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Birth outcomes following immunization of pregnant women with pandemic H1N1 influenza vaccine 2009–2010

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Abstract

Background—Following the H1N1 influenza pandemic in 2009, pregnant women were recommended to receive both seasonal (TIV) and H1N1 influenza vaccines. This study presents incidence of adverse birth and pregnancy outcomes among a population of pregnant women immunized with TIV and H1N1 vaccines at Kaiser Permanente Northern California during 2009–2010.

Methods—We telephone surveyed pregnant Kaiser Permanente Northern California members to assess non-medically-attended reactions following H1N1, TIV or both vaccines during 2009–2010 (n = 5365) in a separate study. Here we assessed preterm birth (<37 weeks), very preterm birth (<32 weeks), low birth weight (<2500 g, LBW), very low birth weight (<1500 g), small for gestational age, spontaneous abortions, stillbirths and congenital anomalies among this cohort by comparing incidence and 95% confidence intervals between the following immunization groups: TIV only, H1N1 only, H1N1 prior to TIV immunization, TIV prior to H1N1 and both immunizations given at the same time.

Results—Results did not vary significantly between groups. Comparing H1N1 with TIV, incidence were similar for preterm births (6.37 vs 6.28/100 births), very preterm births (5.30 vs 8.29/1000 births), LBW (4.19 vs 2.90/100 births), very LBW (4.54 vs 5.52/1000 births), small for gestational age (9.99 vs 9.24/1000 births), spontaneous abortion (7.10 vs 6.83/1000 pregnancies), stillbirths (7.10 vs 4.57/1000 pregnancies), and congenital anomalies (2.67 vs 2.43/100 births).

Conclusions—Although constrained by small sample size, complex vaccine groups, and differential vaccine availability during 2009–2010, this study found no difference in adverse birth outcomes between H1N1 vaccine and TIV.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.08.080.

Keywords

Vaccines; Influenza; H1N1; Pregnancy; Safety

1. Introduction

During the 2009–2010 influenza season, the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practice (ACIP) recommended that pregnant women receive the novel pandemic monovalent H1N1 influenza vaccine, along with the seasonal trivalent influenza vaccine (TIV, which included an A/Brisbane/59/2007(H1N1)-like virus, an A/Brisbane/10/2007(H3N2) like virus, and a B/Brisbane/60/2008-like virus), due to reports of increased adverse outcomes among pregnant women infected with H1N1 influenza. At the time, little was known about H1N1 vaccine safety in this population, including potential adverse birth outcomes.

Since then, several studies have compared pregnant women vaccinated with H1N1 with unvaccinated pregnant women and generally found no increase in adverse pregnancy outcomes between the groups [1–5]. Most of these studies, however, focused mainly on women immunized in the latter half of their pregnancy.

The aim of this study was to assess the safety of H1N1 vaccine compared with TIV vaccine administered during all three trimesters by evaluating birth outcomes following immunization of pregnant women during 2009–2010 within Kaiser Permanente Northern California (KPNC).

2. Methods

2.1. Setting

KPNC is an integrated healthcare delivery system which provides comprehensive health care for its 3.7 million members in more than 15 counties. KPNC employs over 7000 physicians, and operates 51 outpatient clinics and 22 hospitals distributed throughout the greater San Francisco Bay and Sacramento metropolitan areas. KPNC members receive nearly all their care at KPNC facilities. KPNC utilizes a unique medical record number for each member throughout all administrative and clinical databases, linking information for the same individual over time and across all services, including hospitalizations, emergency department, and outpatient visits. KPNC clinical databases include, but are not limited to, pharmacy, laboratory, procedures, radiology, authorized outside medical services, health plan membership and demographic information. KPNC maintains an immunization database which routinely captures all vaccines administered. KPNC has an annual birth cohort of approximately 34,000 (and an Infant Cohort Registry which collects birth information) and excellent retention of members KPNC (which includes Medi-Cal members) is generally representative of the age and ethnic background found in the state of California. Immunizations are provided without charge, and with outreach to improve coverage. KPNC has a strong annual influenza vaccine outreach program strongly encourages everyone, including pregnant women, to receive the influenza vaccine.

