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Safety of the 2011–12, 2012–13, and 2013–14 seasonal influenza vaccines in pregnancy: Preterm delivery and specific malformations, a study from the case-control arm of VAMPSS ☆

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ABSTRACT

Background: Pregnant women have higher risks of influenza complications, but vaccine coverage is incomplete. Because concern about fetal harm limits uptake, we investigated risks for preterm delivery (PTD) and specific birth defects following vaccination in the 2011–12 through 2013–14 influenza seasons.
Methods: We used data from 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 42 specific major birth defects or birth defect categories, propensity score-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated.
Results: For PTD (1803 fullterm deliveries, 107 PTD for all seasons combined), an elevated adjusted risk was observed for only the 2nd trimester of the 2011–12 season (HR = 2.60, 95% CI 1.21, 5.61) – a reduction in gestational length of <2 days. For the 42 specific defects or categories of defects (2866 cases, 1411 controls for all seasons combined) most adjusted risks were close to 1.0; the highest was 2.38 for omphalocele and the lowest was 0.50 for atrioventricular canal defects. None had lower confidence bounds >1.0. For each season separately, only one elevated OR had a lower 95% CI >1.0: omphalocele in 2011–12 (OR = 5.19, 95% CI 1.44, 18.7).
Conclusions: Our results regarding risks for PTD and birth defects are generally reassuring. The few risks that were observed are compatible with chance, but warrant testing in other data. Given that vaccine components and manufacturing processes vary, continuing studies are needed to evaluate risks and safety of each season's vaccine and specific products.

1. Introduction

Pregnant women are at higher risk for complications from influenza [1–4] and have been considered a priority population for receipt of influenza vaccine. However, vaccine coverage among pregnant women has been considerably lower than the HealthyPeople 2020 target of 80% [5]. The reasons for this may vary, but one concern consistently reported by women is the potential risk of the vaccine to their fetus [6–11]. While the safety of the vaccine has long been assumed, the 2009 H1N1 pandemic drew attention to the paucity of available data to support this assumption; since then, there have been many reports assessing the safety of the pandemic H1N1 (pH1N1) vaccine in pregnancy. However, relatively little attention has been focused on the annual seasonal (non-pandemic) vaccines. It is important to recognize that the influenza vaccine typically varies each season both in terms of the antigens it contains and the manufacturing processes used to produce these products; it is therefore critical to monitor the safety of each season's vaccine.

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The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) is a comprehensive program developed specifically to evaluate the risks and safety of the medications and vaccines used by pregnant women [12]. Using two distinct study designs, a prospective cohort and case-control surveillance, with 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. In 2013, it published two reports evaluating the safety of the pH1N1 [13,14] vaccine. Since then, VAMPSS has continued to monitor seasonal influenza vaccine exposure during pregnancy. This report provides safety data from the case-control arm for the 2011–12, 2012–13, and 2013–14 influenza seasons; the results from the cohort arm are provided separately.

2. Methods

The Slone Epidemiology Center at Boston University (SEC) has been conducting case-control surveillance for birth defects since 1976. The methods have been described in detail previously [15–17]. Infants with major structural defects (cases) are identified at study centers that include participating hospitals in the areas surrounding Boston (MA), Philadelphia (PA) San Diego (CA), and Nashville (TN) as well as birth defect registries in New York State and Massachusetts. Non-malformed infants (controls) are randomly selected each month from study hospitals' discharge lists or statewide vital statistics records. 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 by trained study nurses to participate in a computer-assisted telephone interview; the interviewers are unaware of study hypotheses. After informed consent is obtained, the highly-structured interview, designed to maximize recall and minimize recall bias [18,19], 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. The LMP date is calculated from the ultrasound-determined due date if it differs by more than 7 days from the LMP date reported by the mother; if these dates differ by 7 days or less, we use the self-reported LMP date.

Women who respond affirmatively to questions about vaccines received during pregnancy are asked on what date the vaccine was given and the facility where it was administered; they are also asked to sign a form allowing us to obtain details of the specific vaccine from the provider; vaccine records provide the date of vaccine receipt and details such as brand, pre-loaded syringe or multi-dose vial, and lot number. In the absence of a signed release, we contact the facility identified by the subject and, without identifying the subject, ask what influenza vaccines were in use at the time the woman reported being vaccinated. The effectiveness of this method has been described [20,21].

The current analysis is based on subjects pregnant during the 2011–12, 2012–13, or 2013–14 influenza vaccine seasons; the 2011–12 vaccine contained 3 antigens: (A/CALIFORNIA/7/2009/(H1N1), A/PERTH/16/2009/(H3N2), and B/BRISBANE/60/2008), the 2012–13 vaccine contained 3 or 4 antigens: (A/CALIFORNIA/7/2009/(H1N1), A/VICTORIA/361/2011/(H3N2), and B/WISCONSIN/1/2010; quadrivalent doses contained a second B-strain, B/BRISBANE/60/2008) and the 2013–14 vaccine contained 3 or 4 antigens: (A/CALIFORNIA/7/2009/(H1N1), A/VICTORIA/361/2011/(H3N2) and B/MASSACHUSETTS/2/2012; quadrivalent doses contained a second B-strain, B/BRISBANE/60/2008).

2.1. Exposure definition

We defined the 2011–12, 2012–13, and 2013–14 seasons based on the LMP dates of mothers of cases and controls who received the vaccine after August 1st of each year. For each season, the LMP dates generally ranged from early December to early June. To ensure equivalent opportunities for exposure, we required that women not exposed to influenza vaccine have LMP dates within the same range as exposed women for a particular season. Only non-exposed women whose LMP dates fell within this date range were included in the analysis (Fig. 1). 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 vaccine 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, as were 27 women who received a vaccination in two consecutive seasons (see Fig. 1). 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.

