2.75]	1.08	[0.40, 2.95]
2009–10 Season ^b								
All	378	100.0	21	5.6				
None	346	91.5	12	3.5				
Anytime during pregnancy	32	8.5	9	28.1	9.96	[4.19, 23.7]	7.81	[2.66, 23.0]

^a Adjusted for propensity score.

^b Represents the unvaccinated and the vaccinated against seasonal influenza only; 385 vaccinated against pandemic H1N1 were excluded from the analysis (including 20 PTD). PTD, preterm delivery; HR, hazard ratio; CI, confidence interval.

Table 4

Association of influenza vaccination during pregnancy with the risk of small for gestational age (SGA) among mothers of non-malformed infants, stratified by influenza season

Influenza vaccination timing	All		SGA		Unadjusted		Adjusted ^a	
	n	%	n	%	OR	[95% CI]	OR	[95% CI]
2006–07 Season								
All	439	100.0	42	9.6				
None	365	83.2	39	10.7				
Anytime during pregnancy	74	16.8	3	4.1	0.35	[0.11, 1.18]	–	–
2007–08 Season								
All	589	100.0	62	10.5				
None	482	81.8	50	10.4				
Anytime during pregnancy	107	18.2	12	11.2	1.09	[0.56, 2.13]	1.40	[0.63, 3.11]
2008–09 Season								
All	537	100.0	66	12.3				
None	425	79.1	55	12.9				
Anytime during pregnancy	112	20.9	11	9.8	0.73	[0.37, 1.45]	1.23	[0.57, 2.63]
2009–10 Season ^b								
All	387	100.0	37	9.6				
None	346	89.4	33	9.5				
Anytime during pregnancy	41	10.6	4	9.8	1.03	[0.25, 3.13]	0.60	[0.17, 2.04]

^a Adjusted for propensity score.

^b Represents the unvaccinated and the vaccinated against seasonal influenza only; 385 vaccinated against pandemic H1N1 were excluded from the analysis (including 32 SGA).

OR, odds ratio; CI, confidence interval; and SGA, small for gestational age according to reference birthweight percentiles; '–', adjusted results not shown (<4 exposed cases).