2.2. Study population

We originally identified subjects as part of a telephone interview study of pregnant women in 2009. The overall purposes of this telephone study were (1) to learn about non-medically attended adverse events and reactions in pregnant women following vaccination with H1N1 and TIV vaccines; and (2) to assess attitudes, knowledge, and information sources of pregnant women regarding these vaccines. For the original survey, we included women aged ≥18 years who were pregnant during October 2009 through December 2009 and who received at least one influenza vaccine during their pregnancy. We identified pregnant women in real time using a combination of electronic medical record data, including estimated date of delivery, presence of prenatal labs and pregnancy result tests. The original design was to distribute the trimester of immunization (as determined using their expected date of delivery in the electronic medical record) evenly throughout the population. Data on maternal age was also collected in order to ensure that bias would not arise from a large difference in maternal age between comparison groups. We completed all telephone interviews by March 30, 2010. This current study focused only on the birth outcomes of those women who participated in the original telephone interview survey study and whose results were presented in a fall 2012 report to the CDC.

2.3. Sample size

We originally planned to survey a total of 4500 pregnant women distributed among the following vaccination groups: 1. H1N1 only (n = 1500); 2. TIV only (n = 1500); 3. H1N1 and TIV on same date (n = 750); and 4. H1N1 and TIV on separate dates (n = 750). We designed our sampling scheme to collect an even distribution of women vaccinated in the first, second or third trimester of pregnancy. As the main study effort was to determine immediate adverse reactions to the immunization, we based the sample size on an expected fever rate of 5% in one group in order to have 80% power to detect a difference between the 5% fever rate and a 7.5% fever rate using a 2 tailed test ($\alpha = 0.05$).

2.4. Outcomes

We assessed the following birth outcomes using the electronic medical record: preterm birth (<37 weeks), very preterm birth (<32 weeks), low birth weight (LBW, <2500 g), very LBW (<1500 g) [6], small for gestational age (SGA) [7], spontaneous abortions, stillbirths and congenital anomalies through aged 3 years. The term incidence in this study is used to mean cumulative incidence (or incidence proportion) as a measure of risk. We identified stillbirths and spontaneous abortions as described in Appendix A and congenital anomalies in Appendix B.

2.5. Analyses

We categorized all study subjects into one of the following five vaccine groups: TIV only (“*TIV only*”), H1N1 vaccine only (“*H1N1 only*”), H1N1 vaccine prior to TIV vaccine (“*H before T*”), TIV vaccine prior to H1N1 vaccine (“*T before H*”), and both TIV and H1N1 vaccines given on the same day (“*Simultaneous*”). We also created a combined H1N1 vaccine group (“Any H1N1”) which included all subjects who received an H1N1 vaccine

regardless of timing (i.e., all subjects in the “H1N1 only”, “H before T”, “T before H” and “Simultaneous” groups).

For preterm birth and LBW, as is commonly done, multiple births were excluded as these birth weights and gestational ages would be outliers in the data. For certain analyses, we only included women immunized prior to the time when an outcome could occur (e.g. analyses of preterm births only included mothers immunized prior to 37 weeks; analyses of very preterm birth only included mothers immunized prior to 32 weeks). We included all births (i.e., singleton and multiple births) when assessing rates of congenital anomalies.

Because these analyses only evaluated the study population of those who participated in the original telephone survey, the number of observations in each of the vaccine groups and the size of the ‘TIV only’ group was too small to fit regression models. We therefore calculated incidence (cumulative incidence or proportional incidence) and 95% confidence intervals (CIs) for birth outcomes and examined them to see if the CIs were mutually exclusive between vaccine groups. We also compared the “H1N1 only” women with “TIV only” women to determine whether H1N1 immunization was associated with increased incidence of negative birth outcomes. To assess for any potential excess risk following H1N1 vaccine, we compared “TIV only” recipients with women who received “Any H1N1” vaccine. At this time, the CDC recommended routine influenza vaccination for all women who are or will be pregnant during the influenza season as no study to date demonstrated an increased risk of either maternal complications or adverse fetal outcomes associated with inactivated influenza vaccination [8].

3. Results

From December 2009 to March 2010, we telephoned 7975 pregnant women and enrolled 5365 who completed the interview. Of these, we identified 38 (0.7%) who subsequently had a spontaneous abortion, 37 (0.7%) who had a stillbirth, 22 (0.4%) who had other pregnancy outcomes (e.g. therapeutic abortion, ectopic pregnancy and blighted ovum; Appendix A), and 232 (4%) for which pregnancy outcomes were not available in the electronic medical record (e.g., gave birth at non-KPNC hospitals or home births), for a final study population of 5036 women who had 5160 live births (Fig. 1). The singleton births population was 4936 women, the potential preterm birth population was 4808 (immunized prior to 37 weeks), and the potential very preterm population was 4324 (immunized prior to 32 weeks gestation). Overall, 40.7% of women were immunized in the first trimester, 33.1% in the second trimester and 26.2% in the third trimester (Table 1).