2.2. Control of confounding

Because of sparse numbers in many outcome categories and the large number of potential confounders, we used propensity scores to control confounding for the analyses of both PTD and specific malformations [14]. The propensity score was based on maternal age, maternal race/ethnicity, maternal education, family income, marital status, parity, study center, pre-pregnancy body mass index (BMI), pregnancy intention, periconceptional folic acid use, alcohol use, smoking, asthma, diabetes, high blood pressure or toxemia, interpregnancy interval, any infection in pregnancy, LMP quarter, infertility medication use, family history of birth defects, multiple birth, coffee consumption, employment outside the home, illicit medication use, history of miscarriage and season of exposure (2011–12, 2012–13, or 2013–14). For PTD analyses, the propensity score also included any nausea/vomiting in pregnancy, any genital herpes occurrence in pregnancy, and a composite PTD risk variable. We created this 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) to evaluate whether women who received seasonal vaccine were at higher underlying risk for PTD. Covariate selection was based on c-statistics. Separate scores were calculated for each season using the unweighted case-control method [22]. We then calculated HRs, ORs and their 95% CIs, adjusting by propensity score to control confounding. No adjustment was undertaken when there were fewer than 4 exposed cases. All analyses were conducted using SAS 9.4.

2.3. Preterm delivery

For the analysis of PTD, mothers of controls were considered a retrospective cohort, with PTD defined as delivery at gestational age <37 weeks. The analysis was restricted to singleton nonmalformed liveborn subjects. Women who reported flu vaccine exposure after 37 weeks' gestation were excluded. We modeled the hazard of PTD (HR) 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

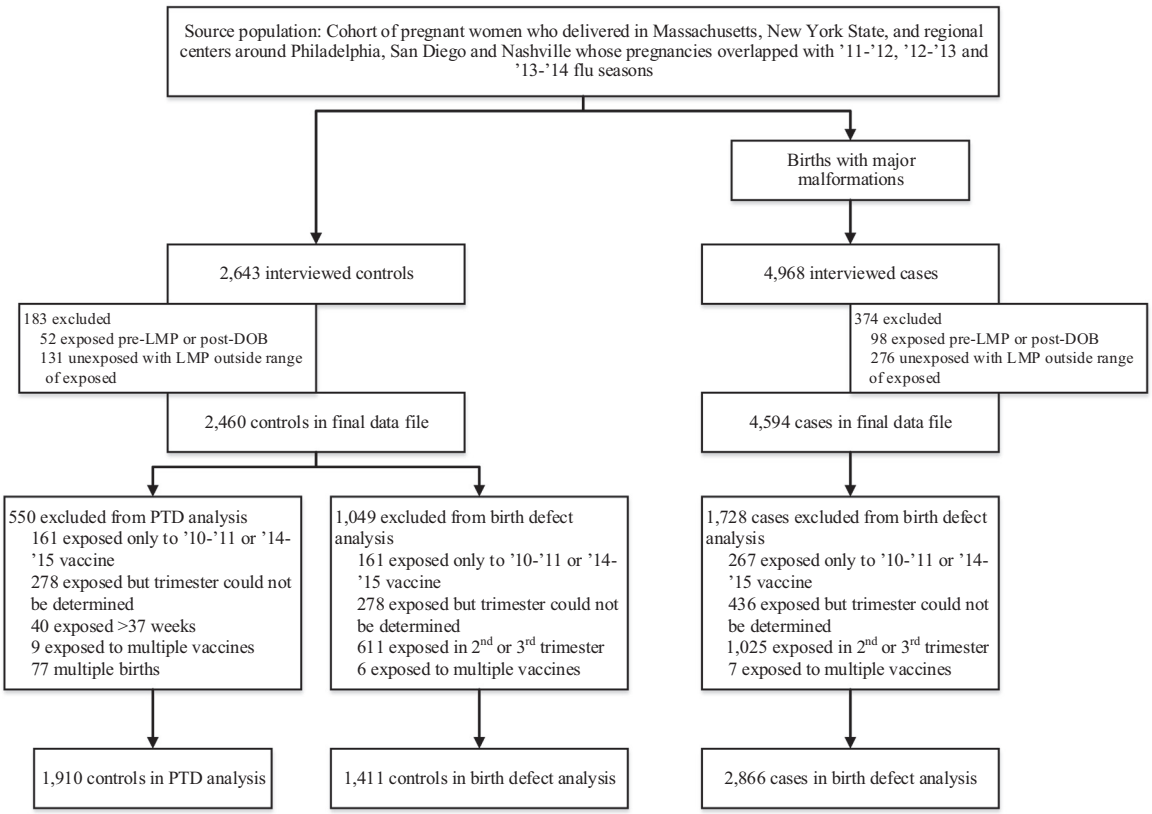

Fig. 1. Study population and eligibility for analyses of influenza vaccine.

gestational length, measured in days. Because we had no information on prior PTD, a known predictor of PTD, we conducted a subanalysis limited to primiparous women (who could not have had a prior PTD). We also conducted a subanalysis in which we compared gestational length among exposed and unexposed restricted to PTD only.

2.4. Specific birth defects

For the analyses of birth defects, we considered the risk of first trimester influenza vaccine exposure using a case-control approach. Cases were coded according to a modification of the British Pediatric Association system and aggregated into 40 categories of specific defects (e.g., cleft palate included 17 codes) and two birth defect categories (birth defects overall and cardiac defects). Infants with multiple defects were assigned to multiple groups. Controls were mothers of infants without malformations. The same controls were used for the analysis of each outcome, except for male genital defects, for which only mothers of male infants were included. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each outcome via logistic regression.

