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Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: Exposure prevalence, preterm delivery, and specific birth defects☆

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ABSTRACT

We estimated exposure prevalence and studied potential risks for preterm delivery (PTD) and specific birth defects associated with exposure to the unadjuvanted pH1N1-containing vaccines in the 2009–2010 and 2010–2011 influenza seasons.

We used data from 4 regional centers in the United States collected as part of the Slone Epidemiology Center's Birth Defects Study. For PTD, propensity score-adjusted time-varying hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for exposure anytime in pregnancy and for each trimester. For 41 specific major birth defects, propensity score-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated.

Among 4191 subjects, there were 3104 mothers of malformed (cases) and 1087 mothers of nonmalformed (controls). Exposure prevalences among controls were 47% for the 2009–2010 season and 38% for the 2010–2011 season; prevalence varied by geographic region. Results for PTD differed between the two seasons, with risks above and below the null for the 2009–2010 and 2010–2011 seasons, respectively. For 41 specific birth defects, most adjusted ORs were close to 1.0. Three defects had adjusted ORs > 2.0 and four had risks < 0.5; however, 95% CIs for these were wide.

Conclusions: Among women exposed to pH1N1 vaccine, we found a decreased risk for PTD in the 2010–2011 season; risk was increased in 2009–2010, particularly following exposure in the first trimester, though the decrease in gestational length was less than 2 days. For specific major defects, we found no meaningful evidence of increased risk for specific congenital malformations following pH1N1 influenza vaccinations in the 2009–2010 and 2010–2011 seasons.

1. Introduction

Until recently, data supporting the safety of influenza vaccination in pregnancy were few. Because influenza poses significant risks in pregnancy [1–4], immunization is recommended by both the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices [5–7] and the American College of Obstetricians and Gynecologists [8]. However, in part because of concerns about vaccine safety [9–11], vaccination rates among pregnant women have remained lower than desired [12]. In June 2009, the World Health Organization declared a pandemic related to a new H1N1 strain, and development of a pandemic H1N1 vaccine (pH1N1) was accelerated [13,14]. With pregnant women identified as a high priority [7], intensive efforts were undertaken to increase the prevalence of vaccination among these women, though data on safety in pregnancy were unavailable.

Recent reports regarding the pH1N1 vaccine have not found increased risks of spontaneous abortion [15,16], preterm delivery (PTD) [15,17–21], stillbirth [16,18,22], low birth weight [15,18], or major congenital anomalies [15,17,18]. However, these studies related primarily to adjuvanted vaccines not used in the United States, and most included few first trimester exposures [23], the time of greatest risk for development of birth defects; further, birth

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defects were considered only in the aggregate although known teratogens increase risks for specific defects [24].

We sought to evaluate the risks and relative safety of the pH1N1 vaccine with respect to PTD and birth defects using data from the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), a comprehensive program developed specifically to evaluate the wide range of medications and vaccines used by pregnant women [25]. By utilizing two distinct study designs, a prospective cohort and case–control surveillance, and collaboration among the investigative team, VAMPSS offers a unique mechanism for assessing a wide range of pregnancy outcomes and for allowing signals raised in one arm to be evaluated in the other. This report describes the results of the case-control arm of VAMPSS; the results of the cohort arm are described separately [26].

2. Methods

The Slone Epidemiology Center at Boston University (SEC) has been conducting case–control surveillance for birth defects since 1976 [27,28]. Infants with major structural defects (cases) are identified at study centers that include participating hospitals in the areas surrounding Philadelphia and San Diego, as well as birth defect registries in New York State and Massachusetts. Nonmalformed infants (controls) are identified at study hospitals in all centers except Massachusetts, where a population-based random sample of newborns is drawn from vital statistics records. The current analysis is based on subjects pregnant during the 2009–2010 season, when pH1N1 vaccine was available in monovalent form (October 2009–July 2010) or the 2010–2011 season, when pH1N1 was included in the trivalent seasonal vaccine (August 2010–July 2011). This study has been approved by the institutional review boards of Boston University Medical Center and all participating institutions, as appropriate.