Incidence of preterm births, low birth weight, and congenital anomalies did not differ between vaccine groups (Table 2). A sub-analysis among women immunized in the first trimester did not detect an association between first trimester H1N1 immunization and congenital anomalies, with similar congenital anomalies incidence after TIV Only [3.11 per 100 births (95% CI 2.34–4.04) and after Any H1N1 [3.16 per 100 births (95% CI 2.87–3.47)]. A further sub-analysis among singleton births only did not find an association between H1N1 immunization and congenital anomalies: after TIV only [2.49 per 100 births (95% CI 2.05–3.01)] and after Any H1N1 [2.63 per 100 births (95% CI 2.48–2.79)]. The

incidence of preterm births was similar between vaccine groups and ranged from 5.88 to 6.74 per 100 births, with the exception of the “H before T” group (2.40 per 100 births, 95% CI 0.49–7.01). Similarly, comparing “TIV only” with combined “Any H1N1” did not detect any difference in preterm births, low birth weight or congenital anomalies, based on lack of mutually exclusive CIs between the groups (Fig. 2). Incidence for babies born very preterm, with very low birth weight or SGA, as well as spontaneous abortions and stillbirths did not differ between vaccine groups, based on lack of mutually exclusive CIs between the groups. Incidence ranged from 0.00 to 8.29 per 1000 births for very preterm births, from 0.00 to 6.73 per 1000 births for very low birth weight, and from 6.77 to 23.62 per 1000 births for SGA infants. Incidence of spontaneous abortions ranged from 4.63 to 13.70 per 1000 pregnancies and incidence of stillbirths ranged from 1.55 to 13.66 per 1000 pregnancies (Tables 2 and 3). A further comparison using Fisher’s exact test found no significant differences among mothers vaccinated with any H1N1 compared with mothers vaccinated with TIV for spontaneous abortion ($p = 0.23$) nor for still births ($p = 0.27$). Comparing “TIV only” with the combined “Any H1N1” group also did not detect any difference in incidence of very preterm birth, very low birth weight, SGA, spontaneous abortions and stillbirths, based on lack of mutually exclusive CIs between the groups (Fig. 3).

4. Discussion

This study compared adverse pregnancy and birth outcomes following immunization of pregnant women with pandemic H1N1 vaccine, TIV alone, and different combinations of H1N1 and TIV vaccines. Because most outcomes examined in our study were relatively rare, we looked for overlap between the 95% confidence intervals around outcome incidence and found incidence for the two groups contained in the ranges of confidence intervals for each incidence indicating no significant difference in adverse pregnancy outcomes for H1N1 immunization during pregnancy compared to TIV. If the point estimates for the incidence in each group are contained in the CI of the incidence for the other group, then no 2-tailed test would produce a significant p-value. Comparing H1N1 with TIV vaccines, we also assessed for potential excess risk of adverse pregnancy and birth outcomes and did not detect an excess risk associated with H1N1 versus TIV vaccines. Overall, this study did not detect any new safety concerns among pregnant women vaccinated with H1N1 vaccine alone or those vaccinated with both H1N1 and TIV vaccines.

Differential influenza vaccine availability at Kaiser Permanente throughout the 2009–2010 influenza season posed substantial challenges regarding our ability to assess H1N1 vaccine risk. H1N1 vaccine was available early in the influenza season and TIV was not. TIV was available later in 2009, during which time there was overlap in availability of both vaccines. This period was then followed by shortages of H1N1 vaccine early in 2010, although it was again available later in the influenza season. Although such variability in influenza vaccine availability is not uncommon because the influenza virus types typically change from year to year, manufacturers, along with the CDC, must work to predict the influenza virus strain and incorporate these changes into the vaccine on an annual basis rather than simply manufacturing the same vaccine as the prior year. During the 2009–2010 influenza season, these influenza vaccine production and distribution challenges were further exacerbated

because both H1N1 and TIV vaccines needed to be rapidly produced and distributed, which led to the differential vaccine availability we observed in this study.

