HHS Public Access

Author manuscript

Pharmacoepidemiol Drug Saf. Author manuscript; available in PMC 2023 August 01.

Published in final edited form as:

Pharmacoepidemiol Drug Saf. 2022 August ; 31(8): 851–862. doi:10.1002/pds.5435.

Influenza vaccination during pregnancy and risk of selected major structural noncardiac birth defects, National Birth Defects Prevention Study 2006–2011

Kristin Palmsten[1], **Jonathan Suhl**[2], **Kristin M. Conway**[2], **Elyse O. Kharbanda**[1], **Elizabeth C. Ailes**[3], **Janet D. Cragan**[3,4], **Eirini Nestoridi**[5], **Eleni A. Papadopoulos**[6], **Stephen M. Kerr**[7], **Sean G. Young**[8,9], **Frank DeStefano**[10], **Paul A. Romitti**[2],

The National Birth Defects Prevention Study

[1]HealthPartners Institute, Minneapolis, Minnesota, USA

[2]Department of Epidemiology, College of Public Health, The University of Iowa, Iowa City, Iowa, USA

[3]Division of Birth Defects and Infant Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[4]Metropolitan Atlanta Congenital Defects Program, Atlanta, Georgia, USA

[5]Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health, Boston, Massachusetts, USA

[6]Birth Defects Registry, New York State Department of Health, Albany, New York, USA

[7]Slone Epidemiology Center, Boston University, Boston, Massachusetts, USA

[8]Arkansas Center for Birth Defects Research and Prevention, Little Rock, Arkansas, USA

[9]Department of Environmental and Occupational Health, Fay W. Boozman College of Public Heath, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

[10]Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Abstract

Purpose: To assess associations between influenza vaccination during etiologically-relevant windows and selected major structural non-cardiac birth defects.

Study Design: We analyzed data from the National Birth Defects Prevention Study, a multisite, population-based case–control study, for 8233 case children diagnosed with a birth defect and

Correspondence: Paul A. Romitti, Department of Epidemiology, College of Public Health, University of Iowa, 145 N Riverside Dr, S416 CPHB, Iowa City, IA 52242, USA. paul-romitti@uiowa.edu.

ETHICS STATEMENT

Each National Birth Defects Prevention Study site obtained institutional review board approval and participants provided informed consent.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

4937 control children without a birth defect with delivery dates during 2006–2011. For all analyses except for neural tube defects (NTDs), we classified mothers who reported influenza vaccination 1 month before through the third pregnancy month as exposed; the exposure window for NTDs was 1 month before through the first pregnancy month. For defects with five or more exposed case children, we used logistic regression to estimate propensity score-adjusted odds ratios (aORs) and 95% confidence intervals (CIs), adjusting for estimated delivery year and season; plurality; maternal age, race/ethnicity, smoking and alcohol use, low folate intake; and, for NTDs, folate antagonist medications.

Results: There were 334 (4.1%) case and 197 (4.0%) control mothers who reported influenza vaccination from 1 month before through the third pregnancy month. Adjusted ORs ranged from 0.53 for omphalocele to 1.74 for duodenal atresia/stenosis. Most aORs (11 of 19) were ≤1 and all adjusted CIs included the null. The unadjusted CIs for two defects, hypospadias and craniosynostosis, excluded the null. These estimates were attenuated upon covariate adjustment (hypospadias aOR: 1.25 (95% CI 0.89, 1.76); craniosynostosis aOR: 1.23 (95% CI: 0.88, 1.74)).

Conclusions: Results for several non-cardiac major birth defects add to the existing evidence supporting the safety of inactivated influenza vaccination during pregnancy. Under-reporting of vaccination may have biased estimates downward.

Keywords

influenza vaccination; pregnancy; birth defects

1 | INTRODUCTION

Pregnant women and infants are at increased risk of morbidity and mortality from influenza infections.[1–3] Infants are not eligible for influenza vaccination until 6 months of age;[4] however, maternal influenza vaccination during pregnancy can confer passive immunogenic protection for infants through transfer of vaccine-induced maternal antibodies via the placenta and breastmilk.[5–8] Maternal influenza vaccination during pregnancy is associated with decreased risks of influenza-related hospitalization in pregnant women and in infants less than 6 months of age.[9,10] Inactivated influenza vaccine has been recommended for pregnant women in any trimester of pregnancy by the Advisory Committee on Immunization Practices (ACIP) and the American College of Obstetricians and Gynecologists since 2004.[11–14] Although influenza vaccination coverage among pregnant women in the United States has increased substantially since the 2009–2010 H1N1 pandemic,[15] it was approximately 60% by 2020.[16–18]

Concerns regarding fetal safety are an important barrier for maternal vaccination.[19,20] Existing evidence on the safety of seasonal and pandemic H1N1 inactivated influenza vaccines in relation to birth defects is reassuring.[21–28] However, ACIP considers the existing data on influenza vaccine administration specifically during the first trimester, the etiologically-relevant period for most structural birth defects, to be relatively limited.[4] Most of the studies investigating any birth defect or any major birth defect have reported null associations with first trimester influenza vaccination[21–26] as have the few studies examining specific major birth defects or groups of major birth defects.[21,22,27,28] Because etiologies of

specific birth defects can vary, safety signals can be missed when grouping all birth defects together.[29] Therefore, we conducted an analysis of early pregnancy influenza vaccination and selected individual and groups (e.g., neural tube defects [NTDs]) of major structural non-cardiac birth defects using data from the National Birth Defects Prevention Study (NBDPS). The association between early pregnancy influenza vaccination and cardiac birth defects is the focus of a separate analysis.

2 | METHODS

2.1 | NBDPS

The NBDPS was a population-based case–control study of more than 30 major structural birth defects conducted at 10 US sites (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah).[29] The study enrolled case and control children with estimated delivery dates (EDDs) from October 1997 through December 2011. Control children were live births without major defects randomly selected from birth certificates or hospital records from the same time period and study region as case children. Each site interviewed the mothers of approximately 100 control children per year. Case children could be live born, stillborn, or pregnancies electively terminated after prenatal diagnosis of birth defects. A case or control mother was eligible for interview if she had legal custody of her child, had not participated in the NBDPS previously, was not incarcerated, and could complete the interview in English or Spanish. The date of conception was estimated by subtracting 266 days from the EDD. Each site obtained institutional review board approval for the NBDPS and participants provided informed consent.