Within 6 months of delivery, mothers of eligible infants are invited to participate in a 45-min computer-assisted telephone interview conducted, after informed consent is obtained, by trained study nurses unaware of study hypotheses. Response rates among women we were able to contact were 70% for mothers of cases and 67% for mothers of controls during the study period (among all potentially eligible women corresponding numbers were 67% and 65%). The interview elicits information on demographic, reproductive, medical, and life-style factors such as cigarette smoking, alcohol and caffeine consumption, and dietary patterns. Detailed data are collected on all medications (prescription, over-the-counter, vitamins, minerals, herbal products and vaccines) used/administered at any time from 2 months before the last menstrual period (LMP) through the end of pregnancy. Interviewed women are asked to sign a medical record release form allowing us to review the infants' medical records. Approximately 70% of women comply with this request.

Women who respond affirmatively to questions about vaccines received during pregnancy are asked on what date the vaccine was given, the facility where it was administered and are asked to sign a form allowing us to obtain details of the specific vaccine from the provider. Approximately 60% of women complete this form. Women unable to recall the specific date of vaccination are asked to report a range of dates within which they received the vaccine (e.g., "sometime in January", "in the winter"). Vaccine records provide the date of vaccine receipt and details such as brand, pre-loaded syringe or multi-dose vial, and lot number. To obtain vaccine details without a signed release, we asked facilities about the vaccines that were in use at the time the woman reported being vaccinated. The effectiveness of this method has been described [29].

Women were considered exposed if they received either the monovalent pH1N1 vaccine in 2009–2010 or the trivalent pH1N1-containing vaccine in 2010–2011. Prevalence of exposure at any time during pregnancy was calculated separately for mothers of cases and controls to avoid any bias that might be introduced if exposure was related, either positively or negatively, to malformations. We also calculated prevalence separately for each of the two seasons.

For PTD and birth defect analyses, we assigned each exposure to a specific trimester of pregnancy. First, second, and third trimesters were defined as LMP through the 14th week, the 15th through the 28th week, and the 29th week through delivery, respectively. To maximize accurate gestational timing of exposure, we limited analyses to exposures that could be assigned to a single trimester of pregnancy, based on medical record confirmation of exposure, the subject's report of an exact exposure date, or the reported exposure date range falling completely within one trimester of pregnancy (in which case we assigned exposure as the midpoint of that range). Women whose vaccine reports did not meet this criterion were excluded. 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. Our referent group comprised women who reported receiving no influenza vaccine at any time from 2 months prior to LMP through the end of pregnancy.

For the analysis of PTD, mothers of controls were considered a retrospective cohort, with PTD defined as delivery at gestational age <37 weeks. We modeled the hazard of PTD using Cox regression with influenza vaccination as a time-varying exposure; gestational age, in days beginning at LMP, was the time-scale. Full-term pregnancies were censored at 37 weeks. We used linear regression to evaluate differences in gestational length, measured in days.

For the analyses of birth defects, we used a case–control approach. Cases were coded according to a modification of the British Pediatric Association system and aggregated into 41 categories of specific defects (e.g., cleft palate included 17 codes). Infants with multiple defects were assigned to multiple groups. Controls were infants without malformations. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each outcome via logistic regression.

Because of sparse numbers in many outcome categories and the large number of potential confounders, we used propensity scores to control confounding for both the PTD and specific malformations analyses. Separate scores were calculated for each trimester of exposure using the unweighted case–control method [30]. Variable selection was based on c-statistics. We then calculated hazard ratios (HRs), ORs and their 95% CIs, adjusting by propensity score to control confounding. All analyses were conducted using SAS 9.2.

3. Results

The 4781 subjects available for analysis included mothers of 3539 cases and 1242 controls. We excluded 35 subjects (27 cases and 8 controls) for whom we were unable to determine which influenza vaccine they received in the 2009–2010 season, 41 (28 and 13) who reported pH1N1 exposure prior to its availability, and 11 (9 and 2) who reported exposure after the date of birth. In addition, there were 108 (79 and 29) who were not exposed but whose LMP dates fell outside the LMP range of exposed women and 395 (292 and 103) who were exposed only to an influenza vaccine other than pH1N1, leaving 4191 subjects (3104 cases and 1087 controls).

