Vaccine 31 (2013) 5026–5032

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# Risks and safety of pandemic h1n1 influenza vaccine in pregnancy: Birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants☆

Christina D. Chambers[a,b,c,d,h,*], Diana Johnson[a,b], Ronghui Xu[c,d,e], Yunjun Luo[a,b], Carol Louik[f,h], Allen A. Mitchell[f,h], Michael Schatz[g,h], Kenneth L. Jones[a,b,h], the OTIS Collaborative Research Group[1]

[a] Department of Pediatrics, University of California San Diego, La Jolla, CA, United States
[b] Rady Children's Hospital, San Diego, CA, United States
[c] Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA, United States
[d] Clinical Translational Research Institute, University of California San Diego, La Jolla, CA, United States
[e] Department of Mathematics, University of California San Diego, La Jolla, CA, United States
[f] Slone Epidemiology Center at Boston University, Boston, MA, United States
[g] American Academy of Allergy Asthma and Immunology, Milwaukee, WI, United States
[h] Vaccines and Medications in Pregnancy Surveillance System, United States

ARTICLE INFO

*Article history:*
Received 21 June 2013
Received in revised form 23 August 2013
Accepted 27 August 2013
Available online 7 September 2013

*Keywords:*
Pandemic H1N1 influenza vaccination
Pregnancy
Birth defects
Preterm delivery
Spontaneous abortion
Small for gestational age

ABSTRACT

*Introduction:* There is a need for additional information on the fetal risks and relative safety of the pandemic H1N1 monovalent or trivalent influenza (pH1N1)-containing vaccines in women exposed during pregnancy.
*Methods:* To assess risks and relative safety of the pH1N1-containing vaccines, we conducted a prospective cohort study of pH1N1-vaccine-exposed and unexposed comparison women residing in the U.S. or Canada who were recruited during pregnancy and followed to outcome between October 2009 and August 2012. For exposure to the pH1N1 vaccine, adjusted relative risks (RRs) and 95% confidence intervals (CIs) were estimated for major birth defects and infants small for gestational age. Adjusted hazard ratios (HRs) and 95% CIs were estimated for spontaneous abortion and preterm delivery for time-varying exposure.
*Results:* There were 1032 subjects available for analysis; 841 women were exposed to a pH1N1-containing vaccine in pregnancy, and 191 women were unexposed to any influenza vaccine in pregnancy. Nine of 328 (2.7%) first-trimester-exposed pregnancies resulted in an infant with a major birth defect compared to 6/188 (3.2%) in the unexposed (adjusted RR 0.79, 95% CI 0.26–2.42). The HR for spontaneous abortion was not elevated (adjusted HR 0.92, 95% CI 0.31–2.72). Adjusted HRs for preterm delivery were elevated for exposure anytime in pregnancy (3.28, 95% CI 1.25–8.63), specifically with exposure in the 1st or 2nd trimester. However, the mean decrease in gestational age in the exposed pregnancies was approximately three days. Adjusted RRs for small for gestational age infants on weight and length approximated 1.0.
*Conclusions:* For the 2009–12 influenza seasons combined, we found no meaningful evidence of increased RR or HR for major birth defects, spontaneous abortion, or small for gestational age infants. There was some evidence of an increased HR for preterm delivery following pH1N1-influenza vaccine exposure; however the decrease in gestational age on average was approximately three days.
© 2013 Elsevier Ltd. All rights reserved.

☆ This project has been funded in whole or in part with Federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, Department of Health and Human Services, under Contract No. HHS0100201000029C and the OTIS Collaborative Research Group.
* Corresponding author at: Department of Pediatrics University of California San Diego, 9500 Gilman Drive MC 0828, La Jolla, CA 92093, United States. Tel.: +1 858 246 1704.
*E-mail address:* chchambers@ucsd.edu (C.D. Chambers).
[1] The members of the OTIS Collaborative Research Group are listed in the Appendix.

0264-410X/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2013.08.097

## 1. Introduction

The potential serious consequences of maternal influenza infection in pregnancy have long been recognized; pregnant women are at increased risk for influenza-associated morbidity and mortality [1,2]. As reviewed recently [3,4], there are limited data on the safety of influenza vaccine in pregnancy; however, to date, there has been no indication that seasonal influenza vaccines containing inactivated virus pose a risk to the mother or the fetus. This has led to the current recommendation that all pregnant women be vaccinated with the seasonal influenza vaccine regardless of trimester [5,6].

Despite these recommendations, vaccination rates remain less than optimal in the U.S. [7]. Surveys have demonstrated that mothers' concerns about safety contribute to poor compliance with vaccine recommendations [8–13]. This situation was escalated during the 2009–10 H1N1 pandemic season, when lack of safety data about the pandemic H1N1 (pH1N1) monovalent vaccine was coupled with intensive public health messaging that emphasized the need for all pregnant women to be vaccinated [14].

Since 2009, a number of reports have been published on pregnancy outcomes following exposure to influenza vaccines. Four communications reported on seasonal vaccines not containing the pH1N1 strain [15–18], four were pharmacovigilance studies [15,19,20,34], and 13 reported on pH1N1 vaccines (six focused on adjuvanted vaccines that were not administered in the U.S.) [21–34]. Most reports addressing pH1N1 vaccine exposure involved fewer than 100 first-trimester exposed pregnancies or did not distinguish gestational timing of exposure at all. Overall, published data have been reassuring with findings that show either no association or a protective effect of influenza vaccination for fetal loss, preterm delivery, fetal growth restriction and congenital anomalies. However, there is a need for additional safety information on pH1N1-containing vaccines when used in pregnancy, especially in the first trimester [4].