Inclusion criteria for case children have been described previously.[29] Briefly, medical records were abstracted for all case children or pregnancies with an eligible defect within each site's catchment area. Clinical geneticists reviewed abstracted information to confirm eligibility; case children with known chromosomal abnormalities or genetic syndromes were excluded. Case children were classified as having isolated (no other additional major birth defect [s] in a different organ system), multiple (one or more additional, major unrelated birth defects in a different organ system), or complex (a pattern of major defects that are embryologically related) major birth defects.[30]

Trained interviewers conducted computer-assisted telephone interviews with participants to collect information on demographics, pregnancy history, health conditions, and pregnancy exposures, including gestational timing of exposures. Interviews were conducted with case and control mothers between six weeks and 24 months after the EDD. Overall, 67% of eligible case and 65% of eligible control mothers participated.[29]

2.2 | Exposure

Vaccination status was classified according to maternal report in response to the computer-assisted telephone interview question, "During this time period [3 months before pregnancy to the end of pregnancy], did you take any medications, remedies, or treatments that we haven't already talked about? For example, flu or allergy shots or medications for asthma,

allergies, infections, STDs or HIV/AIDS? What drug?/Any others?" and a query on the specific dates of exposure. For all analyses except those for NTDs, we classified mothers who reported receiving an influenza vaccination from 1 month before pregnancy through the third pregnancy month (B1P3) as exposed because this is the etiologically-relevant window for most major structural birth defects.[31] For NTDs, the exposure window was from 1 month before pregnancy through the first pregnancy month (B1P1) as this is the etiologically-relevant window for neural tube development.[32] Mothers who did not report vaccination during the relevant exposure window were classified as unexposed during that window. Because of potential error in estimating the date of conception and to allow for exposure effects to carry into early pregnancy, we included the month before pregnancy in the exposure window to help ensure identification of all exposed mothers. We also report vaccination prevalence during the month before pregnancy through delivery (B1P9).

Inclusion and exclusion criteria.—This analysis focused on major structural non-cardiac birth defects or groups of birth defects. We restricted our study to participant mothers who had an EDD on or after January 1, 2006 and responded to the revised computer-assisted telephone interview, generally administered to mothers with an EDD in 2006 or later, because it included the question that referred to vaccinations as described above. Because of this restriction, there were no maternal interviews from New Jersey, which contributed data in earlier study years only. To reduce heterogeneity among case children, we excluded complex cases as etiologies likely differed from non-complex cases (n = 28; Figure 1).[30] We also excluded mothers (n = 53) missing the date of their influenza vaccination and mothers (n = 211) who reported type 1 or type 2 pregestational diabetes diagnosed before the index pregnancy, because it is associated with a range of birth defects.[33]

2.3 | Statistical analysis

We analyzed birth defects with at least five exposed case children to avoid overly imprecise estimates. Only male control children were included in the hypospadias analysis. We used logistic regression analysis to estimate odds ratios (ORs) and 95% confidence intervals (CIs). We identified covariates obtained from maternal interviews a priori from existing knowledge and literature, with B1P3 as the relevant window for non-NTDs and B1P1 as the relevant window for NTDs for covariates noted below: EDD year (<2009, ≥2009 as influenza vaccination coverage during pregnancy increased after the H1N1 influenza pandemic);[15] EDD season (January–March, April–June, July–September, October–December to account for seasonality of the exposure); plurality (singleton or multifetal pregnancies); maternal age (<20 years, 20–34 years, ≥35 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), and education (≤11, 12, ≥13 years) at delivery; gravidity (0, 1, ≥2); pre-pregnancy body mass index (<18.5 kg/m^2, 18.5–24 kg/m^2, 25–29 kg/m^2, ≥30 kg/m^2); cigarette smoking (no active and no passive, active only, passive only, active and passive), any alcohol use (yes, no), any fever, and any respiratory illness during B1P3 or B1P1; low folate intake (no folic acid supplementation during B1P3 or B1P1 and < 600 μg/day dietary folate equivalents in the year before pregnancy, i.e., the cut point for the recommended amount of folate during pregnancy);[34] any hypertension during pregnancy; and any folate

antagonist medication use (i.e., oxcarbazepine, pyrimethamine, sulfasalazine, triamterene, trimethoprim, phenytoin, primidone, phenobarbital, valproate sodium, aminopterin sodium, carbamazepine, cholestyramine resin, and methotrexate) during B1P1.

Due to small numbers for certain birth defects, we used propensity scores to adjust for the above covariates.[35] To calculate propensity scores, we fit a model for the probability of exposure conditional on the covariates in control mothers only and used the parameter estimates to calculate the predicted probability of exposure in all case and control mothers given their observed covariate values. Covariate distributions among control mothers are expected to approach that of the underlying population given that the outcomes are rare.[36] Three separate scores were calculated using: 1) all control mothers and the B1P3 exposure window (all birth defects except NTDs and hypospadias); 2) all control mothers and the B1P1 exposure window (NTDs); 3) all mothers of male control children and the B1P3 exposure window (hypospadias). We also used standard multivariable adjustment to confirm the propensity score-adjusted estimates. In our primary model, the propensity score included a limited set of variables identified a priori that we believed to be the most important for confounding (EDD year and season, maternal age at delivery, race/ethnicity, plurality, cigarette smoking, alcohol use, low folate intake, and, for NTDs, folate antagonist medication use). We additionally included the remaining covariates of interest in an expanded model as a sensitivity analysis. We adjusted exposure-outcome models for quintiles of the propensity score, and conducted a complete case analysis. We conducted the following secondary analyses using the limited set of covariates: 1) included case children with isolated defects only, as etiology may differ from those with multiple defects, 2) included singletons only, as twinning is associated with a range of birth defects,[37] 3) restricted to mothers whose first trimester overlapped with typical influenza vaccination months (September through March) to further account for potential seasonal effects, 4) for positive unadjusted associations with CIs not containing the null, we excluded children with family history of a first-degree relative with the specific defect of interest, and 5) excluded children with mothers who reported influenza vaccination between 2 and 3 months before conception to remove those who were less likely to be vaccinated during pregnancy, regardless of actual vaccination status during B1P3.

3 | RESULTS

There were 8233 case and 4937 control children eligible for the analysis (Figure 1). Among mothers of these children, 11.1% reported having influenza vaccination during the month before pregnancy through delivery (B1P9). Among mothers with an EDD in 2010 or 2011, 18.4% reported having influenza vaccination during B1P9 (data not shown). During B1P3, 334 (4.1%) mothers of case children and 197 (4.0%) mothers of control children reported receiving influenza vaccination during B1P3. No mothers reported receiving nasal mist formulations of the vaccination (i.e. live attenuated influenza vaccine) during B1P3, which are contraindicated during pregnancy.[14] Selected characteristics of control mothers are reported by vaccination status in Table 1. Control mothers who reported influenza vaccination more often delivered after 2009 with an EDD in April through September, had at least 13 years of education, were 35 years of age or older, were non-Hispanic White, more

often reported drinking, and less often reported smoking compared with those who did not report influenza vaccination.