Women whose pregnancies overlapped both seasons were included in each season's analysis. The prevalence of exposure among controls was higher in 2009–2010 (46.8%) than in 2010–2011 (37.3%) and varied considerably according to geographic region, being highest in Massachusetts and lowest in New

Table 1
Prevalence of exposure to pH1N1 influenza vaccine according to study center.[a]

Study center	2009–2010 season[c]		2010–2011 season[d]	
	Cases[b]	Controls[b]	Cases[b]	Controls[b]
Massachusetts	150/262 (57.3)	90/135 (66.7)	131/296 (44.3)	64/126 (50.8)
Philadelphia	240/597 (40.2)	79/177 (44.6)	224/604 (37.1)	76/184 (41.3)
San Diego	202/493 (41.0)	60/155 (38.7)	133/432 (30.8)	58/169 (34.3)
New York	117/398 (29.4)	38/103 (36.9)	154/536 (28.7)	46/176 (26.1)
Total	709/1750 (40.5%)	267/570 (46.8%)	642/1868 (34.4%)	244/655 (37.3%)

[a] *Note*: The numbers in this table cannot be added to obtain the study population. Twelve women whose pregnancies overlapped both seasons were exposed in both.
[b] Number exposed/number with exposure opportunity (%).
[c] Monovalent pH1N1 vaccine.
[d] pH1N1 included in trivalent seasonal vaccine.

York (Table 1). Exposure was generally more common among controls than cases.

For all remaining analyses, women whose exposure could not be assigned to a single trimester were excluded (235 cases, 91 controls). Table 2 provides the distribution of maternal characteristics according to exposure and case-or-control status. Women who were exposed tended to be older, white, better educated, married, work outside the home, and to have higher incomes, LMP dates between April and September, planned their pregnancy, taken folic acid, and had infertility treatments. Mothers of cases were more likely to be less well-educated, obese, to have carried a multiple birth, had a family history of birth defects, smoked during pregnancy, and had diabetes, either pre-existing or gestational.

We created a propensity score based on maternal age, maternal race, maternal education, family income, marital status, parity, study center, body mass index (BMI), family history of birth defects, pregnancy intention, periconceptional folic acid use, alcohol use, smoking, asthma, diabetes, LMP quarter, infertility treatment, treatment for high blood pressure or toxemia, inter-pregnancy interval, and season of exposure (2009–2010 or 2010–2011). Inclusion of additional factors did not improve the score's ability to predict exposure.

The analysis of PTD was restricted to singleton nonmalformed liveborn subjects. Women who reported pH1N1 exposure after 37 weeks' gestation were excluded. Among the remaining 951 subjects for the two seasons combined, we observed no increased risk of PTD following pH1N1 exposure anytime in pregnancy (Table 3). The crude HR for first trimester exposure was slightly elevated, but after adjustment was close to null (HR = 1.29; 95% CI 0.47–3.49). When we examined the two seasons individually, the adjusted HRs for 2009–2010 were elevated for exposure anytime in pregnancy and particularly for 1st trimester exposure (HR = 4.84 95% CI 1.45–16.10). For 2010–2011, only 3 subjects were exposed; the overall adjusted risk was 0.22 (0.06–0.83). For the two seasons combined and for the 2010–2011 season, gestational length differed by less than 1 day for pH1N1 exposure anytime in pregnancy and for each trimester. For the 2009–2010 season, the difference was less than 1 day for exposure anytime in pregnancy and less than 2 days for 1st trimester exposure, and all CIs included 0.0 (Tables e1–e3).

Unique to the 2009–2010 season, two influenza vaccines could be administered separately. Among women who reported exposure to the pH1N1 vaccine, 81% also reported exposure to the 2009–2010 trivalent seasonal vaccine, leaving very few women who were exposed exclusively to the pH1N1 vaccine; for the latter group, the HRs were somewhat attenuated, but confidence intervals were wide (Table 4). To evaluate whether women who received the pH1N1 vaccine were at higher underlying risk for PTD, we created a composite variable of known risk factors for PTD (fever or infection during pregnancy, interpregnancy interval <6 months, more than one prior miscarriage, asthma, high blood pressure, or toxemia); no appreciable differences were observed (data not shown). Because we had no information on prior PTD, a known predictor of PTD, we limited the analysis to primiparous women (who could not have had a prior PTD); however, risks remained increased (data not shown).

Table 5 provides the ORs and 95% CIs for the 41 specific birth defects in the analysis. Most were close to 1.0. Three defects had adjusted ORs greater than 2.0: persistent pulmonary hypertension of the newborn (OR = 2.29, 95% CI = 0.32–16.2); stenosis, atresia, or anomaly of the aqueduct of Sylvius (OR = 3.87, 95% CI = 0.41–36.3), and anophthalmia/microphthalmia (OR = 8.67, 95% CI = 1.10–68.5), but these were based on small numbers of cases and the 95% CIs were quite wide. ORs less than 0.5 were observed for 4 defects, with similarly unstable CIs. Results for each of the two seasons did not differ materially (Tables e4 and e5).