3. Results

Among the 7054 subjects in the final data file, 42% of cases and 47% of controls reported receipt of influenza vaccine at any time during pregnancy. After all exclusion criteria, the datasets for the PTD and birth defects analyses consisted of 1910 and 4277 subjects, respectively (Fig. 1); among the mothers reporting exposure, we were able to obtain the exact vaccine receipt date from a health care provider for 62% and 60%, respectively, and for those for whom a record was not obtained, we used the mother's reported date or date range. These proportions were similar for cases and controls.

Table 1a provides the distribution of maternal characteristics of the controls included in the PTD study according to exposure and preterm-or-term status. Women who were exposed tended to be older, white, better educated, married, work outside the home, and to have LMP dates between April and September, planned their pregnancy, and taken folic acid. PTD mothers were more likely to have the following characteristics: non-white, less well-educated, unmarried, unplanned pregnancy, history of miscarriage, no folic acid use, asthma, high blood pressure or toxemia, illicit drug use, and no nausea/vomiting during pregnancy. Both exposure and outcome varied considerably by center.

For birth defects, Table 1b provides the distribution of maternal characteristics according to first trimester 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 LMP dates between July and September, planned their pregnancy, taken folic acid, and had infertility treatments. Exposure also varied by center. Mothers of cases were more likely to be less well-educated, to have carried a multiple birth, had a family history of birth defects, and had diabetes, either pre-existing or gestational.

3.1. Etiologic analyses

3.1.1. Preterm delivery

Among the 1803 fullterm and 107 PTD subjects included in the analysis for the three seasons combined, the risk of PTD among those exposed at anytime in pregnancy approximated the null (HR = 1.22, 95% CI 0.79, 1.88) (Table 2). Among the three seasons and three trimesters in each analysis, the only risk elevation with a lower confidence bound >1.0 was for the 2011–12 season, where

Table 1a
Characteristics of PTD study population according to exposure to seasonal influenza vaccine and outcome status.[a]

	Seasonal influenza vaccine exposure		Outcome status	
	Yes N (%)	No N (%)	Preterm N (%)	Term N (%)
Total	774	1136	107	1803
Age				
<20	31 (4.0)	108 (9.5)	10 (9.3)	129 (7.2)
20–24	103 (13.3)	211 (18.6)	16 (15.0)	298 (16.5)
25–29	243 (31.4)	310 (27.3)	27 (25.2)	526 (29.2)
30–34	264 (34.1)	321 (28.3)	36 (33.6)	549 (30.5)
35+	133 (17.2)	185 (16.3)	18 (16.8)	300 (16.6)
Race/ethnicity				
White, non-Hispanic	499 (64.5)	568 (50.0)	50 (46.7)	1017 (56.4)
Black, non-Hispanic	44 (5.7)	153 (13.5)	14 (13.1)	183 (10.1)
Hispanic	143 (18.5)	291 (25.6)	29 (27.1)	405 (22.5)
Asian	86 (11.1)	117 (10.3)	13 (12.1)	190 (10.5)
Other	2 (0.3)	7 (0.6)	1 (0.9)	8 (0.4)
Family income				
Low (<$10,000)	136 (17.6)	321 (28.3)	27 (25.2)	430 (23.8)
Medium ($10,000–$45,000)	154 (19.9)	288 (25.4)	38 (35.5)	404 (22.4)
High ($45,000+)	484 (62.5)	527 (46.4)	42 (39.3)	969 (53.7)
Mother's education				
Less than high school	63 (8.1)	129 (11.4)	13 (12.1)	179 (9.9)
High school	117 (15.1)	275 (24.3)	24 (22.4)	368 (20.4)
1–2 years of college	94 (12.1)	214 (18.9)	24 (22.4)	284 (15.8)
3+ years of college	500 (64.6)	515 (45.5)	46 (43.0)	969 (53.8)
Body mass index				
Underweight	31 (4.1)	46 (4.2)	4 (3.8)	73 (4.2)
Normal weight	427 (56.9)	600 (54.8)	59 (56.7)	968 (55.6)
Overweight	175 (23.3)	256 (23.4)	23 (22.1)	408 (23.4)
Obese	117 (15.6)	193 (17.6)	18 (17.3)	292 (16.8)
LMP quarter				
January–March	213 (27.5)	334 (29.4)	30 (28.0)	517 (28.7)
April–June	250 (32.3)	274 (24.1)	28 (26.2)	496 (27.5)
July–September	227 (29.3)	198 (17.4)	27 (25.2)	398 (22.1)
October–December	84 (10.9)	330 (29.0)	22 (20.6)	392 (21.7)
Married				
Not married	220 (28.5)	483 (42.5)	43 (40.2)	660 (36.6)
Married	553 (71.5)	653 (57.5)	64 (59.8)	1142 (63.4)
Parity				
Nulliparous	0 (0)	0 (0)	0 (0)	0 (0)
Primiparous	367 (47.6)	475 (41.9)	52 (48.6)	790 (43.9)
Multiparous	404 (52.4)	659 (58.1)	55 (51.4)	1008 (56.1)
Multiple birth				
Singleton	774 (100)	1136 (100)	107 (100)	1803 (100)
Multiple birth	0 (0)	0 (0)	0 (0)	0 (0)
Center				
Boston	339 (43.8)	358 (31.5)	47 (43.9)	650 (36.1)
Philadelphia	128 (16.5)	176 (15.5)	13 (12.1)	291 (16.1)
San Diego	127 (16.4)	286 (25.2)	29 (27.1)	384 (21.3)
New York	129 (16.7)	277 (24.4)	14 (13.1)	392 (21.7)
Tennessee	51 (6.6)	39 (3.4)	4 (3.7)	86 (4.8)
Miscarriage history				
No previous miscarriages	603 (78.0)	874 (77.1)	76 (71.0)	1401 (77.8)
1+ previous miscarriage	170 (22.0)	260 (22.9)	31 (29.0)	399 (22.2)
Family birth defect history				
No	714 (92.2)	1059 (93.2)	97 (90.7)	1676 (93.0)
Yes	60 (7.8)	77 (6.8)	10 (9.3)	127 (7.0)
Pregnancy planned				
Not planned	224 (29.0)	454 (40.1)	46 (43.0)	632 (35.2)
Planned	549 (71.0)	677 (59.9)	61 (57.0)	1165 (64.8)
Periconceptional folic acid use				
No	385 (49.7)	720 (63.4)	66 (61.7)	1039 (57.6)
Yes	389 (50.3)	416 (36.6)	41 (38.3)	764 (42.4)
Alcohol consumption anytime during pregnancy				
None, or only pre-LMP	359 (46.7)	647 (57.3)	69 (65.7)	937 (52.3)
⩽2 drinks/week and <3 drinks maximum/setting	181 (23.5)	235 (20.8)	16 (15.2)	400 (22.3)
>2 drinks/week OR 3+ drinks maximum/setting	229 (29.8)	247 (21.9)	20 (19.0)	456 (25.4)