We calculated ORs for 19 non-cardiac major birth defects or groups of defects (Table 2). The CIs for only two birth defects, hypospadias and craniosynostosis, excluded the null before adjustment for covariates. However, the estimates were attenuated upon adjustment for the limited set of covariates [hypospadias adjusted (a)OR: 1.25 (95% CI 0.89, 1.76); craniosynostosis aOR: 1.23 (95% CI: 0.88, 1.74); Table 2]. Adjusted ORs for the limited set of covariates ranged from 0.53 for omphalocele with six exposed case children to 1.74 for duodenal atresia/stenosis with eight exposed case children. Most of the aORs (11 of 19) were ≤1 and all CIs included the null after adjustment for covariates. No aORs in the primary analysis exceeded 2.00. Results were similar when adjusting for the limited set of covariates using propensity score adjustment versus standard multivariable adjustment (Supplemental Table S1) and when adjusting for the limited versus expanded sets of covariates (Table 3).

Results from analyses including case children with isolated defects only, singletons only, and mothers whose first trimester overlapped with typical influenza vaccination months are presented in Table 4. Overall, results were similar to the primary analysis. Only two aORs exceeded 2.00 in sensitivity analyses, isolated duodenal atresia/stenosis, and isolated anophthalmia/microphthalmia, although results were imprecise. Adjusted ORs were less than 0.50 in sensitivity analyses for one birth defect, omphalocele. Furthermore, excluding case or control children with hypospadias and craniosynostosis that had a family history of the same birth defect did not change the adjusted associations materially (Table 5). Results were similar when excluding the 107 case and 57 control children with mothers who reported receiving influenza vaccination between 2 and 3 months before conception, including 16 mothers who also reported receiving influenza vaccination during B1P3 (Supplementary Table S2).

4 | DISCUSSION

In our analysis of early pregnancy inactivated influenza vaccination and 19 selected major structural non-cardiac birth defects or birth defect groups in the NBDPS, all aORs had CIs that included the null. All aORs in the primary analysis were less than 2.00 and most were less than 1.00. We conducted several sensitivity analyses, and all analyses yielded similar results.

Our results generally align with previous studies of first trimester maternal influenza vaccination and birth defects. Studies of the association between first trimester inactivated influenza vaccination, either seasonal or pandemic H1N1, and any major birth defect suggest no increased risk.[21,22,24,26] The Slone Epidemiology Center Birth Defects Study, also a multi-site case–control study, investigated selected birth defects in relation to first trimester influenza vaccination.[27,28] The aORs were generally not elevated for seasonal influenza vaccination (2011–2012, 2012–2013, and 2013–2014 seasons) for 42 specific birth defects or categories of defects considered.[27] In an analysis of first trimester pandemic H1N1 influenza vaccination (2009–2010 and 2010–2011 seasons) in the Slone Epidemiology

Center Birth Defects Study, most aORs were close to null for the 41 specific birth defects or categories of defects considered.[28] Three defects had aORs >2.00 following first trimester pandemic H1N1 influenza vaccination; however, each of these associations were based on two exposed cases.[28] We were able to investigate one of these three defects, anophthalmia/microphthalmia, following any influenza vaccination during B1P3 and observed CIs to include the null [aOR: 1.60 (95% CI: 0.62, 4.14)]. Using automated health care data, the Vaccine Safety Datalink, a collaboration between the Centers for Disease Control and Prevention and eight health care systems, reported no association between first trimester inactivated influenza vaccination and risk of any of the major birth defects or categories that were considered, including the defect categories that we evaluated, i.e., NTDs and cleft lip and/or cleft palate.[22] A study using registry data from Sweden reported no increased risk of NTDs, oral clefts, or limb deficiency following first trimester pandemic H1N1 influenza vaccination.[21] Similarly, we observed no increased risk of NTDs aOR: 0.87 (95% CI: 0.41, 1.83), oral clefts aOR: 0.94 (95% CI: 0.70, 1.31), or limb deficiency aOR: 0.98 (95% CI: 0.60, 1.60).

Our study has several strengths including the population-based data source. Furthermore, standardized interview protocols allowed for the collection of information on many potential confounders. NBDPS utilized detailed protocols to classify cases, allowing us to study specific birth defects and ensuring the accuracy of case classification.[30] Also, we were able to separately analyze isolated defects. Although there is an increased risk of type I error when studying multiple specific birth defects, we observed no harmful aOR for inactivated influenza vaccination and the selected birth defects. Although the design of the current study is similar to the Slone Epidemiology Center Birth Defects Study, our analysis had more case children with certain birth defects available.

Our study has limitations to consider. Only 18% reported influenza vaccination during pregnancy among those with an EDD in the last 2 years of the study (2010–2011), whereas seasonal influenza vaccination coverage during pregnancy in the United States was between 32% and 40% during the 2009–2010 and 2012–2013 influenza seasons, respectively, with H1N1 vaccine coverage around 45% during the 2009–2010 influenza season.[38,39] This discrepancy suggests under-reporting of influenza vaccination in our study. Previous validation studies among similar age groups in the general population have demonstrated sensitivities of 90–97%, and specificities of 68–92%, for self-reporting influenza vaccination status, including for the previous influenza season, compared with information from vaccine registries and/or medical records.[40–42] However, we were not able to confirm self-reported vaccination status, and we suspect underreporting of influenza vaccination in the current study to be greater than reported in previous validation studies due to 1) the lag between exposure and interview, especially among women who had to recall vaccination status from an influenza season more than one season before the interview, and 2) the interview indirectly querying about influenza vaccination status (i.e., "… did you take any medications, remedies, or treatments that we haven't already talked about? For example, flu or allergy shots…"). Non-differential exposure misclassification would tend to bias results downward, potentially masking positive associations (i.e., harmful effects). Differential misclassification could bias results in either direction, again potentially masking positive associations. Also, exposure data were available up to three months before

pregnancy only, and we could not exclude women who were less likely to receive influenza vaccination during pregnancy because they had received the vaccine earlier in the season and prior to 3 months before pregnancy. This may have resulted in an underestimate of influenza vaccination prevalence given that the denominator may have included women vaccinated before this reporting period. Furthermore, it may have resulted in violations of the positivity assumption, a requirement for causal inference. However, excluding children whose mothers reported influenza vaccination between 2 and 3 months before conception did not materially change the results. The prevalence of reported influenza vaccination in B1P3 across all study years was only 4%, which limited the number of birth defects we were able to assess and led to imprecise estimates for many of the defects. Additionally, the type of vaccination (seasonal or pandemic) was often unknown, and together with limited statistical power prevented us from studying type and season of influenza vaccination. Selection bias from lack of inclusion of early pregnancy loss could be a concern; however, existing studies generally do not support an association between inactivated influenza vaccination and early pregnancy loss.[1] Missing covariate values were more common among control mothers who were unexposed versus exposed. Nevertheless, the potential for selection bias in the complete case analysis was minimized by the relatively low levels of missing data (i.e., usually 5% or less). Although the vaccines in this study were administered more than a decade ago, we expect the findings to be applicable for contemporary influenza vaccine exposures as the type of influenza vaccines used in pregnant women during the study years (i.e., inactivated influenza vaccine) is still recommended.[14] Influenza virus sub-groups included in influenza vaccines vary by year, but are not expected to affect the safety profile.