Since 2004, the American College of Obstetrics and Gynecology and the ACIP have recommended inactivated influenza vaccine for all pregnant women [8–10]. In our study, we specifically compared pregnancy and birth outcomes following any H1N1 vaccine (regardless of TIV receipt) with recommended seasonal TIV alone in order to detect whether H1N1 was associated with an excess risk of adverse pregnancy and birth outcomes.

Our findings are consistent with other studies which evaluated adverse pregnancy and birth outcomes following immunization with H1N1 vaccine. KPNC's incidence for preterm, low birth weight, very preterm and very low birth weight outcomes were well below the reported incidence for United States singleton births [11]. Studies comparing pregnant women vaccinated with H1N1 vaccine with unvaccinated pregnant women have reported no increase in adverse pregnancy outcomes following H1N1 vaccination [12–17]. Another study found no difference in adverse pregnancy outcomes among pregnant women immunized with TIV during 2008–2009 influenza season compared with pregnant women who received H1N1 vaccine during 2009–2010 influenza season [18], while another found no excess adverse birth outcomes associated with H1N1 vaccine when compared with TIV [19]. A review of reports to the Vaccine Adverse Event Reporting System [20] similarly found no concerning patterns of fetal outcomes during the 2009–2010 influenza season [21]. Finally, case-control studies from a birth defects registry [22] and from live births in Taiwan found no indication that H1N1 immunization was associated with adverse birth outcomes [23]. Our study provides further evidence that H1N1 vaccine administered during pregnancy was not associated with excess adverse birth and pregnancy outcomes by comparing outcomes associated with any H1N1 immunization during the 2009/2010 flu season to outcomes associated with seasonal influenza immunization alone during the same flu season.

Strengths of our study include our selection of pregnant women who received H1N1 vaccine during all three trimesters of pregnancy. While prior studies focused primarily on vaccinations during the second and third trimesters, 40% of the pregnant women in our study were immunized in their first trimester of pregnancy, which is a higher proportion vaccinated in the first trimester than has been reported in other studies of seasonal influenza vaccination during pregnancy [24]. Several recently published studies have found no increase in adverse birth and pregnancy outcomes associated with influenza immunization during the first [25,26]. In particular Baum et al. conducted a sub-analyses of women vaccinated with adjuvanted influenza vaccine (our study examined non adjuvanted influenza vaccine) among mothers in their first trimester and concluded that this exposure did not show any adverse impact on perinatal survival and health which is similar to our findings [27]. An additional strength was our ability to capitalize on KPNC's comprehensive electronic medical record and near complete capture of all birth outcomes, which provided us with confidence that we missed minimal birth outcome data for our study population and allowed us to look at multiple outcomes. Historically there has been hesitancy among pregnant women to receive influenza immunization during the first trimester [28]. Given the potential for pregnancy-related complications of H1N1 in early pregnancy the findings in this study can be used to

support women in their first trimester of pregnancy in a decision to receive influenza vaccine that contains H1N1 [29].

This study had limitations. The primary limitation was the small number of adverse outcomes in each vaccine group, which precluded performing regression models. However, our comparison of incidence and 95% CI across the different vaccine groups potentially provides a reasonable and sensitive alternative approach. Another limitation was that while we had intended to enroll an equal distribution of women immunized during each trimester of pregnancy, the differential availability of the influenza vaccines during the 2009–2010 influenza season limited our ability to create a balanced sample across trimesters and across vaccine groups. Although 232 participants did not have pregnancy outcomes recorded in the EMR, this should not affect the generalizability of the study as the majority of these missing outcomes were due to a change in health care coverage prior to the end of the pregnancy, with a few additional missing outcomes due to home births.

In conclusion, this study found no excess risk for adverse birth outcomes following H1N1 immunization when compared with TIV immunization and provides further support for the safety of H1N1 vaccine administered to pregnant women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of CDC.