4. Discussion

We found rates of pH1N1vaccination coverage among controls of 46.8% in 2009–2010, which approximates the 40% reported by the CDC [31–33]. For the 2010–2011 season, exposure prevalences declined to approximately 37%. However, for both the pandemic and the following season, our observed influenza vaccine exposure prevalences were appreciably higher than for previous seasons [34–38]. Among pH1N1-exposed women during the two seasons, exposure prevalences were not materially increased for higher risk women (e.g., those with asthma or diabetes).

These data reflect that coverage remains far below the target of 80% set by *Healthy People 2020* [39]. Because one commonly reported barrier to vaccination among pregnant women is concern about vaccine safety, particularly for their unborn child [9–11,40], it is critical that studies explore these potential risks and the relative safety of influenza vaccines.

For PTD, the overall adjusted risk estimate for the two pH1N1 seasons combined showed no evidence of increased risk, with narrow confidence bounds, and for each trimester, the point estimates were close to 1.0 with confidence intervals that included 1.0. Two studies of pH1N1 exposure in pregnancy [15,17] found no increased PTD risk, but both involved only adjuvanted vaccine and had limited information on first trimester exposure. When we considered the two seasons separately, we found reduced risks for the 2010–2011 season but elevated risks in the 2009–2010 season, particularly for first trimester exposure. The latter was not explained by higher proportions of women with characteristics known to predict PTD among the vaccinees, and although we had no data regarding the strongest predictor, prior PTD, an analysis limited to only primiparous women did not appreciably alter the risk.

The 2009–2010 season was unusual in that the pH1N1 and seasonal vaccines were administered separately. The large majority of pH1N1 recipients also received the trivalent seasonal vaccine, raising the possibility that the observed increase in risk is attributable to the seasonal vaccine rather than the pH1N1 vaccine. Indeed,

Table 2
Characteristics of the study population according to exposure to pH1N1 influenza vaccine and case–control status.[a]