(*continued on next page*)

Table 1a (*continued*)

	Seasonal influenza vaccine exposure		Outcome status	
	Yes N (%)	No N (%)	Preterm N (%)	Term N (%)
Smoking				
None	684 (88.5)	974 (86.0)	92 (86.0)	1566 (87.1)
Before pregnancy	52 (6.7)	96 (8.5)	7 (6.5)	141 (7.8)
During pregnancy	37 (4.8)	62 (5.5)	8 (7.5)	91 (5.1)
Coffee				
None during pregnancy	322 (41.7)	524 (46.2)	50 (46.7)	796 (44.2)
During pregnancy	451 (58.3)	610 (53.8)	57 (53.3)	1004 (55.8)
Asthma				
No	658 (85.0)	966 (85.0)	87 (81.3)	1537 (85.2)
Yes	116 (15.0)	170 (15.0)	20 (18.7)	266 (14.8)
Diabetes				
Never had diabetes	725 (93.7)	1065 (93.8)	100 (93.5)	1690 (93.7)
Pre-existing diabetes	6 (0.8)	10 (0.9)	2 (1.9)	14 (0.8)
Gestational diabetes	43 (5.6)	61 (5.4)	5 (4.7)	99 (5.5)
Work outside home				
No	186 (24.0)	375 (33.0)	29 (27.1)	532 (29.5)
Yes	588 (76.0)	761 (67.0)	78 (72.9)	1271 (70.5)
Any infection during pregnancy				
No	327 (42.2)	532 (46.8)	54 (50.5)	805 (44.6)
Yes	447 (57.8)	604 (53.2)	53 (49.5)	998 (55.4)
Interpregnancy interval				
No prior pregnancy	285 (37.1)	355 (31.8)	44 (41.5)	596 (33.5)
<6 months	88 (11.5)	93 (8.3)	15 (14.2)	166 (9.3)
6 months–2 years	177 (23.1)	265 (23.7)	19 (17.9)	423 (23.8)
>2 years	217 (28.3)	405 (36.2)	28 (26.4)	594 (33.5)
Infertility treatment				
No	735 (95.0)	1085 (95.5)	100 (93.5)	1720 (95.4)
Yes	39 (5.0)	51 (4.5)	7 (6.5)	83 (4.6)
High blood pressure or toxemia				
No	708 (91.5)	1007 (88.6)	80 (74.8)	1635 (90.7)
Yes	66 (8.5)	129 (11.4)	27 (25.2)	168 (9.3)
Illicit drug use				
No	757 (97.8)	1113 (98.0)	100 (93.5)	1770 (98.2)
Yes	17 (2.2)	23 (2.0)	7 (6.5)	33 (1.8)
Any genital herpes occurrence				
No	756 (97.7)	1115 (98.2)	102 (95.3)	1769 (98.1)
Yes	18 (2.3)	21 (1.8)	5 (4.7)	34 (1.9)
Any nausea/vomiting during pregnancy				
No	210 (27.1)	360 (31.7)	41 (38.3)	529 (29.3)
Yes	564 (72.9)	776 (68.3)	66 (61.7)	1274 (70.7)
Composite PTD risk factors[b]				
None	327 (42.2)	481 (42.3)	39 (36.4)	769 (42.7)
1	252 (32.6)	413 (36.4)	30 (28.0)	635 (35.2)
2 or more	195 (25.2)	242 (21.3)	38 (35.5)	399 (22.1)

[a] For some variables, totals do not equal the total study population due to missing values. Population includes 2011–12 through 2013–14 subjects.
[b] Any fever during pregnancy, any infection during pregnancy, asthma, high blood pressure or toxemia, interpregnancy interval <6 months, more than one previous miscarriage.

the adjusted risk for second trimester exposure was 2.60 (1.21, 5.61). This risk translated to a reduction in gestational length of 1.5 days (Tables e1–e4). For women whose vaccinations were confirmed by vaccine record, the risk for second trimester exposure for the 2011–12 season was HR = 4.05 (1.80–9.10) (data not shown). In our sub-analysis limited to primiparous women, the risk for the second trimester of the 2011–12 season was 3.38 (1.23, 9.24) (data not shown). The second trimester finding for the 2011–12 season accounted for the modest risk for second trimester exposure in the data from the three seasons combined; for the same season, it also accounted for the modestly increased risk for exposure anytime in pregnancy.