Although we cannot rule out small increased risks for some of the birth defects analyzed due to imprecise estimates, we observed no aORs of 2.00 or higher for early pregnancy inactivated influenza vaccination and any of the 19 selected major structural non-cardiac birth defects or birth defect groups that we studied. Furthermore, we cannot entirely rule out increased risks for the birth defects analyzed due to the potential for exposure misclassification. Our study, together with other studies using automated health care data, population-based registry data, and population-based case–control study design, strengthens the evidence that inactivated influenza vaccination in early pregnancy, including the month before conception, is not strongly associated with the risk for major structural birth defects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. KP conducted the analysis and JS independently replicated the analysis.

Funding information

Centers for Disease Control and Prevention, Grant/Award Numbers: DD001223, U01, DD18–001, DD13–003, DD09–001; This project was supported through Centers for Disease Control and Prevention (CDC) cooperative agreements under PA #96043, PA #02081, FOA #DD09–001, FOA #DD13–003, and NOFO #DD18–001 to the Centers for Birth Defects Research and Prevention participating in the National Birth Defects Prevention Study

(NBDPS) and/or the Birth Defects Study To Evaluate Pregnancy exposureS and the Iowa Center for Birth Defects Research and Prevention U01 DD001223 (PAR).

REFERENCES

1. Centers for Disease Control and Prevention. Background Document for “Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2019–20 Influenza Season” https://www.cdc.gov/flu/professionals/acip/background-epidemiology.htm. Accessed April 13, 2021].
2. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. N Engl J Med 2006;355:31–40. doi:10.1056/NEJMoa054869 [PubMed: 16822994]
3. Shang M, Blanton L, Brammer L, Olsen SJ, Fry AM. Influenza-associated pediatric deaths in the United States, 2010–2016. Pediatrics 2018;141(4):e20172918. doi:10.1542/peds.2017-2918 [PubMed: 29440502]
4. Grohskopf LA, Alyanak E, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices - United States, 2020–21 influenza season. MMWR Recomm Rep 2020;69:1–24. doi:10.15585/mmwr.rr6908a1
5. Munoz FM, Jamieson DJ. Maternal immunization. Obstet Gynecol 2019;133:739–753. [PubMed: 30913173]
6. Helmig RB, Maimburg RD, Erikstrup C, et al. Antibody response to influenza a(H1N1)pdm09 in vaccinated, serologically infected and unaffected pregnant women and their newborns. Acta Obstet Gynecol Scand 2015;94(833–839):833–839. doi:10.1111/aogs.12668 [PubMed: 25958884]
7. Ahmad SM, Alam MJ, Khanam A, et al. Vitamin a supplementation during pregnancy enhances pandemic H1N1 vaccine response in mothers, but enhancement of Transplacental antibody transfer may depend on when mothers are vaccinated during pregnancy. J Nutr 2018;148(1968–1975):1968–1975. doi:10.1093/jn/nxy228 [PubMed: 30517724]
8. Schlaudecker EP, Steinhoff MC, Omer SB, et al. IgA and neutralizing antibodies to influenza a virus in human milk: a randomized trial of antenatal influenza immunization. PLoS One 2013;8(e70867):e70867. doi:10.1371/journal.pone.0070867 [PubMed: 23967126]
9. Thompson MG, Kwong JC, Regan AK, et al. Influenza vaccine effectiveness in preventing influenza-associated hospitalizations during pregnancy: a multi-country retrospective test negative design study, 2010–2016. Clin Infect Dis 2019;68(9):1444–1453. doi: 10.1093/cid/ciy737 [PubMed: 30307490]
10. Nunes MC, Madhi SA. Influenza vaccination during pregnancy for prevention of influenza confirmed illness in the infants: a systematic review and meta-analysis. Hum Vaccin Immunother 2018;14:758–766. doi:10.1080/21645515.2017.1345385 [PubMed: 28708952]
11. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB, Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP). Prevention and control of influenza: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep 2004;53:1–40.
12. ACOG Committee. Opinion No. 732: Influenza Vaccination During Pregnancy. Obstet Gynecol 2018;131:e109–e114. doi: 10.1097/AOG.0000000000002588 [PubMed: 29578985]
13. Practice ACoO. ACOG committee opinion number 305. Influenza vaccination and treatment during pregnancy. Obstet Gynecol 2004; 2004(104):1125–1126.
14. Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices, United States, 2021–22 influenza season. MMWR Recomm Rep 2021;70:1–28. doi: 10.15585/mmwr.rr7005a1
15. Rasmussen SA, Jamieson DJ. Influenza and pregnancy: no time for complacency. Obstet Gynecol 2019;133(23–26):23–26. doi: 10.1097/aog.0000000000003040 [PubMed: 30531576]
16. Ghaswalla P, Poirrier JE, Packnett ER, Irwin DE, Gray SR, Buck PO. Maternal immunization in the U.S.: a Nationwide retrospective cohort study. Am J Prev Med 2019;57:e87–e93. doi:10.1016/j.amepre.2019.04.013 [PubMed: 31427034]