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
ICD-9	The International Classification of Diseases, 9th Revision
KPNC	Kaiser Permanente of Northern California
LBW	Low birth weight
SGA	Small for gestational age

TIV	Trivalent influenza vaccine

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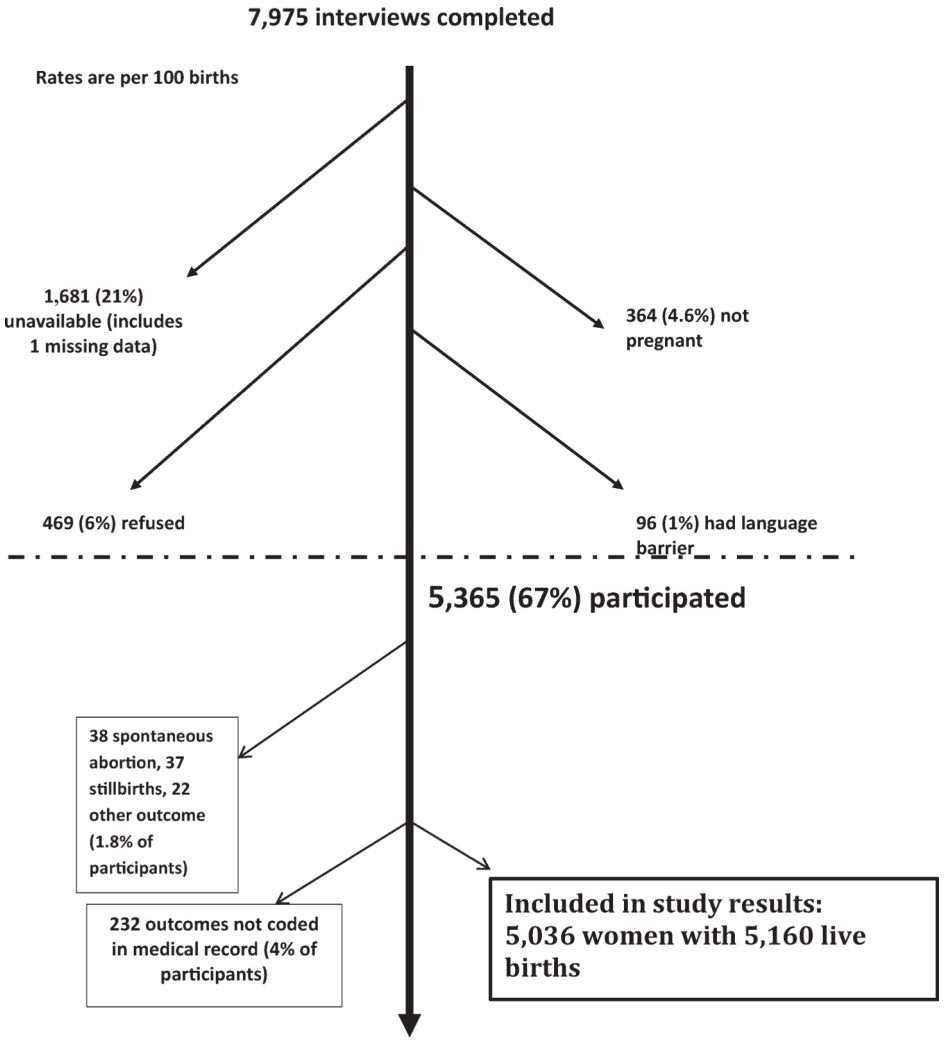

Fig. 1.
Original study population.

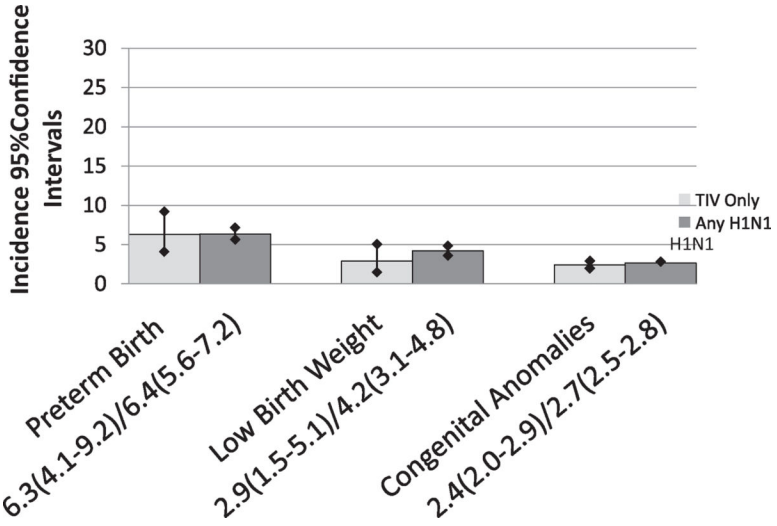

Fig. 2.

Incidence (with 95% confidence intervals) of preterm birth, low birth weight and congenital anomalies of babies born to mothers immunized by TIV only or any H1N1 among the study population of vaccinated pregnant women, October 2009–March 2010.