3.1.2. Specific birth defects

For the 2866 cases and 1411 controls, Table 3 provides the ORs and 95% CIs for the 42 specific birth defects or birth defect categories considered in the analysis. For all seasons combined, most adjusted risks were close to 1.0, and none had lower confidence bounds >1.0. For all major birth defects combined, the OR was 1.01 (95% CI 0.85, 1.21). When we examined each season separately (Tables e5–e7), only one elevated risk had a lower confidence bound excluding 1.0: omphalocele in 2011–12 (OR = 5.19; 1.44, 18.7—5 exposed cases). None of the exposed omphalocele cases was exposed to medications known or suspected to be teratogenic [23]. Modestly elevated risks were observed for certain defects in a single season and extra or horseshoe kidney in two seasons (OR = 2.22 [0.71, 7.00] in 2011–12 and OR = 2.28 [0.72, 7.21] in 2012–13), but 95% confidence intervals included 1.0. We repeated our analyses after excluding infants with known chromosomal defects and recognized syndromes; risk estimates were not appreciably changed, but CIs were wider due to smaller numbers of cases (data not shown).

Table 1b
Characteristics of birth defect study population according to first trimester exposure to seasonal influenza vaccine and case-control status.[a]

	Seasonal influenza vaccine exposure in first trimester		Case-control status	
	Yes N (%)	No N (%)	Case N (%)	Control N (%)
Total	711	3566	1411	2866
Age				
<20	27 (3.8)	333 (9.3)	244 (8.5)	116 (8.2)
20–24	91 (12.8)	728 (20.4)	578 (20.2)	241 (17.1)
25–29	179 (25.2)	999 (28.0)	784 (27.4)	394 (27.9)
30–34	267 (37.6)	941 (26.4)	786 (27.4)	422 (29.9)
35+	147 (20.7)	563 (15.8)	473 (16.5)	237 (16.8)
Race/ethnicity				
White, non-Hispanic	471 (66.2)	1799 (50.4)	1512 (52.8)	758 (53.7)
Black, non-Hispanic	32 (4.5)	446 (12.5)	317 (11.1)	161 (11.4)
Hispanic	143 (20.1)	955 (26.8)	756 (26.4)	342 (24.2)
Asian	65 (9.1)	350 (9.8)	272 (9.5)	143 (10.1)
Other	0 (0.0)	16 (0.4)	9 (0.3)	7 (0.5)
Family income				
Low (<$10,000)	111 (15.6)	1070 (30.0)	821 (28.6)	360 (25.5)
Medium ($10,000–$45,000)	123 (17.3)	966 (27.1)	757 (26.4)	332 (23.5)
High ($45,000+)	477 (67.1)	1530 (42.9)	1288 (44.9)	719 (51.0)
Mother's education				
Less than high school	56 (7.9)	467 (13.1)	377 (13.2)	146 (10.4)
High school	108 (15.2)	955 (26.9)	749 (26.2)	314 (22.3)
1–2 years of college	100 (14.1)	716 (20.1)	570 (19.9)	246 (17.5)
3+ years of college	447 (62.9)	1417 (39.9)	1162 (40.7)	702 (49.9)
Body mass index				
Underweight	18 (2.6)	148 (4.3)	113 (4.1)	53 (3.9)
Normal weight	406 (58.2)	1776 (51.7)	1436 (51.9)	746 (54.7)
Overweight	158 (22.6)	867 (25.2)	701 (25.3)	324 (23.8)
Obese	116 (16.6)	643 (18.7)	519 (18.7)	240 (17.6)
LMP quarter				
January–March	32 (4.5)	1028 (28.8)	705 (24.6)	355 (25.2)
April–June	45 (6.3)	844 (23.7)	601 (21.0)	288 (20.4)
July–September	407 (57.2)	651 (18.3)	699 (24.4)	359 (25.4)
October–December	227 (31.9)	1043 (29.2)	861 (30.0)	409 (29.0)
Married				
Not married	183 (25.8)	1576 (44.2)	1217 (42.5)	542 (38.4)
Married	526 (74.2)	1986 (55.8)	1644 (57.5)	868 (61.6)
Parity				
Nulliparous	2 (0.3)	3 (0.1)	3 (0.1)	2 (0.1)
Primiparous	312 (43.9)	1476 (41.4)	1207 (42.1)	581 (41.2)
Multiparous	397 (55.8)	2084 (58.4)	1655 (57.7)	826 (58.5)
Multiple birth				
Singleton	666 (93.8)	3427 (96.1)	2724 (95.1)	1369 (97.0)
Multiple birth	44 (6.2)	139 (3.9)	141 (4.9)	42 (3.0)
Center				
Boston	291 (40.9)	830 (23.3)	616 (21.5)	505 (35.8)
Philadelphia	111 (15.6)	591 (16.6)	491 (17.1)	211 (15.0)
San Diego	140 (19.7)	994 (27.9)	800 (27.9)	334 (23.7)
New York	119 (16.7)	977 (27.4)	793 (27.7)	303 (21.5)
Tennessee	50 (7.0)	174 (4.9)	166 (5.8)	58 (4.1)
Miscarriage history				
No previous miscarriages	525 (73.9)	2671 (75.1)	2111 (73.8)	1085 (77.0)
1+ previous miscarriage	185 (26.1)	887 (24.9)	748 (26.2)	324 (23.0)
Family birth defect history				
No	631 (88.7)	3175 (89.0)	2497 (87.1)	1309 (92.8)
Yes	80 (11.3)	391 (11.0)	369 (12.9)	102 (7.2)
Pregnancy planned				
Not planned	183 (25.8)	1511 (42.5)	1177 (41.1)	517 (36.8)
Planned	527 (74.2)	2048 (57.5)	1687 (58.9)	888 (63.2)
Periconceptional folic acid use				
No	323 (45.4)	2302 (64.6)	1788 (62.4)	837 (59.3)
Yes	388 (54.6)	1264 (35.4)	1078 (37.6)	574 (40.7)
Alcohol consumption anytime during pregnancy				
None, or only pre-LMP	320 (45.1)	2074 (58.5)	1625 (56.9)	769 (54.9)
⩽2 drinks/week and <3 drinks maximum/setting	175 (24.7)	716 (20.2)	599 (21.0)	292 (20.8)
>2 drinks/week OR 3+ drinks maximum/setting	214 (30.2)	758 (21.4)	631 (22.1)	341 (24.3)