The purpose of our study was to evaluate the fetal risk and relative safety of the pH1N1 influenza vaccine using data from the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), a research program developed specifically to evaluate medications and vaccines used by pregnant women [35]. The VAMPSS program is composed of two complementary study designs, a prospective cohort study and case–control surveillance, each of which is conducted in parallel with coordination provided by the American Academy of Allergy, Asthma & Immunology. In 2009, VAMPSS initiated a study of the pH1N1 vaccine in pregnancy. This report presents results of the cohort arm of VAMPSS; results of the case–control arm are described separately [36].

## 2. Methods

### 2.1. Design and setting

The Organization of Teratology Information Specialists (OTIS) Research Group has been conducting collaborative prospective pregnancy cohort studies across the U.S. and Canada using a single study Research Center since 1998. The objectives of OTIS studies are to evaluate a range of adverse pregnancy outcomes following exposure to a medication or vaccine among women who are enrolled while pregnant and before they have knowledge regarding an adverse outcome of that pregnancy. The methods of the OTIS Research Group have been described previously [37,38]. In brief, OTIS services, located in academic institutions or hospitals throughout the U.S. and Canada, provide counseling to ~70,000 callers annually who present with questions about the risks of exposures in pregnancy. From this pool of pregnant callers, women who meet the criteria for a study (women who are exposed to the agent of interest or women who are unexposed and qualify as comparison women) are referred to the OTIS Research Center at the University of California San Diego where they are confirmed eligible, consented and enrolled into the study. Additional methods of recruitment are also employed, including physician referrals and direct to consumer marketing.

### 2.2. Participants

The sample available for the current analysis was enrolled in the pH1N1 vaccine study starting in October, 2009 and continuing through April, 2012 and thus was exposed or not exposed to either the monovalent (2009–10 season) or trivalent (2009–12 seasons) pH1N1 vaccine in one of three influenza seasons. This study was approved by the institutional review board of the University of California San Diego.

The target sample size for the study was 1100 pregnancies with approximately 300 exposed to pH1N1 vaccine in each of the three trimesters of pregnancy for a total of 900 exposed, and a comparison group of 200 women unexposed to any influenza vaccine. Women met the inclusion criteria if they had received a pH1N1-containing vaccine at any time in pregnancy from the first day of the last menstrual period (LMP) to the end of pregnancy and were currently pregnant. Women were excluded who had prenatal diagnosis prior to first contact with the study staff indicating that the fetus had a major birth defect, as this constituted a retrospective report of anticipated pregnancy outcome. Women met the inclusion criteria for the comparison group if they had received no influenza vaccine in pregnancy and were currently pregnant. Women were excluded who reported exposure to a known human teratogen, or who had prenatal diagnosis prior to first contact with study staff indicating they were carrying a fetus with a major birth defect.

### 2.3. Maternal interviews

Women in both the exposed and unexposed cohorts completed one to three telephone interviews during pregnancy and one interview at the completion of pregnancy. These were administered by trained study staff in English or Spanish. The first interview obtained information on demographic, pregnancy and family medical history, tobacco, alcohol and caffeine consumption, and illicit drug use, as well as infections, fever, any diagnosis of influenza, and prenatal tests. Data regarding dosages and dates of exposure were collected on all vaccines and medications (prescription, over-the-counter, vitamins/minerals, and herbal products) used/administered from LMP through the date of the interview. Subsequent maternal interviews elicited information on additional exposures or events since the last interview. To the extent medications were recorded in the medical record, maternal report was validated. The Slone Epidemiology Center's Drug Dictionary was used to code exposures [39].

Questions were added to the standard OTIS pregnancy interviews specifically for this study regarding the vaccine received, the date, and the medical setting in which it was given. Methods that were used for verifying vaccine exposure and for obtaining brand, lot number and single syringe vs. multi-dose vial have been described previously [40]. Briefly, the interviewers first asked the study participant to verify information from their personal vaccine record. If this was not available, permission to contact the participant's provider was obtained and the vaccine record obtained from the provider. Finally, in situations where the vaccine was given in a non-traditional setting, an attempt was made to determine the specific product that was being administered on the date and the location where the participant received the vaccine.

### 2.4. Exposure definitions

We classified women exposed to a pH1N1 vaccine into one of four categories by timing of exposure: (1) the two weeks between LMP and date of conception, (2) conception to 13 weeks' gestation, (3) >13–26 weeks' gestation, or (4) >26 weeks' gestation. In cases where the date of vaccination was uncertain, we assigned the exposure based on the midpoint of possible dates. In the 2009–10 season, some women received the 2009–10 seasonal vaccine (not containing the pH1N1 strain) prior to the pH1N1 monovalent vaccine becoming available, and were subsequently vaccinated with the monovalent pH1N1 vaccine. These women were classified as pH1N1 vaccine exposed; however, previous receipt of the non-pandemic vaccine was considered a covariate. The comparison group consisted of women who received no influenza vaccine of any type throughout pregnancy.

### 2.5. Outcomes

Outcomes were collected by maternal interview and by medical records obtained from the obstetrician, pediatrician, and delivery hospital as well as pathology reports if relevant. Data were collected on outcome status of each pregnancy (live birth, stillbirth, spontaneous abortion, and elective termination), gestational age at outcome, maternal weight gain, mode of delivery, sex and number of infants, birth weight, length, and head circumference and the presence or absence of major birth defects. Maternal report of major birth defects was confirmed by medical record review.

Major structural defects were classified using the Metropolitan Atlanta Congenital Defects Program coding system [41]. Spontaneous abortion was defined as spontaneous pregnancy loss at <20 gestational weeks. Preterm delivery was defined as delivery at <37 completed gestational weeks. Ultrasound dating was used to correct gestational weeks, as necessary, using a standard algorithm, or if the LMP was unknown. Small for gestational age was defined as <10th centile for sex and gestational age in live born infants using standard U.S. growth charts for full and preterm infants [42–44].