	pH1N1 vaccine exposure		Case-control status	
	Yes *N* (%)	No *N* (%)	Case *N* (%)	Control *N* (%)
Total	1524	2341	2869	996
Age				
<20	61 (4.0)	219 (9.4)	224 (7.8)	56 (5.6)
20–24	207 (13.6)	467 (20.0)	499 (17.4)	175 (17.6)
25–29	419 (27.5)	662 (28.3)	795 (27.7)	286 (28.8)
30–34	504 (33.1)	591 (25.3)	800 (27.9)	295 (29.7)
35+	332 (21.8)	398 (17.0)	548 (19.1)	182 (18.3)
Race/ethnicity				
White, non-Hispanic	993 (65.2)	1225 (52.3)	1616 (56.3)	602 (60.4)
Black, non-Hispanic	116 (7.6)	311 (13.3)	317 (11.0)	110 (11.0)
Hispanic	289 (19.0)	562 (24.0)	667 (23.2)	184 (18.5)
Asian	76 (5.0)	123 (5.3)	138 (4.8)	61 (6.1)
Other	50 (3.3)	120 (5.1)	131 (4.6)	39 (3.9)
Family income				
<$10,000	99 (7.2)	299 (15.4)	310 (12.6)	88 (10.0)
$10,000–$45,000	323 (23.4)	706 (36.3)	788 (32.1)	241 (27.5)
$45,000+	959 (69.4)	942 (48.4)	1354 (55.2)	547 (62.4)
Mother's education				
<HS	129 (8.5)	325 (13.9)	366 (12.8)	88 (8.9)
HS	268 (17.6)	634 (27.1)	711 (24.8)	191 (19.2)
1–2 years college	219 (14.4)	471 (20.2)	518 (18.1)	172 (17.3)
3+ years college	906 (59.5)	906 (38.8)	1269 (44.3)	543 (54.6)
Body mass index				
Underweight	39 (2.6)	90 (4.0)	96 (3.5)	33 (3.4)
Normal weight	813 (55.2)	1179 (53.0)	1412 (51.6)	580 (60.4)
Overweight	361 (24.5)	533 (24.0)	684 (25.0)	210 (21.9)
Obese	261 (17.7)	423 (19.0)	547 (20.0)	137 (14.3)
LMP quarter				
January–March	373 (24.5)	749 (32.0)	797 (27.8)	325 (32.6)
April–June	438 (28.7)	404 (17.3)	664 (23.1)	178 (17.9)
July–September	493 (32.3)	462 (19.7)	688 (24.0)	267 (26.8)
October–December	220 (14.4)	726 (31.0)	720 (25.1)	226 (22.7)
Married				
Married	1102 (72.4)	1330 (56.9)	1748 (61.0)	684 (68.9)
Not married	420 (27.6)	1006 (43.1)	1117 (39.0)	309 (31.1)
Parity				
No previous liveborns	0 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)
Primiparous	674 (44.3)	979 (41.9)	1232 (43.0)	421 (42.3)
Multiparous	849 (55.7)	1357 (58.1)	1632 (57.0)	574 (57.7)
Maternal birth				
Singleton	1458 (95.7)	2264 (96.7)	2741 (95.5)	981 (98.5)
Multiple birth	66 (4.3)	77 (3.3)	128 (4.5)	15 (1.5)
Center				
Boston	364 (23.9)	290 (12.4)	443 (15.4)	211 (21.2)
Philadelphia	497 (32.6)	735 (31.4)	939 (32.7)	293 (29.4)
San Diego	383 (25.1)	620 (26.5)	744 (25.9)	259 (26.0)
New York	280 (18.4)	696 (29.7)	743 (25.9)	233 (23.4)
Miscarriage history				
No previous miscarriages	1101 (72.4)	1727 (74.1)	2092 (73.2)	736 (74.1)
1+ previous miscarriage	419 (27.6)	605 (25.9)	767 (26.8)	257 (25.9)
Family birth defect history				
No	1320 (86.6)	2073 (88.6)	2480 (86.4)	913 (91.7)
Yes	204 (13.4)	268 (11.4)	389 (13.6)	83 (8.3)
Pregnancy planned				
Not planned	485 (31.8)	1075 (46.0)	1188 (41.5)	372 (37.3)
Planned	1038 (68.2)	1263 (54.0)	1677 (58.5)	624 (62.7)
Periconceptional folic acid use				
Yes	785 (51.9)	834 (35.9)	1162 (40.8)	457 (46.3)
No	727 (48.1)	1488 (64.1)	1684 (59.2)	531 (53.7)
Alcohol consumption				
None, or only pre-LMP	766 (50.3)	1375 (58.9)	1633 (57.1)	508 (51.1)
≤2 drinks/week and <3 drinks maximum	355 (23.3)	459 (19.7)	567 (19.8)	247 (24.8)
>2 drinks/week OR 3+ drinks maximum	402 (26.4)	500 (21.4)	662 (23.1)	240 (24.1)
Smoking				
None	1319 (86.5)	1932 (82.6)	2385 (83.2)	866 (86.9)
Before pregnancy only	121 (7.9)	202 (8.6)	249 (8.7)	74 (7.4)
During pregnancy	84 (5.5)	206 (8.8)	234 (8.2)	56 (5.6)
Coffee				
None	689 (45.4)	1228 (52.5)	1432 (50.0)	485 (48.8)
Before pregnancy only	12 (0.8)	9 (0.4)	16 (0.6)	5 (0.5)
During pregnancy	818 (53.9)	1103 (47.1)	1418 (49.5)	503 (50.7)

Table 2 (*Continued*)

	pH1N1 vaccine exposure		Case-control status	
	Yes *N* (%)	No *N* (%)	Case *N* (%)	Control *N* (%)
Asthma				
No	1285 (84.3)	1950 (83.3)	2393 (83.4)	842 (84.5)
Yes	239 (15.7)	391 (16.7)	476 (16.6)	154 (15.5)
Diabetes				
Never had diabetes	1388 (91.1)	2116 (90.4)	2565 (89.4)	939 (94.3)
Pre-existing diabetes	32 (2.1)	46 (2.0)	73 (2.5)	5 (0.5)
Gestational diabetes	103 (6.8)	179 (7.6)	230 (8.0)	52 (5.2)
Work outside home				
No	404 (26.5)	835 (35.7)	945 (32.9)	294 (29.5)
Yes	1120 (73.5)	1506 (64.3)	1924 (67.1)	702 (70.5)
Any infection during pregnancy				
No	475 (31.2)	840 (35.9)	966 (33.7)	349 (35.0)
Yes	1049 (68.8)	1501 (64.1)	1903 (66.3)	647 (65.0)
Interpregnancy interval				
No prior pregnancy	502 (33.2)	738 (32.1)	930 (32.9)	310 (31.6)
<6 months	161 (10.7)	221 (9.6)	279 (9.9)	103 (10.5)
6 months–2 years	424 (28.1)	601 (26.1)	746 (26.4)	279 (28.5)
>2 years	424 (28.1)	739 (32.1)	875 (30.9)	288 (29.4)
Infertility treatment				
No	1384 (90.8)	2218 (94.7)	2659 (92.7)	943 (94.7)
Yes	140 (9.2)	123 (5.3)	210 (7.3)	53 (5.3)
High blood pressure or toxemia				
No	1309 (85.9)	2037 (87.0)	2470 (86.1)	876 (88.0)
Yes	215 (14.1)	304 (13.0)	399 (13.9)	120 (12.0)
Illicit drug use				
No	1497 (98.2)	2273 (97.1)	2794 (97.4)	976 (98.0)
Yes	27 (1.8)	68 (2.9)	75 (2.6)	20 (2.0)
Composite PTD risk factors[b]				
None	262 (17.2)	501 (21.4)	546 (19.0)	217 (21.8)
1	626 (41.1)	934 (39.9)	1145 (39.9)	415 (41.7)
2 or more	636 (41.7)	906 (38.7)	1178 (41.1)	364 (36.6)