(*continued on next page*)

Table 1b (*continued*)

	Seasonal influenza vaccine exposure in first trimester		Case-control status	
	Yes N (%)	No N (%)	Case N (%)	Control N (%)
Smoking				
None	638 (89.9)	2992 (84.2)	2411 (84.4)	1219 (86.6)
Before pregnancy	43 (6.1)	300 (8.4)	229 (8.0)	114 (8.1)
During pregnancy	29 (4.1)	262 (7.4)	217 (7.6)	74 (5.3)
Coffee				
None during pregnancy	298 (42.0)	1668 (46.9)	1331 (46.5)	635 (45.1)
During pregnancy	412 (58.0)	1890 (53.1)	1529 (53.5)	773 (54.9)
Asthma				
No	599 (84.2)	3006 (84.3)	2410 (84.1)	1195 (84.7)
Yes	112 (15.8)	560 (15.7)	456 (15.9)	216 (15.3)
Diabetes				
Never had diabetes	642 (90.3)	3222 (90.4)	2539 (88.6)	1325 (93.9)
Pre-existing diabetes	16 (2.3)	60 (1.7)	63 (2.2)	13 (0.9)
Gestational diabetes	53 (7.5)	284 (8.0)	264 (9.2)	73 (5.2)
Work outside home				
No	162 (22.8)	1232 (34.6)	961 (33.6)	433 (30.7)
Yes	548 (77.2)	2328 (65.4)	1898 (66.4)	978 (69.3)
Any infection during pregnancy				
No	274 (38.5)	1650 (46.3)	1282 (44.7)	642 (45.5)
Yes	437 (61.5)	1916 (53.7)	1584 (55.3)	769 (54.5)
Interpregnancy interval				
No prior pregnancy	254 (35.9)	1129 (32.2)	930 (32.9)	453 (32.5)
<6 months	77 (10.9)	296 (8.4)	244 (8.6)	129 (9.3)
6 months–2 years	184 (26.0)	880 (25.1)	737 (26.1)	327 (23.5)
>2 years	192 (27.2)	1205 (34.3)	914 (32.4)	483 (34.7)
Infertility treatment				
No	643 (90.4)	3379 (94.8)	2692 (93.9)	1330 (94.3)
Yes	68 (9.6)	187 (5.2)	174 (6.1)	81 (5.7)
High blood pressure or toxemia				
No	607 (85.4)	3122 (87.5)	2479 (86.5)	1250 (88.6)
Yes	104 (14.6)	444 (12.5)	387 (13.5)	161 (11.4)
Illicit drug use				
No	693 (97.5)	3467 (97.2)	2780 (97.0)	1380 (97.8)
Yes	18 (2.5)	99 (2.8)	86 (3.0)	31 (2.2)

[a] For some variables, totals do not equal the total study population due to missing values. Population includes 2011–12 through 2013–14 subjects.

4. Discussion

For PTD, the overall adjusted HR was 1.22 (95% CI 0.79–1.88) for the three seasons combined. The one elevated risk we observed occurred in the 2011–12 season and was associated only with second trimester vaccination. This translated to a shortening of gestational length of 1.5 days, which likely has limited clinical significance. Apart from our earlier study of pH1N1 vaccine [14], the study by Chambers et al. [13] that accompanied that report, and our earlier study of seasonal vaccines [24], most other studies that have investigated PTD in relation to seasonal vaccines have found either no effect or a decreased risk [25] of PTD.

For birth defects overall, we found an OR of 1.01 with an upper bound of 1.21, in contrast to Chambers et al.'s, finding of 1.87, reported in the accompanying manuscript [26]. There is little information available on risks of specific birth defects in relation to influenza vaccination. A recent review [27] identified 15 studies that focused on birth defects [13,14] and while none reported an increased risk, they all considered birth defects as a single outcome rather than examining risks for specific defects, which is a more appropriate method to evaluate risks of birth defects [19]. Our study had sufficient power to consider 42 different defects or defect groups, and for the three seasons combined, most ORs were close to 1.0 and none had lower confidence bounds that exceeded 1.0. In season-specific analyses, we identified a few increased risks, including an approximately two-fold increased risk for extra or horseshoe kidney in the 2011–12 and 2012–13 seasons, but their lower confidence bounds included 1.0; however, the adjusted OR for omphalocele in 2011–12 was 5.19 with a lower bound of 1.44, based on 5 exposed cases. In our study of the pH1N1 vaccine [14] we found a slightly increased risk for omphalocele (OR = 1.88 for the 2010–2011 season) and no increased risk for extra or horseshoe kidney, but the number of exposed cases was considerably smaller. In the context of multiple comparisons, the current observed risk estimates may be due to chance.