17. Kaur R, Callaghan T, Regan AK. Disparities in maternal influenza immunization among women in rural and urban areas of the United States. Prev Med 2021;147:106531. doi:10.1016/j.ypmed.2021.106531 [PubMed: 33771563]
18. Razzaghi H, Kahn KE, Black CL, et al. Influenza and Tdap vaccination coverage among pregnant women - United States, April 2020. MMWR Morb Mortal Wkly Rep 2020;69:1391–1397. doi:10.15585/mmwr.mm6939a2 [PubMed: 33001873]
19. Lutz CS, Carr W, Cohn A, Rodriguez L. Understanding barriers and predictors of maternal immunization: identifying gaps through an exploratory literature review. Vaccine 2018;36(7445–7455):7445–7455. doi:10.1016/j.vaccine.2018.10.046 [PubMed: 30377064]
20. King JP, Hanson KE, Donahue JG, et al. Survey of influenza vaccine knowledge, attitudes, and beliefs among pregnant women in the 2016–17 season. Vaccine 2020;38(2202–2208):2202–2208. doi: 10.1016/j.vaccine.2020.01.039 [PubMed: 31992481]
21. Ludvigsson JF, Ström P, Lundholm C, et al. Risk for congenital malformation with H1N1 influenza vaccine: a cohort study with sibling analysis. Ann Intern Med 2016;165(848–855):848–855. doi: 10.7326/m16-0139 [PubMed: 27654505]
22. Kharbanda EO, Vazquez-Benitez G, Romitti PA, et al. First trimester influenza vaccination and risks for major structural birth defects in offspring. J Pediatr 2017;187:234–239. doi:10.1016/j.jpeds.2017.04.039 [PubMed: 28550954]
23. Conlin AMS, Bukowinski AT, Levine JA, et al. A follow-up comparative safety analysis of pandemic H1N1 vaccination during pregnancy and risk of infant birth defects among U.S. military mothers. Vaccine 2018; 36(2855–2860):2855–2860. doi:10.1016/j.vaccine.2018.03.061 [PubMed: 29625766]
24. Polyzos KA, Konstantelias AA, Pitsa CE, Falagas ME. Maternal influenza vaccination and risk for congenital malformations: a systematic review and meta-analysis. Obstet Gynecol 2015;126(1075–1084): 1075–1084. doi:10.1097/aog.0000000000001068 [PubMed: 26444106]
25. McMillan M, Porritt K, Kralik D, Costi L, Marshall H. Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. Vaccine 2015; 33(2108–2117):2108–2117. doi:10.1016/j.vaccine.2015.02.068 [PubMed: 25758932]
26. Chambers CD, Johnson DL, Xu R, et al. Safety of the 2010–11, 2011–12, 2012–13, and 2013–14 seasonal influenza vaccines in pregnancy: birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants, a study from the cohort arm of VAMPSS. Vaccine 2016;34:4443–4449. doi:10.1016/j.vaccine.2016.06.054 [PubMed: 27449682]
27. Louik C, Kerr S, Van Bennekom CM, et al. 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. Vaccine 2016;34:4450–4459. doi:10.1016/j.vaccine.2016.06.078 [PubMed: 27452865]
28. Louik C, Ahrens K, Kerr S, et al. Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: exposure prevalence, preterm delivery, and specific birth defects. Vaccine 2013;31(5033–5040):5033–5040. doi:10.1016/j.vaccine.2013.08.096 [PubMed: 24016804]
29. Reefhuis J, Gilboa SM, Anderka M, et al. The National Birth Defects Prevention Study: a review of the methods. Birth Defects Res A Clin Mol Teratol 2015;103(656–669):656–669. doi:10.1002/bdra.23384 [PubMed: 26033852]
30. Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol 2003; 67(193–201):193–201. doi:10.1002/bdra.10012 [PubMed: 12797461]
31. Jones KL, del Campo M, Jones MC. Smith's Recognizable Patterns of Human Malformation Seventh ed. Philadelphia, PA: Saunders; 2013.
32. Greene ND, Copp AJ. Neural tube defects. Annu Rev Neurosci 2014; 37(221–242):221–242. doi:10.1146/annurev-neuro-062012-170354 [PubMed: 25032496]
33. Correa A, Gilboa SM, Besser LM, et al. Diabetes mellitus and birth defects. Am J Obstet Gynecol 2008;199(237):e231–e239. doi: 10.1016/j.ajog.2008.06.028

34. U.S. Food and Drug Administration. Folate and Folic Acid on the Nutrition and Supplement Facts Labels https://www.fda.gov/food/new-nutrition-facts-label/folate-and-folic-acid-nutrition-and-supplement-facts-labels. [Accessed June 7, 2021].

35. Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clin Pharmacol Toxicol 2006;98(253–259):253–259. doi:10.1111/j.1742-7843.2006.pto_293.x [PubMed: 16611199]

36. Mansson R, Joffe MM, Sun W, Hennessy S. On the estimation and use of propensity scores in case-control and case-cohort studies. Am J Epidemiol 2007;166(332–339):332–339. doi:10.1093/aje/kwm069 [PubMed: 17504780]

37. Dawson AL, Tinker SC, Jamieson DJ, et al. Twinning and major birth defects, National Birth Defects Prevention Study. J Epidemiol Community Health 1997–2007;2016(70):1114–1121. doi:10.1136/jech-2015-206302

38. Ding H, Santibanez TA, Jamieson DJ, et al. Influenza vaccination coverage among pregnant women–National 2009 H1N1 Flu Survey (NHFS). Am J Obstet Gynecol 2011;204(6 Suppl 1):S96–S106. doi:10.1016/j.ajog.2011.03.003 [PubMed: 21640233]

39. Lu P-j, Hung M-C, O'Halloran AC, et al. Seasonal influenza vaccination coverage trends among adult populations, U.S., 2010–2016. American Journal of Preventive Medicine 2019;57:458–469. doi:10.1016/j.amepre.2019.04.007 [PubMed: 31473066]

40. Irving SA, Donahue JG, Shay DK, Ellis-Coyle TL, Belongia EA. Evaluation of self-reported and registry-based influenza vaccination status in a Wisconsin cohort. Vaccine 2009;27:6546–6549. doi:10.1016/j.vaccine.2009.08.050 [PubMed: 19729083]

41. Rolnick SJ, Parker ED, Nordin JD, et al. Self-report compared to electronic medical record across eight adult vaccines: do results vary by demographic factors? Vaccine 2013;31(3928–3935):3928–3935. doi: 10.1016/j.vaccine.2013.06.041 [PubMed: 23806243]

42. King JP, McLean HQ, Belongia EA. Validation of self-reported influenza vaccination in the current and prior season. Influenza Other Respir Viruses 2018;12:808–813. doi:10.1111/irv.12593 [PubMed: 30028081]

Key Points

- In our analysis of early pregnancy inactivated influenza vaccination and 19 selected major structural non-cardiac birth defects or birth defect groups, all aORs had CIs that included the null.
- Although we cannot rule out small increased risks for some of the birth defects analyzed, there were no aORs of 2.00 or higher for early pregnancy inactivated influenza vaccination and any of the 19 selected major structural non-cardiac birth defects or birth defect groups.
- Our study contributes to the evidence that inactivated influenza vaccination in early pregnancy, including the month before conception, is not strongly associated with the risk for major structural birth defects.