### 2.6. Statistical methods

All statistical comparisons were performed between the group of women exposed to a pH1N1-containing vaccine in the relevant gestational time period and the women with no exposure to any influenza vaccine in pregnancy. Exact methods were used to calculate relative risks (RRs) and their 95% confidence intervals (CIs) for major birth defects overall and for small for gestational age crude comparisons. First trimester exposure to pH1N1 vaccine was considered the relevant exposure window for major structural defects. Because the inclusionary/exclusionary criteria for the study allowed for women to enroll who had already undergone prenatal diagnosis (e.g., ultrasound scan for fetal structure, amniocentesis or chorionic villous sampling) with a normal result, while women who had already received an abnormal result were excluded, we further stratified the analysis for major structural defects based on whether prenatal diagnosis had been performed prior to enrollment.

For spontaneous abortion, the subset of those women who enrolled prior to 20 weeks' gestation (and therefore still at risk) was used for the analysis. Survival analysis methods, i.e., Kaplan–Meier (KM) estimates at 20 weeks of gestation, were used to estimate the probability of spontaneous abortion accounting for left truncation due to varying gestational timing of enrollment, and data were censored at 20 weeks' gestation [45]. As demonstrated in previous work [45], for time-to-event endpoints such as spontaneous abortion, in order to avoid selection bias it is also crucial to account for the fact that women may receive vaccination after enrollment in the study. Therefore, Cox proportional hazards modeling with time varying exposure to vaccine was used to estimate HRs and 95% CIs. Similar methods were used for preterm delivery, where the sample was restricted to live births among women who enrolled prior to 37 weeks' gestation, and data were censored at 37 weeks' gestation. Twins were excluded due to high preterm birth risk in multiple gestations.

Control for confounding was conducted where numbers permitted. All covariates including maternal age, race/ethnicity, socioeconomic status, tobacco, alcohol, pre-pregnancy body mass

**Table 1**
Selected maternal characteristics of women exposed during pregnancy to pandemic H1N1-containing monovalent or trivalent influenza vaccine and pregnant women not exposed to any influenza vaccine 2009–2012.

| Characteristic | Exposed, $N = 841$, $n$ (%) | Unexposed, $N = 191$, $n$ (%) |
|---|---|---|
| Maternal age – years | | |
| <25 | 47 (5.6) | 13 (6.8) |
| 25–29 | 221 (26.3) | 42 (22.2) |
| 30–34 | 270 (32.1) | 70 (36.6) |
| >34 | 302 (36.0) | 66 (34.6) |
| Maternal race/ethnicity | | |
| White non-Hispanic | 683 (81.2) | 148 (77.5) |
| Black non-Hispanic | 20 (2.4) | 10 (5.2) |
| Hispanic | 97 (11.5) | 15 (7.9) |
| Asian | 35 (4.2) | 13 (6.8) |
| Other | 6 (0.7) | 5 (2.6) |
| Maternal education – years | | |
| <12 | 32 (3.8) | 6 (3.1) |
| 12–15 | 205 (24.4) | 51 (26.7) |
| >15 | 604 (71.8) | 134 (70.2) |
| Family SES[a] | | |
| 1 | 349 (41.9) | 77 (40.5) |
| 2 | 313 (37.6) | 72 (37.9) |
| 3 | 90 (10.8) | 25 (13.2) |
| 4 | 55 (6.6) | 11 (5.8) |
| 5 | 26 (3.1) | 5 (2.6) |
| Country of residence | | |
| U.S. | 750 (89.2) | 127 (66.5) |
| Canada | 91 (10.8) | 64 (33.5) |
| Gravidity >1 | 526 (62.5) | 119 (62.3) |
| Parity >0 | 411 (48.9) | 88 (46.1) |
| Previous spontaneous abortion (any) | 211 (25.1) | 62 (32.5) |
| Previous elective termination (any) | 60 (7.1) | 16 (8.5) |
| Pre-pregnancy body mass index | | |
| <18.5 | 26 (3.1) | 7 (3.7) |
| 18.5–24.9 | 473 (56.9) | 121 (63.7) |
| 25–29.9 | 190 (22.9) | 42 (22.1) |
| ≥30 | 142 (17.1) | 20 (10.5) |
| Alcohol – any | 209 (24.9) | 45 (23.6) |
| Tobacco – any | 21 (2.5) | 2 (1.0) |
| Folic acid containing supplements | | |
| Started prior to conception | 580 (69.0) | 138 (72.3) |
| Post-conception only | 256 (30.4) | 52 (27.2) |
| Not at all | 5 (0.6) | 1 (0.5) |
| Hypertension | 72 (8.9) | 7 (3.9) |
| Pre-eclampsia | 43 (5.3) | 6 (3.3) |
| Any influenza-like symptom | 148 (17.6) | 31 (16.2) |
| Gestational age at enrollment – weeks | | |
| <13 | 111 (13.2) | 56 (29.3) |
| 13-26 | 372 (44.2) | 82 (42.9) |
| >26 | 358 (42.6) | 53 (27.7) |
| Gestational age at H1N1 vaccine exposure | | |
| <13 | 348 (41.4) | – |
| 13–26 | 332 (39.5) | |
| >26 | 161 (19.1) | |
| Also received seasonal vaccine not containing pandemic H1N1 2009–10 | 232 (27.6) | – |

[a] Calculated using Hollingshead categories [47] based on maternal and paternal education and occupation; 1, highest; 5, lowest.

index, use of vitamin supplements, pregnancy history, previous preterm delivery, infection, fever, asthma, depression, autoimmune disease, hypertension, and seasonal vaccine not containing the pH1N1 strain were considered as possible confounders. Using a criterion of ≥10% change in the estimate of the RR or the HR of pH1N1-containing vaccine exposure with the addition of each covariate in a model containing exposure and outcome, potential confounders were selected for each outcome. Due to the small number of events in each analysis, if more than two confounders were identified for a particular outcome, a propensity score was created [46]. The outcome of spontaneous abortion met this criterion of more than two confounders. Propensity scores were computed using Cox regression taking time to exposure as the outcome, and all confounders as covariates. Propensity score-adjusted HRs were then computed using Cox regression. As some covariates, such as receipt of seasonal vaccine not containing the pH1N1 strain, could not be balanced between exposure groups, these covariates were not considered for the propensity score and direct adjustment was utilized. For major birth defects and small for gestational age infants on weight, length and head circumference, adjusted odds ratios were used to approximate the RRs for these outcomes. All analyses were conducted using R open-source statistical software.