In contrast to these few risks, this analysis offers considerable information related to relative safety. VAMPSS has established criteria for declaring a risk estimate approximating the null to show "no evidence of risk" (upper confidence bound <4) or "evidence of relative safety" (upper confidence bound <2) [12]; based on these criteria, and considering that point estimates of $\leqslant$1.3 approximate the null, the adjusted risks and CIs from the three seasons combined suggest that, among the 35 defects or defect categories for which numbers were adequate to allow adjustment for confounding, 31 specific defects meet criteria of "no evidence of risk" and 19 of these meet the higher standard of "evidence of relative safety". These data, together with the season-specific analyses, offer reassurance that with respect to the large majority of the most commonly-encountered defects, the seasonal influenza vaccines over the years of study appear to be relatively safe.

Among the study's limitations, misclassification of vaccine exposure was possible because we relied on self-report of vaccine

Table 2
Association between seasonal influenza vaccination during pregnancy and risk of preterm delivery.

Influenza vaccine exposure	Number of subjects	Preterm delivery N (%)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]
2011–2012, 2012–2013 and 2013–2014 seasons combined				
Non-exposed	1136	63 (5.5)	Reference	Reference
Exposed any time in pregnancy	774	44 (5.7)	1.12 (0.76, 1.64)	1.22 (0.79, 1.88)
First trimester	233	11 (4.7)	0.85 (0.45, 1.61)	0.96 (0.48, 1.92)
Second trimester	300	24 (8.0)	1.47 (0.92, 2.35)	1.59 (0.93, 2.74)
Third trimester	241	9 (3.7)	0.79 (0.39, 1.58)	0.90 (0.43, 1.88)
All subjects	1910	107 (5.6)		
2011–2012 Season				
Non-exposed	590	30 (5.1)	Reference	Reference
Exposed any time in pregnancy	213	15 (7.0)	1.50 (0.81, 2.79)	1.40 (0.70, 2.83)
First trimester	64	4 (6.3)	1.24 (0.44, 3.53)	1.10 (0.32, 3.79)
Second trimester	88	11 (12.5)	2.56 (1.28, 5.10)	2.60 (1.21, 5.61)
Third trimester	61	0 (0)	–	–
All subjects	803	45 (5.6)		
2012–2013 Season				
Non-exposed	538	25 (4.6)	Reference	Reference
Exposed any time in pregnancy	271	11 (4.1)	0.92 (0.45, 1.87)	1.05 (0.47, 2.39)
First trimester	92	3 (3.3)	0.70 (0.21, 2.31)	1.02 (0.27, 3.81)
Second trimester	102	5 (4.9)	1.05 (0.40, 2.75)	1.08 (0.35, 3.34)
Third trimester	77	3 (3.9)	0.96 (0.29, 3.18)	1.12 (0.32, 3.86)
All subjects	809	36 (4.4)		
2013–2014 Season				
Non-exposed	394	31 (7.9)	Reference	Reference
Exposed any time in pregnancy	290	18 (6.2)	0.87 (0.49, 1.56)	0.92 (0.48, 1.80)
First trimester	77	4 (5.2)	0.65 (0.23, 1.85)	0.79 (0.26, 2.36)
Second trimester	110	8 (7.3)	0.94 (0.43, 2.04)	1.03 (0.41, 2.60)
Third trimester	103	6 (5.8)	0.86 (0.36, 2.06)	0.91 (0.36, 2.28)
All subjects	684	49 (7.2)		

[a] Adjusted for propensity score including (maternal age, maternal race/ethnicity, maternal education, family income, marital status, parity, study center, pre-pregnancy BMI, pregnancy intention, periconceptional folic acid use, alcohol use, smoking, diabetes, high blood pressure or toxemia, interpregnancy interval, any infection in pregnancy, LMP quarter, any nausea/vomiting in pregnancy, any genital herpes occurrence in pregnancy, composite PTD risk variable, seasonal indicator variable).

receipt. However, our exposure prevalences are compatible with those for receipt during pregnancy reported by CDC for a similar time period [9,11]. Further, for most exposed mothers, we obtained the exact vaccination date from the vaccine record and relied on the maternal reports for the remainder. In a previous validation study of our vaccine reports, we found that 83% of self-reported receipt dates or date ranges agreed, within a given trimester of pregnancy, with the receipt date obtained from the vaccine record [20]. Thus, we do not believe that misclassification bias affected our results. Recall bias is always a concern in studies that collect information retrospectively. However, if recall bias were present, we would expect it to affect risks for all or virtually all outcomes. Given that nearly all of our findings are null, we believe that recall bias is unlikely to explain our results.

For our study of PTD, we must consider that the proportion of women with PTD in BDS is lower than in the US population, and in particular, the proportion with very early deliveries is lower than in the general population, limiting the generalizability of our findings. In addition, we did not have information on prior history of PTD, an important predictor of this condition. However, findings for our sub-analysis of primiparous women were similar to the overall results.

The H1N1 pandemic in 2009–10 raised awareness of the need for safety information for influenza vaccination in pregnancy. While a number of studies considered the issue, most focused either on the pH1N1 vaccine itself [13,14,28–43] or on seasonal vaccine in the years preceding the pandemic [24,44–48]. We are aware of only one other study that has examined vaccine safety in pregnancy in the years following the pandemic [49]; it found a decreased risk for PTD and did not evaluate risks for birth defects. Together with our prior report [13], our studies specifically address the vaccines in the four years following the pandemic season.

Our results for the 2011–12, 2012–13, and 2013–14 influenza seasons are generally reassuring regarding fetal risks following influenza vaccination in pregnancy, and add to earlier reassuring data. The few risks that were observed are compatible with chance findings but warrant testing in other data. Vaccine components and manufacturing vary from year to year, so studies of each season's vaccine are necessary to identify risks and safety that may be related to one season or product and not others [50,51].