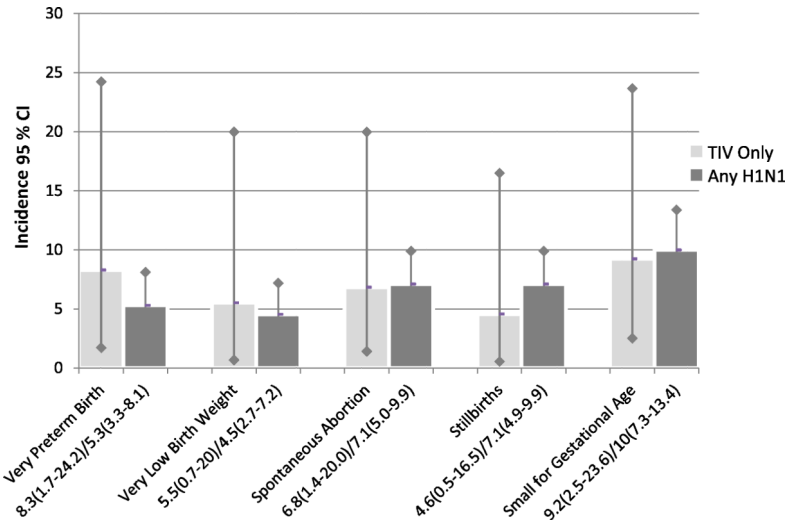

Fig. 3.

Incidence (with 95% confidence intervals of very preterm birth, very low birth weight, spontaneous abortion, stillbirth and small for gestational age following immunization by TIV only or any H1N1 among the study population of vaccinated pregnant women, October 2009–March 2010. * Incidence are per 100 births with the exception of spontaneous abortion and stillbirths, which are per 1000 pregnancies

Table 1:

Trimester of vaccination and advanced maternal age by vaccine group among the study population of vaccinated pregnant women, October 2009–March 2010.

Vaccine group	First trimester	Second trimester	Third trimester	Mother over 35 years old	Total
TIV only[a]	*44.0% (194)*	*32.6% (144)*	*23.4% (103)*	*16.6% (73)*	441
H1N1 only[b]	*59.1% (819)*	*25.6% (355)*	*15.3% (212)*	*19.6% (271)*	1386
H before T[c]	*26.7% (39)*	*39.7% (58)*	*33.6% (49)*	*16.4% (24)*	146
T before H[d]	*29.8% (578)*	*36.6% (712)*	*33.6% (653)*	*20.7% (403)*	1943
Simultaneous[e]	*38.2% (553)*	*35.1% (509)*	*26.7% (387)*	*16.6% (240)*	1449
Total	*40.7% (2183)*	*33.1% (1778)*	*26.2% (1404)*	*18.8% (1011)*	5365

[a]Received only TIV.

[b]Received only H1N1 vaccine.

[c]Received H1N1 vaccine prior to TIV.

[d]Received TIV vaccine prior to H1N1 vaccine.

[e]Received both TIV and H1N1 vaccines given on the same day.

Table 2:

Incidence (with 95% confidence intervals) of early gestational age, low birth weight, congenital anomalies, spontaneous abortion and stillbirth by vaccine group among the study population of vaccinated pregnant women, October 2009–March 2010.

Outcome	Vaccine group	Numerator	Denominator	Incidence	Upper 95%CI	Lower 95% CI
<37 weeks *	TIV only[a]	26	414	6.28	4.10	9.20
<37 weeks *	H1N1 only[b]	73	1242	5.88	4.61	7.39
<37 weeks *	H before T[c]	3	125	2.40	0.49	7.01
<37 weeks *	T before H[d]	115	1706	6.74	5.56	8.09
<37 weeks *	Simultaneous[e]	89	1321	6.74	5.41	8.29
<37 weeks *	Any H1N1[f]	280	4394	6.37	5.65	7.16
<2500 g *	TIV only	12	414	2.90	1.50	5.06
<2500 g *	H1N1 only	45	1241	3.62	2.64	4.85
<2500 g *	H before T	3	125	2.40	0.49	7.01
<2500 g *	T before H	73	1706	4.28	3.35	5.38
<2500 g *	Simultaneous	63	1321	4.77	3.66	6.10
<2500 g *	Any H1N1	184	4394	4.19	3.06	4.84
Congenital anomalies **	TIV only	108	444	2.43	1.99	2.93
Congenital anomalies **	H1N1 only	382	1331	2.87	2.59	3.17
Congenital anomalies **	H before T	31	129	2.40	1.63	3.41
Congenital anomalies **	T before H	500	1878	2.66	2.43	2.91
Congenital anomalies **	Simultaneous	343	1377	2.49	2.23	2.77
Congenital anomalies **	Any H1N1	1256	4715	2.66	2.52	2.82
Spontaneous abortion ***	TIV only	3	439	6.83	1.41	19.97
Spontaneous abortion ***	H1N1 only	11	1383	7.95	3.97	14.23
Spontaneous abortion ***	H before T	2	146	13.70	1.66	49.48
Spontaneous abortion ***	T before H	9	1944	4.63	2.12	8.79
Spontaneous abortion ***	Simultaneous	13	1453	8.95	4.76	15.30