## 3. Results

There were 1032 subjects available for analysis: 841 exposed to a pH1N1-containing vaccine, and 191 unexposed to any influenza vaccine at anytime in pregnancy. A total of 23 subjects (<3%) were lost-to-follow-up (Table 2). Women in the exposed cohort were more likely to enroll in the study later in gestation, to have comorbidities such as hypertension and less likely to reside in Canada (Table 1).

The proportion of live births, stillbirths or elective terminations did not differ between exposed and unexposed (Table 2). Nine infants of 328 (2.7%) who had first-trimester pH1N1 vaccine exposure were diagnosed with major birth defects compared to 6/188 (3.2%) in unexposed (adjusted RR 0.79, 95% CI 0.26–2.42). Among the 226 pregnancies with no prenatal diagnosis prior to enrollment, there were 7 (3.1%) with major birth defects (adjusted RR 0.77, 95% CI 0.21–2.85) and among the 102 pregnancies with prior prenatal testing with normal results, 2 (2.0%) had major defects (adjusted RR 0.35, 95% CI 0.03–3.95).

The defects reported in first-trimester pH1N1 exposed infants included two cases of hypertrophic pyloric stenosis, and single cases of unilateral renal agenesis, pulmonic stenosis, proximal femoral deficiency, ventricular septal defect with peripheral pulmonary artery stenosis, unilateral undescended testis requiring surgery, bilateral club foot and Down Syndrome.

The HRs for spontaneous abortion (Table 3) did not vary by exposure status, with the point estimate of the HR approximating 1.0 (adjusted HR 0.92, 95% CI 0.31–2.72).

The overall adjusted HR for preterm delivery with exposure at anytime in pregnancy compared to unexposed was 3.28, 95% CI 1.25–8.63. The elevated risk was highest in the subsets of women with preconception exposure (crude HR 11.33, 95% CI 2.83–45.50), with first trimester exposure (adjusted HR 2.22, 95% CI 0.70–7.02) and second trimester exposure (adjusted HR 4.12, 95% CI 1.21–14.1) (Table 4). However, the mean difference in gestational age in exposed vs. unexposed was approximately three days (data not shown). Due to small numbers (8 exposed, 3 preterm births), no multivariate analysis was performed for the preconception exposure group.

For preterm delivery, we conducted further analyses stratifying on pH1N1 vaccination season (2009–10 vs. 2010–11 and 2011–12 combined) and found some evidence of differences between these two groups, although CIs were wide and overlapping (2009–10

**Table 2**
Pregnancy outcomes of women exposed to pandemic H1N1 vaccine by gestational timing of exposure compared to women not exposed to any influenza vaccine 2009–2012.

| Outcome | Unexposed, $N=191$, $n$ (%) | Pandemic H1N1 vaccine exposed LMP-DOC[a], $N=10$, $n$ (%) | RR (95% CI) | Pandemic H1N1 vaccine exposed 1st trimester, $N=338$, $n$ (%) | RR (95% CI) | Pandemic H1N1 vaccine exposed any trimester, $N=831$, $n$ (%) | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| Live birth | 177 (92.7) | 9 (90.0) | 0.97 (0.79–1.20) | 319 (94.4) | 1.02 (0.97–1.07) | 801 (96.4) | 1.04 (1.00–1.08) |
| Male | 95 (53.7) | (66.7) | 1.24 (0.77–2.01) | 171 (53.6) | 1.0 (0.85–1.19) | 407 (50.9) | 0.95 (0.82–1.11) |
| Twin | 9 (5.1) | 0 | – | 8 (2.5) | 0.49 (0.19–1.26) | 24 (3.0) | 0.59 (0.28–1.25) |
| Stillbirth | 1 (0.5) | 0 | – | 1 (0.3) | 0.57 (0.03–9.57) | 1 (0.1) | 0.23 (0.01–3.93) |
| Termination | 1 (0.5) | 0 | – | 1 (0.3) | 0.57 (0.03–9.57) | – | – |
| Lost-to-follow-up | 3 (1.6) | 0 | – | 10 (3.0) | 1.88 (0.56–9.22) | 20 (2.4) | 1.53 (0.49–5.07) |
| | Unexposed, $n/N$ (%) | Pandemic H1N1 vaccine exposed LMP-DOC[a], $n/N$ (%) | | Crude RR (95% CI) | Pandemic H1N1 vaccine exposed 1st trimester, $n/N$ (%) | Crude RR (95% CI) | Adjusted RR[b] (95% CI) |
| Birth defects | | | | | | | |
| Major birth defects in live born infants | 5/177 (2.8) | 0/9 | | – | 9/319 (2.8) | 1.00 (0.34–2.93) | 0.96 (0.29–3.12) |
| Major birth defects in all pregnancies[c] | 6/188 (3.2) | 0/10 | | – | 9/328 (2.7) | 0.86 (0.31–2.38) | 0.79 (0.26–2.42) |

[a] LMP-DOC defined as exposure between 1st day of last menstrual period and estimated date of conception.
[b] Adjusted for pre-pregnancy body mass index and seasonal vaccine not containing pandemic H1N1 strain.
[c] Denominator includes all pregnancies with outcome: live births, stillbirths, terminations, and spontaneous abortions (9 spontaneous abortions in unexposed group and 7 spontaneous abortions in 1st trimester exposed group).