[a] For some variables, totals do not equal the total study population due to missing values. Population includes both 2009–2010 and 2010–2011 subjects; women who received only trivalent 2009–2010 seasonal vaccine are excluded.

[b] Any fever during pregnancy, any infection during pregnancy, asthma, high blood pressure or toxemia, interpregnancy interval <6 months, more than one previous miscarriage.

in our own separate analysis of seasonal vaccine risks in recent years, we observed a higher risk only for PTD among women exposed to the 2009–2010 trivalent vaccine (Ahrens, in preparation). However, when we confined the current analysis to women who received only the pH1N1 vaccine, the HR was only slightly reduced, though the small numbers yielded unstable results. While studies of seasonal vaccines have not found increased risks for PTD [41–43], none has estimated the risk for the 2009–2010 trivalent vaccine. Only two reports that considered that two vaccines were available that season. In studies from Ontario [19], Alabama [44], only 8% and 20% of women, respectively, received both vaccines. Neither study examined risks associated with the seasonal vaccine

Table 3
Association between pH1N1 influenza vaccination during pregnancy and risk of preterm delivery.

H1N1 vaccine exposure	Number of subjects	Preterm delivery *N* (%)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]
2009–2010 and 2010–2011 seasons combined				
Non-exposed	573	23 (4.0)		
Exposed any time in pregnancy	378	21 (5.6)	1.50 (0.83, 2.70)	1.03 (0.50, 2.10)
First trimester	137	10 (7.3)	1.85 (0.88, 3.88)	1.29 (0.47, 3.49)
Second trimester	143	8 (5.6)	1.39 (0.62, 3.12)	0.55 (0.18, 1.66)
Third trimester	98	3 (3.1)	0.95 (0.28, 3.16)	1.32 (0.32, 5.35)
All subjects	951	44 (4.6)		
2009–2010 season (with or without trivalent seasonal vaccine)				
Non-exposed	300	11 (3.7)	Reference	
Exposed any time in pregnancy	213	18 (8.5)	2.51 (1.19, 5.32)	2.82 (1.16, 6.86)
First trimester	75	9 (12.0)	3.40 (1.41, 8.22)	4.84 (1.45, 16.1)
Second trimester	87	7 (8.0)	2.22 (0.86, 5.73)	2.17 (0.48, 9.84)
Third trimester	51	2 (3.9)	1.36 (0.30, 6.18)	0.75 (0.12, 4.59)
All subjects	513	29 (5.7)		
2010–2011 season				
Non-exposed	406	18 (4.4)	Reference	Reference
Exposed any time in pregnancy	166	3 (1.8)	0.43 (0.13,1.47)	0.22 (0.06, 0.83)
First trimester	62	1 (1.6)	0.36 (0.05, 2.71)	0.14 (0.01, 1.43
Second trimester	56	1 (1.8)	−0.40 (0.05, 2.96)	0.12 (0.01, 1.23)
Third trimester	48	1 (2.1)	0.56 (0.08, 4.24	1.98 (0.21, 18.8)
All subjects	572	21 (3.7)		

[a] Adjusted for propensity score.