Outcome	Vaccine group	Numerator	Denominator	Incidence	Upper 95%CI	Lower 95% CI
Spontaneous abortion ***	Any H1N1	35	4927	7.1	4.95	9.88
Stillbirth ***	TIV only	2	438	4.57	0.55	16.49
Stillbirth ***	H1N1 only	19	1391	13.66	8.22	21.33
Stillbirth ***	H before T	1	145	6.90	0.17	38.42
Stillbirth ***	T before H	3	1938	1.55	0.32	4.52
Stillbirth ***	Simultaneous	12	1453	8.26	4.27	14.43
Stillbirth ***	Any H1N1	35	4927	7.1	4.95	9.88

*Mothers immunized <37 weeks prior to birth – singletons (rate is per 100).

**All births (rate is per 100).

***All pregnancies (rate is per 1000).

[a]Received only TIV.

[b]Received only H1N1 vaccine.

[c]Received H1N1 vaccine prior to TIV.

[d]Received TIV vaccine prior to H1N1 vaccine.

[e]Received both TIV and H1N1 vaccines given on the same day.

[f]Combined H1N1 vaccine group which included all subjects who received an H1N1 vaccine regardless of timing (i.e., all subjects in the “H1N1 only”, “H before T”, “T before H” and “Simultaneous” groups).

Table 3:

Incidence (with 95% confidence limits) of very early gestational age, very low birth weight, small for gestational age (SGA) among babies born to mothers in the study population of vaccinated pregnant women, October 2009–March 2010.

Vaccine group	Outcome	Numerator (N)	Denominator (N)	Incidence Per 1000	Upper 95%CI	Lower 95% CI
TIV only[a]	<32 weeks *	3	362	8.29	1.71	24.22
H1N1 only[b]	<32 weeks *	4	1160	3.45	0.94	8.83
H before T[c]	<32 weeks *	0	109	0.00	0.00	27.48
T before H[d]	<32 weeks *	9	1504	5.98	2.74	11.36
Simultaneous[e]	<32 weeks *	8	1189	6.73	2.90	13.26
Any H1N1[f]	<32 weeks *	21	3962	5.30	3.28	8.10
TIV only	<1500 g *	2	362	5.52	0.67	19.96
H1N1 only	<1500 g *	4	1160	3.45	0.94	8.83
H before T	<1500 g *	0	109	0.00	0.00	27.48
T before H	<1500 g *	6	1504	3.99	1.46	8.68
Simultaneous	<1500 g *	8	1189	6.73	2.90	13.26
Any H1N1	<1500 g *	18	3962	4.54	2.69	7.18
TIV only	SGA **	4	433	9.24	2.52	23.65
H1N1 only	SGA	13	1260	10.32	5.48	17.64
H before T	SGA	3	127	23.62	4.87	69.03
T before H	SGA	12	1772	6.77	3.59	11.83
Simultaneous	SGA	17	1344	12.65	7.37	20.25
Any H1N1	SGA	45	4503	9.99	7.29	13.37

*Includes mothers immunized <32 weeks prior to singleton birth (n = 4324).

**Small for gestational age.

[a]Received only TIV.

[b]Received only H1N1 vaccine.

[c]Received H1N1 vaccine prior to TIV.

[d] Received TIV vaccine prior to H1N1 vaccine.

[e] Received both TIV and H1N1 vaccines given on the same day.

[f] Combined H1N1 vaccine group which included all subjects who received an H1N1 vaccine regardless of timing (i.e., all subjects in the "H1N1 only", "H before T", "T before H" and "Simultaneous" groups).