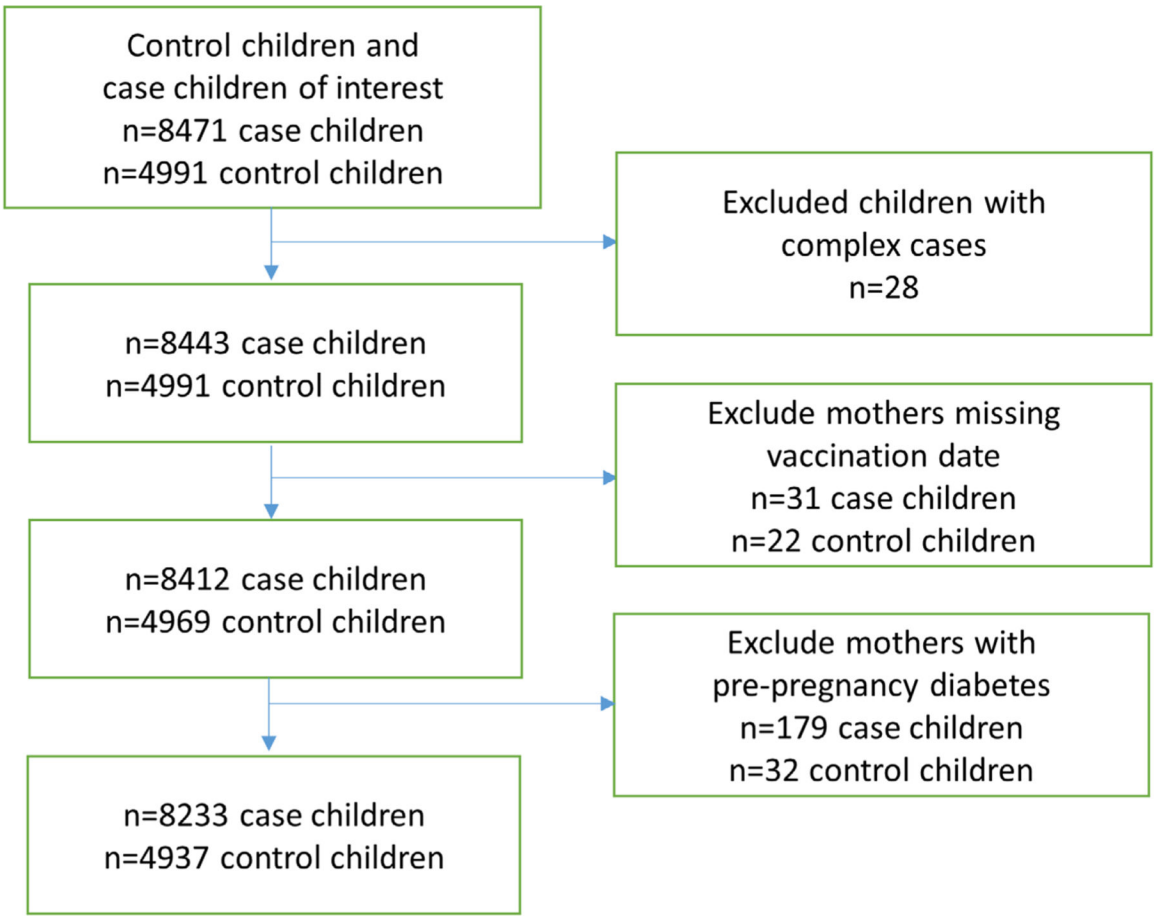

FIGURE 1.

Exclusions for case and control children among mothers who had an estimated delivery date during 2006 to 2011 in the analysis of the National Birth Defects Prevention Study

TABLE 1

Characteristics by exposure status among mothers of control children, National Birth Defects Prevention Study 2006 to 2011

	Influenza vaccination During B1P3 (*n* = 197)		No influenza vaccination during B1P3 (*n* = 4740)	
Characteristic	***n***	**%**	***n***	**%**
Estimated date of delivery year				
2006–2009	89	45.2	3250	68.6
2010–2011	108	54.8	1490	31.4
Estimated delivery date season				
Winter (January–March)	17	8.6	1183	25.0
Spring (April–June)	98	49.7	1096	23.1
Summer (July–September)	63	32.0	1267	26.7
Fall (October–December)	19	9.6	1194	25.2
Plurality				
Twins and higher order	5	2.5	141	3.0
Singletons	192	97.5	4598	97.0
Missing	0		1	
Maternal age at delivery				
<20 years	6	3.0	427	9.0
20 to 34 years	153	77.7	3646	76.9
≥35 years	38	19.3	667	14.1
Maternal race/ethnicity				
Non-Hispanic White	145	73.6	2588	54.7
Non-Hispanic Black	13	6.6	489	10.3
Hispanic	21	10.7	1328	28.1
Other	18	9.1	329	6.9
Missing	0		6	
Education				
≤11 years	10	5.2	744	16.5
12 years	23	11.9	1031	22.8
≥13 years	161	83.0	2745	60.7
Missing	3		220	

	Influenza vaccination During B1P3 (*n* = 197)		No influenza vaccination during B1P3 (*n* = 4740)	
Characteristic	***n***	**%**	***n***	**%**
Gravidity				
0	57	28.9	1421	30.2
1	59	29.9	1272	27.0
≥2	81	41.1	2020	42.9
Missing	0		27	
Pre-pregnancy body mass index				
Underweight <18.5 kg/m^2	9	4.6	226	4.8
Normal weight 18.5–24 kg/m^2	106	57.3	2272	53.3
Overweight 25–29 kg/m^2	34	18.4	1046	24.5
Obese ≥30 kg/m^2	45	24.3	948	22.2
Missing	3		248	
Smoking B1P3				
No active and no passive smoking	154	79.4	3306	73.2
Active smoking only	11	5.7	354	7.8
Passive smoking only	12	6.2	455	10.1
Active and passive smoking	17	8.8	400	8.9
Missing	3		225	
Alcohol B1P3				
Drinking	86	44.8	1676	37.2
No drinking	106	55.2	2831	62.8
Missing	5		233	
Low folate intake B1P3[a]				
Yes	5	2.6	359	7.8
No	190	97.4	4240	92.2
Missing	2		141	
Hypertension during pregnancy				
Yes	24	12.2	446	9.6
No	172	87.8	4221	90.4
Missing	1		73	
Respiratory illness B1P3				

	Influenza vaccination During B1P3 (*n* = 197)		No influenza vaccination during B1P3 (*n* = 4740)	
Characteristic	***n***	**%**	***n***	**%**
Yes	53	27.7	1035	22.8
No	138	72.3	3510	77.2
Missing	6		195	
Fever B1P3				
Yes	21	11.2	399	9.1
No	167	88.8	3969	90.9
Missing	9		372	
Folate antagonist medication B1P1[b]				
Yes	1	1.6	25	0.5
No	60	98.4	4732	99.5
Missing	2		117	

Abbreviations: B1P3, 1 month before pregnancy through the third pregnancy month; B1P1, 1 month before pregnancy through the first pregnancy month.

[a]No folic acid supplementation during B1P3 and < 600 μg/day dietary folate equivalents in the year before pregnancy.

[b]For B1P1: *n* exposed to influenza vaccine = 63, *n* unexposed = 4874.