**Table 3**
Estimated probabilities of spontaneous abortion for those enrolled and exposed prior to 20 weeks' gestation to pandemic H1N1 vaccine compared to women enrolled prior to 20 weeks' gestation and not exposed to any influenza vaccine 2009–2012.

| Pandemic H1N1 vaccine exposure | Number of subjects | Number of spontaneous abortions | KM estimate (95% CI) | Crude HR (95% CI) | Adjusted HR[a] (95% CI) |
|---|---|---|---|---|---|
| Unexposed | 116 | 9 | 25.1 (12.7–45.8) | Reference | Reference |
| LMP-DOC[b] | 8 | 1 | 20.0 (3.1–79.6) | 1.26 (0.16–10.0) | – |
| 1st trimester | 184 | 7 | 15.6 (6.5–34.6) | 0.76 (0.28–2.06) | 0.84 (0.27–2.64) |
| Prior to 20 weeks' gestation | 248 | 8 | 13.9 (6.0–30.1) | 0.89 (0.34–2.35) | 0.92 (0.31–2.72) |

[a] Adjusted for propensity score comprised of race, previous elective termination, infection and directly adjusted for autoimmune disease.
[b] LMP-DOC defined as exposure between 1st day of last menstrual period and estimated date of conception.

season: adjusted HR 3.32, 95% CI 1.20–9.18; 2010–12 seasons: adjusted HR 2.25, 95% CI 0.88–5.75). Further stratification of women in the 2009–10 season who received only the trivalent seasonal vaccine not containing the pH1N1 strain vs. those who received the monovalent pH1N1 vaccine (or both) was not possible as only 16 women were enrolled in that season who did not receive the pH1N1 vaccine.

Point estimates of the adjusted RR for small for gestational age on birth weight and length were close to unity for exposure in each trimester, and in all cases the 95% CIs included 1.0. Risks were elevated for small for gestational age on head circumference; however, head circumference measurement was not available for one third of the subjects in the sample (Table 5).

## 4. Discussion

We found no association between pregnancy exposure to pH1N1-containing vaccine and the risk of major structural defects overall, spontaneous abortion, or small for gestational age infants on birth weight or length in comparison to unexposed pregnancies. These findings are consistent with previous studies that have been published on pH1N1-containing vaccines [29–33] and consistent with previous findings on seasonal vaccine not containing the pandemic strain [3,15–18]. The finding of no increased risk for major structural defects overall is also consistent with the analysis of specific defects in the case–control surveillance arm of VAMPSS [36].

For preterm delivery, the overall adjusted HR was elevated with point estimates above 2 following first and second trimester exposures to pH1N1 vaccine compared to unexposed, after adjustment for important confounders including previous preterm delivery. Due to small numbers in the pre-conception exposure period, it was not possible to adjust for confounding in that window of exposure. Our findings are somewhat consistent with the observation by Louik et al. who noted an increase in preterm delivery following 1st trimester vaccine exposure in the 2009–10 season [36]; however, elevated HRs in our study were not restricted to the 2009–10 season nor to first trimester exposure. This is in contrast with previous reports that indicated either a reduced risk of preterm delivery or no association at all [22,24,29,30,33]. Among these previous reports, only two studies differentiated exposure by trimester, both were focused entirely on a single brand of adjuvanted vaccine and only the 2009–10 season [24,33]. It is possible that our findings are due to unmeasured confounding and/or chance. Furthermore, taken in context, the clinical relevance of a three-day shortening of gestational age is questionable.

Our findings regarding fetal growth, similar to previous studies, are reassuring. With respect to head circumference, the relatively high proportion of missing values for this measure raises the possibility that these values are not missing at random, and therefore measurements that were reported could have been biased.

VAMPSS has proposed criteria to guide the identification of risk and safety signals [35]; these include "no evidence of risk" when a RR or HR approximates 1.0 with an upper 95% CI $\leq$4.0 and "evidence of relative safety" when a RR or HR approximates 1.0 with an upper 95% CI $\leq$2.0. Applying these guidelines, we found that major birth defects overall, spontaneous abortion, and small for gestational age on weight and length outcomes in this study met the criteria of "no evidence of risk".

Our study has several strengths and some limitations. We recruited women during pregnancy before the outcome was known and evaluated pregnancies for a range of endpoints. We were able to determine trimester of exposure with precision, and the study sample included over 300 first trimester pH1N1 vaccine-exposed pregnancies. In addition, we experienced very low lost-to-follow-up rates.

We collected information on vaccination exposure directly from the woman during pregnancy which allowed us to identify exposures that might not be recorded in medical or claims records. Although it is possible that some women were misclassified as unexposed if they failed to report being vaccinated, the direct method of questioning during the maternal interviews regarding vaccination suggests this would be unlikely to occur. Our study involved a volunteer sample that was not population-based; however, we concurrently recruited comparison women using the same methods supporting the internal validity of conclusions. Our ability to identify risks for specific birth defects is limited in a cohort study of this size; however, the complementary nature of the VAMPSS system allows both study designs to test hypotheses using different methods. Specifically, the cohort arm of VAMPSS addresses major birth defects overall and risk of preterm delivery using a prospective design; while in parallel, the case–control arm of VAMPSS evaluates specific major birth defects and preterm delivery using

**Table 4**
Estimated probabilities of preterm delivery in women enrolled and exposed prior to 37 weeks' gestation to pandemic H1N1 vaccine compared to women enrolled prior to 37 weeks' gestation and not exposed to any influenza vaccine 2009–12.