Table 4
Association between pH1N1 influenza vaccination without trivalent seasonal vaccine during pregnancy and risk of preterm delivery – 2009–2010 season.

pH1N1 vaccine exposure	Number of subjects	Preterm delivery *N* (%)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Non-exposed	300	11 (3.7)	Reference	Reference
Exposed any time in pregnancy	45	4 (8.9)	2.58 (0.82, 8.10)	2.17 (0.65, 7.20)[a]
First trimester	15	2 (13.3)	3.64 (0.81, 16.4)	2.81 (0.60, 13.1)[b]
Second trimester	19	1 (5.3)	1.42 (0.18, 11.0)	1.03 (0.13, 8.15)[b]
Third trimester	11	1 (9.1)	3.40 (0.44, 26.5)	2.19 (0.28, 17.4)[b]
All subjects	345	15 (4.4)		

[a] Adjusted for propensity score.
[b] Adjusted for study center.

alone. Our result could also be due to chance, but whatever the explanation, it is important to note that in every analysis we conducted, no difference in gestational length exceeded two days, a difference that is of little clinical importance.

For specific birth defects, we found no meaningful evidence of increased risks for any of the 41 different defects studied. Most observed ORs were quite close to 1.0. Only 3 case groups had ORs > 2.0, and each of these groups included only 2 exposed subjects. In this setting of multiple comparisons, the one OR with a CI that excluded 1.0 (anophthalmia/microphthalmia) may well be due to chance. The results for the two seasons considered separately did not differ materially. The only other studies that have assessed risks of congenital anomalies following pH1N1 immunization [15,17] found no increased risk, but each included very few women exposed in the first trimester (the critical period of organogenesis) and both considered major birth defects only as a single outcome, an approach that can fail to identify increased risks of specific defects [24].

Our study has strengths and limitations. We identify exposed women based on self-report of vaccination during pregnancy. Since approximately 20% of influenza vaccinations (including to pregnant women) were given in non-medical settings in recent years [29,45,46], reliance on maternal report captures exposures that would not be identified in medical or claims records (such records were used by Richards [43]). Our interview is structured to enhance accurate recall [47], and our exposure estimates

Table 5
Risk estimates for first trimester pH1N1 influenza vaccine exposure and specific birth defects (2009–2010 and 2010–2011 seasons combined).