TABLE 2

Unadjusted and adjusted limited model odds ratios (OR) and 95% confidence intervals (CI) for associations between influenza vaccination and non-cardiac birth defects, National Birth Defects Prevention Study 2006 to 2011

	Case children	Unadjusted	Adjusted limited model[a]
Birth defect[b,c]	**Exposed/Unexposed[b,c,d]**	**OR (95% CI)**	**OR (95% CI)**
Central nervous system			
Any neural tube defects[e]	8/805	0.77 (0.37, 1.62)	0.87 (0.41, 1.83)
Hydrocephaly	6/171	0.82 (0.36, 1.87)	0.88 (0.38, 2.05)
Eye and ear			
Anophthalmia/microphthalmia	5/76	1.53 (0.61, 3.83)	1.60 (0.62, 4.14)
Cataracts	5/149	0.78 (0.32, 1.93)	0.71 (0.28, 1.79)
Anotia/microtia	6/247	0.57 (0.25, 1.29)	0.67 (0.29, 1.55)
Orofacial			
Choanal atresia	5/61	1.91 (0.76, 4. 81)	1.48 (0.57, 3.85)
Oral clefts	69/1745	0.92 (0.70, 1.22)	0.94 (0.71, 1.26)
Cleft lip w/wo cleft palate	46/1172	0.91 (0.60, 1.27)	0.94 (0.70, 1.31)
Cleft palate	23/573	0.94 (0.60, 1.45)	0.96 (0.61, 1.51)
Gastrointestinal			
Esophageal atresia	15/277	1.26 (0.74, 2.16)	1.20 (0.69, 2.08)
Duodenal atresia/stenosis	8/104	1.79 (0.86, 3.73)	1.74 (0.81, 3.73)
Anorectal atresia/stenosis	13/364	0.83 (0.47, 1.47)	0.94 (0.52, 1.68)
Genitourinary			
Hypospadias second/third degree	62/1087	1.56 (1.11, 2.18)	1.25 (0.89, 1.76)
Musculoskeletal			
Limb deficiency[f]	19/452	0.98 (0.61, 1.58)	0.98 (0.60, 1.60)
Longitudinal limb deficiency	9/164	1.28 (0.64, 2.54)	1.42 (0.70, 2.89)
Transverse limb deficiency	8/273	0.68 (0.33, 1.40)	0.65 (0.31, 1.35)
Craniosynostosis	45/696	1.51 (1.08, 2.10)	1.23 (0.88, 1.74)
Diaphragmatic hernia	14/313	1.04 (0.60, 1.81)	1.27 (0.72, 2.26)
Gastroschisis	16/608	0.61 (0.37, 1.03)	0.75 (0.44, 1.27)

[a] Limited model adjusted for estimated date of delivery year and season, maternal age at delivery, maternal race/ethnicity, plurality, cigarette smoking, alcohol use, low folate intake, and, for neural tube defects, folate antagonist medication use.

[b] Children with missing values of covariates in the limited model have been excluded.

[c] Exposure window is 1 month before pregnancy through the first pregnancy month for neural tube defects and 1 month before pregnancy through the third pregnancy month for all other defects.

[d] Neural tube defects analysis included 59 exposed and 4576 unexposed control children; hypospadias analysis included 84 exposed and 2298 unexposed control children; all other analyses included 191 exposed and 4447 unexposed control children.

[e] Subtypes of neural tube defects with <5 exposed case children are not presented: anencephaly, encephalocele, spina bifida.

[f] Subtypes of limb deficiency with <5 exposed case children are not presented: intercalary limb deficiency, NOS limb deficiency.

TABLE 3

Unadjusted and adjusted expanded model odds ratios (OR) and 95% confidence intervals (CI) for associations between influenza vaccination and non-cardiac birth defects, National Birth Defects Prevention Study 2006 to 2011

	Case children	Unadjusted	Adjusted expanded model[a]
Birth defect[b,c]	**Exposed/Unexposed[b,c,d]**	**OR (95% CI)**	**OR (95% CI)**
Central nervous system			
Any neural tube defects[e]	5/671	0.53 (0.21, 1.33)	0.58 (0.23, 1.45)
Hydrocephaly	6/146	0.89 (0.39, 2.04)	1.06 (0.45, 2.49)
Eye and ear			
Anophthalmia/microphthalmia	5/72	1.51 (0.60, 3.77)	1.82 (0.70, 4.73)
Cataracts	5/133	0.82 (0.33, 2.01)	0.75 (0.30, 1.90)
Anotia/microtia	6/197	0.66 (0.29, 1.51)	0.89 (0.38, 2.06)
Orofacial			
Choanal atresia	4/56	NC	NC
Oral clefts	61/1512	0.87 (0.65, 1.18)	0.89 (0.66, 1.21)
Cleft lip w/wo cleft palate	42/1019	0.89 (0.63, 1.26)	0.92 (0.65, 1.31)
Cleft palate	19/493	0.84 (0.52, 1.35)	0.84 (0.51, 1.37)
Gastrointestinal			
Esophageal atresia	13/238	1.18 (0.66, 2.11)	1.07 (0.59, 1.94)
Duodenal atresia/stenosis	8/87	1.99 (0.95, 4.17)	1.79 (0.83, 3.86)
Anorectal atresia/stenosis	13/311	0.91 (0.51, 1.61)	1.00 (0.55, 1.80)
Genitourinary			
Hypospadias second/third degree	56/970	1.44 (1.01, 2.04)	1.13 (0.79, 1.61)
Musculoskeletal			
Limb deficiency[f]	18/383	1.02 (0.62, 1.67)	1.11 (0.67, 1.84)
Longitudinal limb deficiency	8/140	1.24 (0.60, 2.56)	1.50 (0.71, 3.19)
Transverse limb deficiency	8/231	0.75 (0.37, 1.54)	0.78 (0.37, 1.62)
Craniosynostosis	40/597	1.45 (1.02, 2.07)	1.21 (0.84, 1.74)
Diaphragmatic hernia	12/265	0.98 (0.54, 1.78)	1.24 (0.67, 2.30)
Gastroschisis	16/551	0.63 (0.37, 1.06)	0.86 (0.51, 1.47)

Abbreviations: NC, not calculated because <5 exposed cases.

[a] Expanded model adjusted for estimated date of delivery year and season, maternal age at delivery, maternal race/ethnicity, plurality, cigarette smoking, alcohol use, low folate intake, and, for neural tube defects, folate antagonist medication use, education, body mass index, gravidity, hypertension during pregnancy, fever, and respiratory illness.

[b] Children with missing values of covariates in the expanded model have been excluded.

[c] Exposure window is 1 month before pregnancy through the first pregnancy month for neural tube defects and 1 month before pregnancy through the third pregnancy month for all other defects.

[d] Neural tube defects analysis included 56 exposed and 3996 unexposed control children; hypospadias analysis included 82 exposed and 2040 unexposed control children; all other analyses included 182 exposed and 3943 unexposed control children.

[e] Subtypes of neural tube defects with <5 exposed case children are not presented: anencephaly, encephalocele, spina bifida.

[f] Subtypes of limb deficiency with <5 exposed case children are not presented: intercalary limb deficiency, NOS limb deficiency.