| Pandemic H1N1 vaccine exposure | Number of subjects | Number of preterm deliveries | KM estimate (95% CI) | Crude HR (95% CI) | Adjusted HR[a] (95% CI) |
|---|---|---|---|---|---|
| Unexposed | 157 | 6 | 5.1 (1.8–8.6) | Reference | Reference |
| LMP-DOC[b] | 8 | 3 | 37.5 (13.9–77.1) | 11.33 (2.83–45.5) | – |
| 1st trimester | 304 | 34 | 11.8 (8.6–16.2) | 3.02 (1.27–7.18) | 2.22 (0.70–7.02) |
| 2nd trimester | 297 | 24 | 9.0 (6.1–13.2) | 2.26 (0.92–5.53) | 4.12 (1.21–14.1) |
| 3rd trimester | 127 | 8 | 7.0 (3.5–13.4) | 2.09 (0.72–6.06) | 1.47 (0.22–9.84) |
| Anytime in pregnancy | 736 | 69 | 10.4 (8.2–13.1) | 2.93 (1.27–6.76) | 3.28 (1.25–8.63) |

[a] Adjusted for maternal race/ethnicity, previous preterm delivery, autoimmune disease, and seasonal vaccine not containing pandemic H1N1 strain.
[b] LMP-DOC defined as exposure between 1st day of last menstrual period and estimated date of conception.

**Table 5**
Small for gestational age infants[a] at birth among infants live born to women exposed to pandemic H1N1 vaccine compared to women not exposed to any influenza vaccine 2009–2012.

| Pandemic H1N1 vaccine exposure | Number of subjects[b] | Number SGA on weight (%) | Crude RR (95% CI) | Adjusted RR[c] (95% CI) |
|---|---|---|---|---|
| Unexposed | 175 | 9 (5.1) | Reference | Reference |
| LMP-DOC[d] | 9 | 0 | – | – |
| 1st trimester | 313 | 15 (4.8) | 0.93 (0.42–2.09) | 1.23 (0.47–3.24) |
| 2nd trimester | 321 | 19 (5.9) | 1.15 (0.53–2.49) | 0.73 (0.25–2.17) |
| 3rd trimester | 159 | 9 (5.7) | 1.10 (0.45–2.70 | 1.27 (0.39–4.10) |
| Anytime in pregnancy | 802 | 43 (5.4) | 1.26 (0.56–2.87) | 1.08 (0.46–2.54) |

| Pandemic H1N1 vaccine exposure | Number of subjects[b] | Number SGA on length (%) | Crude RR (95% CI) | Adjusted RR (95% CI) |
|---|---|---|---|---|
| Unexposed | 162 | 5 (3.1) | Reference | Reference |
| LMP-DOC | 9 | 1 (11.1) | 3.60 (0.47–27.7) | – |
| 1st trimester | 304 | 8 (2.6) | 0.85 (0.28–2.56) | 0.65 (0.18–2.42) |
| 2nd trimester | 305 | 14 (4.6) | 1.49 (0.55–4.06) | 0.89 (0.27–2.98) |
| 3rd trimester | 154 | 2 (1.3) | 0.42 (0.08–2.14) | 0.54 (0.10–3.10) |
| Anytime in pregnancy | 772 | 25 (3.2) | 0.98 (0.37–2.62) | 0.82 (0.28–2.34) |

| Pandemic H1N1 vaccine exposure | Number of subjects[b] | Number SGA on head circumference (%) | Crude RR (95% CI) | Adjusted RR (95% CI) |
|---|---|---|---|---|
| Unexposed | 104 | 9 (8.7) | Reference | Reference |
| LMP-DOC | 4 | 0 | – | – |
| 1st trimester | 213 | 34 (16.0) | 1.84 (0.92–3.70) | 2.54 (1.08–5.97) |
| 2nd trimester | 212 | 29 (13.7) | 1.58 (0.78–3.22) | 1.88 (0.74–4.81) |
| 3rd trimester | 111 | 15 (13.5) | 1.56 (0.71–3.41) | 2.33 (0.86–6.36) |
| Anytime in pregnancy | 540 | 78 (14.4) | 1.99 (0.93–4.26) | 2.24 (1.02–4.94) |

[a] Small for gestational age (SGA) defined as <10th centile for sex and gestational age using NCHS 2000 growth curves or Lubchenko [35–37].
[b] Numbers of subjects vary for each outcome measure due to missing values.
[c] For weight, adjusted for maternal age and autoimmune disease; for length, adjusted for prepregnancy body mass index and autoimmune disease; for head circumference, adjusted for autoimmune disease and seasonal vaccine not containing pandemic H1N1 strain.
[d] LMP-DOC defined as exposure between 1st day of last menstrual period and estimated date of conception.

a retrospective design. The overall lack of evidence of an increased risk of birth defects in both studies provides evidence supporting the relative safety of first trimester pH1N1-containing vaccination.

In conclusion, our findings related to preterm delivery are not consistent with previous reports, could be due to chance or unmeasured confounding, but require further study. Importantly, the magnitude of reduction in gestational age (three days) noted in this study is unlikely to be clinically meaningful. For the other outcomes evaluated, we found no evidence of increased risks. Taken together with the known risks of maternal influenza infection for both mother and infant, this study adds to the overall reassuring body of evidence about influenza vaccine in pregnancy.

## Acknowledgements

We are especially indebted to the members of the VAMPSS Vaccine and Asthma Advisory Committee for their contributions to the design, conduct, and analysis of this study: Margaret Honein (chair), Dixie Snider, Robert Glynn, James Mills, Elizabeth Conradson Cleary, Joseph Bocchini, and Peter Gergen. We make special note of the continuing support of Jo Schweinle and Tanima Sinha at BARDA and for the ongoing support provided by Lauri Sweetman and Sheila Heitzig at AAAAI.