Category	Number of cases	Exposed cases	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Ventricular septal defects	363	68	0.96 (0.70, 1.33)	0.92 (0.63, 1.35)
Undescended testicle	230	30	0.62 (0.41, 0.96)	0.69 (0.42, 1.14)
Hypospadias	197	36	0.93 (0.62, 1.40)	0.90 (0.56, 1.46)
1st degree	152	27	0.90 (0.57, 1.42)	0.86 (0.50, 1.48)
2nd or 3rd degree	36	6	0.83 (0.34, 2.04)	0.71 (0.25, 2.03)
Renal collecting system anomalies	167	36	1.14 (0.76, 1.73)	1.20 (0.73, 1.97)
Left-sided defects	122	24	1.02 (0.63, 1.65)	1.13 (0.63, 2.00)
Conotruncal and major arch anomalies	117	22	0.96 (0.59, 1.59)	0.83 (0.46, 1.49)
Right-sided defects	113	24	1.12 (0.69, 1.83)	1.01 (0.56, 1.82)
Chromosomal	106	26	1.35 (0.84, 2.19)	1.02 (0.57, 1.82)
Cleft lip ± cleft palate	106	23	1.15 (0.70, 1.90)	1.42 (0.77, 2.60)
Pyloric stenosis	102	21	1.08 (0.65, 1.81)	1.31 (0.70, 2.46)
Atrial septal defects	82	14	0.86 (0.47, 1.57)	1.05 (0.51, 2.16)
Clubfoot	64	9	0.68 (0.33, 1.41)	1.19 (0.51, 2.78)
Cleft palate only	58	7	0.57 (0.25, 1.29)	0.71 (0.28, 1.81)
Cystic kidney	50	7	0.68 (0.30, 1.54)	0.97 (0.38, 2.49)
Anal atresia/stenosis	47	6	0.61 (0.25, 1.46)	0.72 (0.26, 1.97)
Renal atresia/stenosis	43	5	0.55 (0.21, 1.42)	0.69 (0.23, 2.04)
Limb reduction defects	41	6	0.71 (0.29, 1.73)	1.13 (0.40, 3.21)
AV canal defects and AV septal defects	41	5	0.58 (0.22, 1.50)	0.47 (0.16, 1.41)
Small intestinal atresia/stenosis	38	7	0.94 (0.41, 2.18)	1.39 (0.51, 3.77)
Agenesis, dysgenesis or anomalies of corpus collosum	37	6	0.81 (0.33, 1.97)	1.00 (0.35, 2.87)
Neural tube defect	35	4	0.54 (0.14, 1.56)	0.59 (0.18, 1.98)
Intestinal malrotation	34	10	1.74 (0.81, 3.71)	1.79 (0.70, 4.59)
Gastroschisis	27	2	0.33 (0.04, 1.36)	0.83 (0.17, 4.09)
Tracheoesophageal fistula	25	4	0.79 (0.19, 2.40)	1.50 (0.42, 5.29)
Hirschsprung's disease	23	5	1.16 (0.42, 3.17)	1.92 (0.57, 6.47)
Diaphragmatic hernia	18	3	0.83 (0.15, 3.00)	0.59 (0.13, 2.57)
Extra or horseshoe kidney	18	1	0.25 (0.01, 1.59)	0.14 (0.02, 1.25)
Omphalocele	17	4	1.28 (0.30, 4.23)	1.08 (0.27, 4.34)
Situs anomalies and looping defects	16	3	0.96 (0.17, 3.56)	0.50 (0.11, 2.21)
Anomalous pulmonary venous return	15	3	1.04 (0.19, 3.93)	1.09 (0.24, 5.07)
Anotia/microtia	14	3	1.14 (0.20, 4.38)	1.47 (0.31, 6.96)
Choanal atresia/stenosis	14	3	1.14 (0.20, 4.38)	0.63 (0.14, 2.90)
Craniosynostosis	11	3	1.56 (0.26, 6.61)	1.46 (0.27, 7.83)
Brain reduction	11	1	0.42 (0.01, 2.97)	0.34 (0.03, 3.37)
Cataract	9	1	0.52 (0.01, 3.94)	0.69 (0.06, 7.48)
Persistent pulmonary hypertension of the newborn	8	2	1.39 (0.14, 7.87)	2.29 (0.32, 16.2)
Stenosis, atresia, or anomaly of aqueduct of sylvius	5	2	2.77 (0.23, 24.4)	3.87 (0.41, 36.3)
Anophthalmia/microphthalmia	5	2	2.77 (0.23, 24.4)	8.67 (1.10, 68.5)
Dandy walker	3	1	2.08 (0.04, 40.2)	1.02 (0.05, 19.2)

[a] Adjusted for propensity score.

approximate those cited by the CDC [32,48]. On the other hand, for the 2009–2010 season, it is possible that subjects confused the pH1N1 and seasonal vaccines that were given separately that year, a limitation minimized by confirmation of maternal reports through vaccine records; a comparison of maternal reports with their vaccine records has shown that women's reports are quite accurate [49]. However, we have no way to confirm that women who did not report exposure did not receive the vaccine.

Our examination of PTD is limited by the fact that our overall prevalence of PTD was lower than that in the general population and included a narrow range of gestational ages (e.g., only four infants were born prior to 34 weeks' gestation). However, because inclusion in the study is unlikely to be conditional on vaccine exposure status, internal validity should not be affected. A more significant limitation is the fact that we have no information on prior PTD, a strong predictor of PTD; however, though based on small numbers, our results restricted to primiparous women were not appreciably different from the overall results.

In considering risks of birth defects following vaccination, we were limited by small numbers in some defect categories, resulting in wide confidence intervals and precluding exclusion of increased risks for some defects. However, for 20 commonly occurring specific defects, our estimates excluded risks greater than 4-fold, and for 14 specific defects, they excluded risks greater than 2-fold, providing reassurance about the relative safety with respect to these outcomes.

The results of this study of the pH1N1 vaccine are reassuring. No clinically meaningful differences in gestational length were observed, and for risks of specific birth defects, which have not been previously studied, our findings are compatible with no increased risks for most defects. Nonetheless, continuing vigilance is required for each year's influenza vaccines, since adverse effects can vary from year to year; in addition, where possible, studies should consider risks associated with specific brands or formulations, since these, too, can vary [50,51].

Pregnant women are at high risk for complications should they develop influenza, and our results add to the growing body of data that offers reassurance about the relative safety of influenza vaccines for an increasing number of specific pregnancy outcomes. Nonetheless, further study is required to provide the additional information necessary for pregnant women and their health care providers to make appropriate decisions regarding influenza immunization.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.08.096.

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