Conflict of interest

Drs. Chambers and Jones receive research support from AbbVie, Amgen, Bristol Myers Squibb, Celgene, GSK, Janssen, Pfizer, Roche Genentech, Sandoz, Sanofi Genzyme, Takeda, Teva, UCB; Dr. Mitchell is a member of Biogen's Tecfidera Pregnancy Registry Advisory Committee.

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Table 3
Risk estimates for first trimester influenza vaccine exposure and specific birth defects (combined 11–12, 12–13 and 13–14 seasons). Based on 1411 controls, 250 of whom were exposed in first trimester (17.7%).

Category	Number of cases[b]	Exposed cases	Crude OR (95% CI)	Adjusted[b] OR (95% CI)
Any malformation	2866	461	0.89 (0.75, 1.05)	1.01 (0.85, 1.21)
Any cardiac defect	1260	203	0.89 (0.73, 1.09)	0.99 (0.83, 1.18)
Ventricular septal defects	581	101	0.98 (0.76, 1.26)	1.18 (0.90, 1.54)
Renal collecting system anomalies	307	48	0.86 (0.61, 1.21)	1.07 (0.75, 1.52)
Hypospadias[a]	250	45	1.10 (0.75, 1.60)	1.24 (0.83, 1.85)
1st degree[a]	133	21	0.94 (0.56, 1.56)	1.06 (0.63, 1.81)
2nd or 3rd degree[a]	27	4	0.87 (0.21, 2.61)	0.74 (0.24, 2.28)
Any oral cleft	245	36	0.80 (0.55, 1.17)	0.87 (0.58, 1.29)
Cleft lip ± cleft palate	141	16	0.59 (0.35, 1.02)	0.61 (0.35, 1.07)
Cleft palate only	104	20	1.11 (0.67, 1.83)	1.28 (0.75, 2.19)
Conotruncal and major arch anomalies	188	33	0.99 (0.66, 1.47)	1.03 (0.67, 1.59)
Left-sided defects	188	31	0.92 (0.61, 1.38)	0.91 (0.59, 1.41)
Right-sided defects	175	26	0.81 (0.52, 1.26)	0.88 (0.55, 1.38)
Clubfoot	165	31	1.07 (0.71, 1.63)	1.25 (0.81, 1.94)
Undescended testicle[a]	161	21	0.75 (0.45, 1.24)	0.93 (0.55, 1.57)
Pyloric stenosis	107	17	0.88 (0.51, 1.50)	0.92 (0.53, 1.62)
Renal agenesis/dysgenesis	82	14	0.96 (0.53, 1.73)	1.24 (0.66, 2.35)
Cystic kidney	79	12	0.83 (0.44, 1.56)	1.16 (0.60, 2.23)
Anal atresia/stenosis	69	9	0.70 (0.34, 1.42)	0.80 (0.37, 1.75)
Extra or horseshoe kidney	61	12	1.14 (0.60, 2.17)	1.47 (0.75, 2.91)
Neural tube defect	62	8	0.69 (0.32, 1.46)	0.91 (0.41, 1.99)
Small intestinal atresia/stenosis	60	9	0.82 (0.40, 1.69)	0.87 (0.41, 1.86)
Atrial septal defects	59	11	1.06 (0.54, 2.08)	1.06 (0.51, 2.22)
Agenesis, dysgenesis or anomalies of corpus callosum	55	10	1.03 (0.51, 2.08)	1.23 (0.59, 2.57)
Gastroschisis	55	1	0.09 (0.00, 0.51)	–
Limb reduction defects	54	7	0.69 (0.31, 1.55)	1.07 (0.47, 2.47)
Situs anomalies/looping defects	51	11	1.28 (0.65, 2.52)	1.19 (0.56, 2.51)
Hirschsprung's disease	41	6	0.80 (0.33, 1.91)	0.96 (0.38, 2.40)
AV canal defects and AV septal defects	40	5	0.66 (0.26, 1.71)	0.50 (0.17, 1.46)
Tracheoesophageal fistula	38	8	1.24 (0.56, 2.73)	1.57 (0.68, 3.64)
Intestinal malrotation	37	6	0.90 (0.37, 2.18)	0.82 (0.32, 2.07)
Diaphragmatic hernia	34	7	1.20 (0.52, 2.80)	1.15 (0.45, 2.95)
Anomalous pulmonary venous return	31	4	0.69 (0.17, 2.00)	0.64 (0.21, 1.94)
Omphalocele	29	8	1.77 (0.77, 4.04)	2.38 (0.99, 5.70)
Craniosynostosis	22	4	1.03 (0.25, 3.17)	0.82 (0.26, 2.58)
Cataract	22	3	0.73 (0.14, 2.52)	–
Anotia/microtia	21	5	1.45 (0.53, 4.00)	1.63 (0.56, 4.77)
Choanal atresia/stenosis	16	2	0.66 (0.07, 2.92)	–
Persistent pulmonary hypertension of the newborn	16	2	0.66 (0.07, 2.92)	–
Dandy Walker	11	3	1.74 (0.30, 7.32)	–
Stenosis, atresia, or anomaly of aqueduct of Sylvius	10	3	1.99 (0.33, 8.79)	–
Anophthalmia/microphthalmia	6	1	0.93 (0.02, 8.35)	–

[a] Limited to male controls.
[b] Adjusted for propensity score including (maternal age, maternal race/ethnicity, maternal education, family income, marital status, parity, study center, pre-pregnancy BMI, pregnancy intention, periconceptional folic acid use, alcohol use, smoking, asthma, diabetes, high blood pressure or toxemia, interpregnancy interval, any infection in pregnancy, LMP quarter, infertility medication use, family history of birth defects, multiple births, coffee consumption, employment outside the home, illicit medication use, and history of miscarriage).

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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.2016.06.078.

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