## Appendix.

Members of the OTIS Collaborative Research Group who contributed to this study: Arizona Teratology Information Program, University of Arizona, Tucson, AZ: D. Quinn, S. Riordan; California Teratogen Information Service Pregnancy Health Information Line, University of California San Diego, La Jolla, CA: K. Kao; Connecticut Pregnancy Exposure Information Service, University of Connecticut Health Center, Farmington, CT: J. Brochu, S. Lavigne; Nebraska Teratogen Project, University of Nebraska Medical Center, Omaha, NE: E. Conover; Pregnancy Environmental Hotline, Massachusetts General Hospital, Boston, MA: P. Cole, M. Feingold; New York Pregnancy Risk Network, Ferre Institute, Binghamton, NY: M. Roth; Perinatal Environmental and Drug Exposure Consultation Service, University of Rochester Medical Center, Rochester, NY: R. Miller; Texas Teratogen Information Service, University of North Texas, Denton, TX: B. Debus, L. Wolfe; Utah Pregnancy Risk Line, Utah Department of Health, Salt Lake City, UT: J. Carey, J. Robertson; Motherisk Program, Hospital for Sick Children, Toronto, Ontario, Canada: N. Djokanovic, A. Pupco, G. Koren; Long Beach Memorial Hospital, Long Beach, CA: G. Briggs; University of Washington, Seattle, WA: J. Polifka; Consultants in Epidemiology and Occupational Health, Washington, DC: S. Lamm; Georgetown University Medical Center, Washington, DC: O.P. Soldin; University of Montreal, Montreal, Quebec, Canada: A. Berard; Northwestern University, Chicago, IL: K. Wisner; University of New Mexico, Albuquerque, NM: L. Bakhireva.

## References

[1] Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol 2011;204:S3–8.
[2] Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1)-United States, April 2009–August 2010. MMWR Morb Mortal Wkly Rep 2011;60:1193–6.
[3] Tamma PD, Ault KA, del Rio C, Steinhoff MC, Halsey NA, Omer SB. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol 2011;204:S47–52.
[4] Bednarczyk RA, Adjaye-Gbewonyo D, Omer SB. Safety of influenza immunization during pregnancy for the fetus and the neonate. Am J Obstet Gyn 2012:S38–46.
[5] Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2005;54:1–40.
[6] ACOG Committee Opinion No. 468: influenza vaccination during pregnancy. Obstet Gynecol 2010;116:1006–7.
[7] Influenza vaccination coverage among pregnant women-29 states and New York City, 2009–10 season. MMWR Morb Mortal Wkly Rep 2012;61:113–8.
[8] Fisher BM, Scott J, Hart J, Winn VD, Gibbs RS, Lynch AM. Behaviors and perceptions regarding seasonal and H1N1 influenza vaccination during pregnancy. Am J Obstet Gynecol 2011;204:S107–11.
[9] Meharry PM, Colson ER, Grizas AP, Stiller R, Vazquez M. Reasons why women accept or reject the trivalent inactivated influenza vaccine (TIV) during pregnancy. Matern Child Health J 2012;17:156–64.