TABLE 4

Secondary analysis adjusted odds ratios (OR) and 95% confidence intervals (CI) for associations between influenza vaccination and non-cardiac birth defects, National Birth Defects Prevention Study 2006 to 2011

Birth defect[d]	Case children with isolated defects[a]		Singletons only[b]		First trimester overlapping with September–March Only[c]	
	Case children exposed/ unexposed[d]	Adjusted, limited model[e,f] OR (95% CI)	Case children exposed/ unexposed[d]	Adjusted, limited model[e,f] OR (95% CI)	Case children exposed/ unexposed[d]	Adjusted, limited model[e,f] OR (95% CI)
Central nervous system						
Any neural tube defects[g]	7/793	0.74 (0.32, 1.72)	9/879	0.88 (0.42, 1.86)	8/752	0.81 (0.37, 1.80)
Hydrocephaly	6/126	1.27 (0.54, 3.00)	7/177	0.91 (0.39, 2.13)	7/158	0.92 (0.40, 2.15)
Eye and ear						
Anophthalmia/microphthalmia	5/50	2.22 (0.84, 5.88)	5/81	1.82 (0.70, 4.72)	5/76	1.60 (0.62, 4.15)
Cataracts	5/137	0.79 (0.32, 2.00)	4/150	NA	5/131	0.73 (0.29, 1.85)
Anotia/microtia	6/175	0.84 (0.33, 2.10)	6/252	0.59 (0.24, 1.47)	7/222	0.68 (0.30, 1.58)
Orofacial						
Choanal atresia	3/35	NA	5/57	1.69 (0.65, 4.43)	5/55	1.65 (0.63, 4.30)
Oral clefts	61/1598	0.97 (0.71, 1.31)	67/1774	0.94 (0.70, 1.26)	69/1545	0.98 (0.74, 1.32)
Cleft lip w/wo cleft palate	41/1096	0.96 (0.67, 1.36)	45/1190	0.96 (0.68, 1.34)	45/1050	0.97 (0.69, 1.36)
Cleft palate	20/502	0.98 (0.61, 1.59)	22/584	0.90 (0.56, 1.44)	24/495	1.02 (0.65, 1.60)
Gastrointestinal						
Esophageal atresia	7/137	1.19 (0.54, 2.63)	12/278	1.04 (0.56, 1.91)	15/256	1.20 (0.69, 2.10)
Duodenal atresia/stenosis	6/71	2.30 (0.94, 5.61)	8/107	1.83 (0.85, 3.93)	8/96	1.76 (0.82, 3.80)
Anorectal atresia/stenosis	7/168	1.13 (0.51, 2.49)	12/355	0.96 (0.53, 1.77)	12/322	0.86 (0.47, 1.57)
Genitourinary						
Hypospadias second/third degree	53/1027	1.16 (0.81, 1.67)	57/1079	1.18 (0.83, 1.68)	61/966	1.24 (0.87, 1.76)
Bilateral renal agenesis or hypoplasia	4/49	NA	5/56	1.79 (0.61, 5.26)	5/51	1.61 (0.55, 4.70)
Musculoskeletal						
Limb deficiency[h]	17/355	0.90 (0.51, 1.59)	22/447	0.99 (0.60, 1.65)	22/396	1.03 (0.63, 1.69)
Longitudinal limb deficiency	6/96	1.60 (0.67, 3.81)	9/162	1.35 (0.64, 2.86)	10/145	1.47 (0.72, 3.01)
Transverse limb deficiency	10/241	0.64 (0.29, 1.39)	11/269	0.69 (0.33, 1.44)	10/236	0.68 (0.33, 1.42)
Craniosynostosis	42/683	1.25 (0.87, 1.77)	42/709	1.22 (0.85, 1.73)	44/613	1.30 (0.92, 1.85)

Birth defect[d]	Case children with isolated defects[a]		Singletons only[b]		First trimester overlapping with September–March Only[c]	
	Case children exposed/ unexposed[d]	Adjusted, limited model[e,f] OR (95% CI)	Case children exposed/ unexposed[d]	Adjusted, limited model[e,f] OR (95% CI)	Case children exposed/ unexposed[d]	Adjusted, limited model[e,f] OR (95% CI)
Diaphragmatic hernia	10/244	1.23 (0.63, 2.41)	12/323	1.13 (0.61, 2.08)	14/281	1.28 (0.72, 2.28)
Omphalocele	3/98	NA	5/128	0.41 (0.10, 1.68)	5/125	0.34 (0.08, 1.42)
Gastroschisis	19/600	0.82 (0.48, 1.40)	18/660	0.72 (0.42, 1.23)	19/578	0.76 (0.45, 1.29)

Abbreviations: NA, not applicable as point estimates were not calculated when there were <5 exposed case children.

[a] Neural tube defect analysis included 63 exposed and 4874 unexposed control children; hypospadias analysis included 87 exposed and 2457 unexposed control children; all other analyses included 197 exposed and 4740 unexposed control children.

[b] Neural tube defect analysis included 62 exposed and 4728 unexposed control children; hypospadias analysis included 85 exposed and 2386 unexposed control children; all other analyses included 192 exposed and 4598 unexposed control children.

[c] Neural tube defect analysis included 59 exposed and 4080 unexposed control children; hypospadias analysis included 85 exposed and 2043 unexposed control children; all other analyses included 189 exposed and 3950 unexposed control children.

[d] Exposure window is 1 month before pregnancy through the first pregnancy month for neural tube defects and 1 month before pregnancy through the third pregnancy month for all other defects.

[e] Counts in adjusted analyses were slightly lower than presented because of missing covariate values.

[f] Adjusted for estimated date of delivery year and season, maternal age at delivery, maternal race/ethnicity, plurality, cigarette smoking, alcohol use, low folate intake, and, for neural tube defects, folate antagonist medication use.

[g] Subtypes of neural tube defects with <5 exposed case children are not presented: anencephaly, encephalocele, spina bifida.

[h] Subtypes of limb deficiency with <5 exposed case children are not presented: intercalary limb deficiency, NOS limb deficiency.

TABLE 5

Adjusted odds ratios (OR) and 95% confidence intervals (CI) for associations between influenza vaccination and non-cardiac birth defects for craniosynostosis and hypospadias excluding case children with a family history of the specific birth defect, National Birth Defects Prevention Study 2006 to 2011

	Case children		Adjusted, limited model[c,d]
Birth defect[a,b]	**Exposed**	**Unexposed**	**OR (95% CI)**
Craniosynostosis	44	714	1.28 (0.90, 1.81)
Hypospadias second/third degree	58	1106	1.21 (0.85, 1.72)

[a] Exposure window is 1 month before through the third pregnancy month.

[b] Hypospadias analysis included 87 exposed and 2453 unexposed control children; craniosynostosis analysis included 197 exposed and 4740 unexposed control children.

[c] Counts in adjusted analyses were slightly lower than presented because of missing covariate values.

[d] Adjusted for estimated date of delivery year and season, maternal age, maternal, plurality, cigarette smoking, alcohol use, low folate intake, and, for neural tube defects, folate antagonist medication use.