[10] Dlugacz Y, Fleischer A, Carney MT, Copperman N, Ahmed I, Ross Z, et al. 2009 H1N1 vaccination by pregnant women during the 2009–10 H1N1 influenza pandemic. Am J Obstet Gynecol 2012;206:e1–8.
[11] Drees M, Tambourelli B, Denstman A, Zhang W, Zent R, McGraw P, et al. Sustained high influenza vaccination rates and decreased safety concerns among pregnant women during the 2010-11 influenza season. Vaccine 2012;31:362–6.
[12] Gorman JR, Brewer NT, Wang JB, Chambers CD. Theory-based predictors of influenza vaccination among pregnant women. Vaccine 2012;31:213–8.
[13] Eppes C, Wu A, You W, Cameron KA, Garcia P, Grobman W. Barriers to influenza vaccination among pregnant women. Vaccine 2013;31:2874–8.
[14] Use of influenza A (H1N1) 2009 monovalent vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Morb Mortal Wkly Rep 2009;58:1–8.
[15] Moro PL, Broder K, Zheteyeva Y, Walton K, Rohan P, Sutherland A, et al. Adverse events in pregnant women following administration of trivalent inactivated influenza vaccine and live attenuated influenza vaccine in the Vaccine Adverse Event Reporting System, 1990–2009. Am J Obstet Gynecol 2011;146:e1–7.
[16] Omer SB, Goodman D, Steinhoff MC, Rochat R, Klugman KP, Stoll BJ, et al. Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retorspective cohort study. PLoS Med 2011;8:e1000441.
[17] Steinhoff MC, Omer SB, Roy E, El Arifeen S, Raqib R, Dodd C, et al. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. CMAJ 2012;184:645–53.
[18] Dodds L, Macdonald N, Scott J, Spencer A, Allen VM, McNeil S. The association between influenza vaccine in pregnancy and adverse neonatal outcomes. J Obstet Gynaecol Can 2012;34:714–20.
[19] Huang WT, Chen WC, Teng HJ, Huang WI, Huang YW, Hsu CW, et al. Adverse events following pandemic A (H1N1) 2009 monovalent vaccines in pregnant women-Taiwan, November 2009–August 2010. PLoS One 2011;6:e23049.
[20] Parretta E, Ianniello B, Ferrazin F, Rossi F, Capuano A. Italian post-marketing surveillance for adverse event reports after MF59-adjuvanted H1N1v vaccination. Vaccine 2011;9:3708–13.
[21] Tavares F, Nazareth I, Monegal JS, Kolte I, Verstraeten T, Vauchau V. Pregnancy and safety outcomes in women vaccinated with an AS03-adjuvanted split virion H1N1 (2009) pandemic influenza vaccine during pregnancy: a prospective cohort study. Vaccine 2011;29:6358–65.
[22] Fell DB, Sprague AE, Liu N, Yasseen AS, Wen S-W, Smith G, et al. H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. Am J Public Health 2012;102:e33–40.
[23] Pasternak B, Molgaard-Nielsen Svanstrom HD, Krause TG, Emborg HD, Melbye M, Hviid A. Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark. BMJ 2012;344:e2794.
[24] Pasternak B, Svanstrom H, Molgaard-Nielsen D, Krause TG, Emborg H-D, Melbye M, et al. Risk of adverse fetal outcomes following administration of a pandemic influenza A (H1N1) vaccine during pregnancy. JAMA 2012;308:165–80.
[25] Oppermann M, Fritzsche J, Weber-Schoendorfer C, Keller-Stanislawski B, Allignol A, Meister R, et al. A(H1N1)v2009: a controlled observational prospective cohort study on vaccine safety in pregnancy. Vaccine 2012;30:4445–52.
[26] Heikkinen T, Young J, van Beek E, Franke H, Verstraeten T, Weil JG, et al. Safety of MF59-adjuvanted A/H1N1 influenza vaccine in pregnancy: a comparative cohort study. Am J Obstet Gynecol 2012;177:e1–8.
[27] Lin TH, Lin S-Y, Lin C-H, Lin R-I, Lin H-C, Chiu T-H, et al. AdimFlu-S influenza A (H1N1) vaccine during pregnancy the Taiwanese Pharmacovigilance Survey. Vaccine 2012;l30:267–75.
[28] Omon E, Damase-Michel C, Hurault-Delarue C, Lacroix I, Monstastruc JL, Oustric S, et al. Non-adjuvanted 2009 influenza A (H1N1)v vaccine in pregnant women: the results of a French prospective descriptive study. Vaccine 2011;29:9649–54.
[29] Launay O, Krivine A, Charlier C, Truster V, Tsatsaris V, Lepercq J, et al. Low rate of pandemic A/H1N1 2009 influenza infection and lack of severe complication of vaccination in pregnant women: a prospective cohort study. PLoS One 2012;7:e52303.
[30] Richards JL, Hansen C, Bredfeldt C, Bednarczyk RA, Steinhoff MC, Adjaye-Gbewonyo D, et al. Neonatal outcomes after antenatal influenza immunization during the 2009 H1N1 influenza pandemic: impact on preterm birth, birth weight, and small for gestational age. Clin Infect Dis 2013;56:1216–22.
[31] Sammon CJ, Snowball J, McGrogan A, de Vries CS. Evaluating the hazard of foetal death following H1N1 influenza vaccination; A population based cohort study in the UK GPRD. PLoS One 2012;7:e51734.
[32] Haberg S, Trogstad L, Gunnes N, Wilcox AJ, Gjessing HK, Samuelsen SO, et al. Risk of fetal death after pandemic influenza infection or vaccination during pregnancy. N Engl J Med 2013;368:333–40.
[33] Kallen B, Olausson PO. Vaccination against H1N1 influenza with Pandemrix® during pregnancy and delivery outcome: a Swedish register study. BJOG 2012;119:1583–90.
[34] Chavant F, Ingrand I, Jonville-Bera AP, Plazanet C, Gras-Champel V, Lagarce L, et al. The PREGVAXGRIP study: a cohort study to assess foetal and neonatal consequences of in utero exposure to vaccination against A(H1N1)v2009 influenza. Drug Saf 2013;36:455–65.
[35] Schatz M, Chambers CD, Jones KL, Louik C, Mitchell AA. Safety of influenza immunizations and treatment during pregnancy: the Vaccines and Medications in Pregnancy Surveillance System. Am J Obstet Gynecol 2011;204:S64–8.
[36] Louik C, Ahrens K, Kerr S, Pyo J, Chambers CD, Jones KL, et al. Risks and safety of H1N1 influenza vaccine in pregnancy: exposure prevalence, preterm delivery, and specific birth defects. Vaccine 2013.
[37] Chambers CD, Braddock SR, Briggs GG, Einarson A, Johnson YR, Miller RK, et al. Postmarketing surveillance for human teratogenicity: a model approach. Teratology 2001;64:252–61.
[38] Bakhireva LN, Jones KL, Schatz M, Johnson D, Chambers CD. Organization of Teratology Information Services Research Group. Asthma medication use in pregnancy and fetal growth. J Allergy Clin Immunol 2005;116:503–9.
[39] Kelley KE, Kelley TP, Kaufman DW, Mitchell AA. The Slone Drug Dictionary: a research driven pharmacoepidemiology tool. Pharmacoepidemiol Drug Saf 2003;12(S1):S168–98.
[40] Louik C, Chambers C, Jacobs D, Rice F, Johnson D, Mitchell AA. Influenza vaccine safety in pregnancy: can we identify exposures. Drug Saf 2013;22:33–9.
[41] Correa A, Cragan JD, Kucik JE, Alverson CJ, Gilboa SM, Balakrishnan R, et al. Reporting birth defects surveillance data 1968–2003. Birth Defects Res A Clin Mol Teratol 2007;79:65–186.
[42] U.S. National Center for Health Statistics 2000 growth charts. Accessed 15 November 2012 at: http://www.cdc.gov/growth charts/clinical_charts.htm
[43] Lubchenco LO, Hansmann CO, Dressler M, Boyd E. Intrauterine growth as estimated from liveborn birthweight data at 24 to 42 weeks of gestaton. Pediatrics 1963;32:793–800.
[44] Lubchenco LO, Hansmann C, Boyd E. Intrauterine growth in length and head circumference as estimated from libirth at gestational ages from 26 to 42 weeks. Pediatrics 1966;37:403–7.
[45] Xu R, Luo Y, Chambers C. Assessing the effect of vaccine on spontaneous abortion using time-dependent covariates Cox models. Drug Saf 2012;21:844–50.
[46] Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. Am J Epidemiol 2006;163:1149–56.
[47] Hollingshead A. Four Factor Index of Social Status. Unpublished working paper. New Haven, CT: Department of Sociology, Yale University; 1975. Accessed at: http://yale.edu/sociology/faculty/